Ru- and Rh-catalyzed [2+2+2] cycloadditions: an access to fluorenone, 2-aminopyridine, and 1,3-dihydroisobenzofuran derivatives

Par Fei YE

Thèse de doctorat de Chimie Organique

Dirigée par les Drs. Véronique MICHELET et Virginie VIDAL

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« If we knew what we were doing, it wouldn’t be called research, would it? »

Albert Einstein
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<tr>
<td>atm</td>
<td>Atmosphere</td>
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<tr>
<td>B</td>
<td>Boc</td>
<td>tert-Butyloxycarbonyl</td>
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<tr>
<td>BINAP</td>
<td>2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl</td>
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<td>Bn</td>
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<tr>
<td>DRX</td>
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<td>δ</td>
<td>Chemical shift (units: ppm)</td>
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<td>E</td>
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<tr>
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<td>H</td>
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<td>N</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td></td>
<td>nBu</td>
<td>n-Butyl</td>
</tr>
<tr>
<td></td>
<td>nd</td>
<td>Not detected</td>
</tr>
<tr>
<td></td>
<td>NIS</td>
<td>N-iodosuccinimide</td>
</tr>
<tr>
<td></td>
<td>NHCs</td>
<td>N-heterocyclic carbenes</td>
</tr>
<tr>
<td></td>
<td>NMI</td>
<td>N-methylimidazole</td>
</tr>
<tr>
<td></td>
<td>NMP</td>
<td>N-methyl-2-pyrrolidone</td>
</tr>
<tr>
<td></td>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td></td>
<td>NOESY</td>
<td>Nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td></td>
<td>nr</td>
<td>No reaction</td>
</tr>
<tr>
<td>O</td>
<td>o-</td>
<td>ortho-</td>
</tr>
<tr>
<td></td>
<td>oct</td>
<td>Octyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>OLEDs</td>
<td>Organic light-emitting diodes</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>para-</td>
<td></td>
</tr>
<tr>
<td>$p$-cymene</td>
<td>4-Isopropyltoluene</td>
<td></td>
</tr>
<tr>
<td>pbq</td>
<td>1,4-Benzquinone</td>
<td></td>
</tr>
<tr>
<td>pent</td>
<td>Pentyl</td>
<td></td>
</tr>
<tr>
<td>Q</td>
<td>quant.</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>rac, Racemic</td>
<td></td>
</tr>
<tr>
<td>Rdt</td>
<td>Rendement</td>
<td></td>
</tr>
<tr>
<td>ref</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Rf</td>
<td>Retention factor</td>
<td></td>
</tr>
<tr>
<td>RMN</td>
<td>Résonance magnétique nucléaire</td>
<td></td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>SFC, Supercritical fluid chromatography</td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>$T$, Temperature</td>
<td></td>
</tr>
<tr>
<td>t</td>
<td>Time</td>
<td></td>
</tr>
<tr>
<td>t.a.</td>
<td>Température ambiante</td>
<td></td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
<td></td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-Butyldiphenylsilyl</td>
<td></td>
</tr>
<tr>
<td>$t$Bu</td>
<td>tert-Butyl</td>
<td></td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
<td></td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
<td></td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
<td></td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>$v$, Volume</td>
<td></td>
</tr>
</tbody>
</table>
Résumé
Résumé

Ce manuscrit présente le développement de nouveaux systèmes catalytiques à base de ruthénium et de rhodium pour des réactions de cyclisation [2+2+2].

Chapitre 1. Réactions de cycloaddition [2+2+2]: bibliographie

Au cours de ce chapitre nous examinerons les différents types de cycloaddition en fonction de la nature des fonctions alcynes impliquées dans la cycloaddition (Schéma R1).

(1) Intermoléculaire:

(2) Partiellement intramoléculaire:

(3) Totalement intramoléculaire:

Schéma R1

Pour chaque cas, des exemples seront donnés afin d’illustrer les résultats de la littérature.

Dans une seconde partie, nous détaillerons les différents métaux de transition utilisés pour mettre en œuvre les réactions. Parmi les complexes de métaux de transition, on verra que ceux qui sont le plus couramment utilisés sont des complexes au cobalt avec le complexe CpCo(CO)₂; au rhodium (par exemple le complexe de Wilkinson RhCl(PPh₃)₃ ou encore au rhodium sous forme cationique tel Rh(cod)₂BF₄ associé à un ligand phosphine type BINAP); le nickel a aussi été utilisé sous forme Ni(dppe)Br₂ par exemple ou bien Ni(CO)₂(PPh₃)₂; ensuite on peut citer l’iridium dont le complexe dimère [Ir(cod)Cl]₂ a été souvent employé; pour finir nous citerons le ruthénium, dont le complexe le plus connu est le catalyseur de Grubbs de 1ère génération.
Résumé

Chapitre 2. Vers un nouvel accès aux dérivés florénones via une cycloaddition [2+2+2] catalysée par le trichlorure de ruthénium hydraté.

Au cours de notre étude sur la synthèse de carbocycles et d’hétérocycles, catalysée par les métaux de transition, nous avons mis en évidence la possibilité d’accéder relativement facilement à des florénones substituées ainsi qu’à des analogues, à partir de diynes-1,6 pontés et d’alcynes, en présence de RuCl₃·nH₂O comme catalyseur. Nous avons étudié la cycloaddition [2+2+2] catalysée par le complexe RuCl₃·nH₂O, en utilisant le diyne 17, qui contient un pont benzoyle, avec le 1,4-diméthoxy-but-2-ynyl 51 comme substrat modèle. Nous avons examiné différents paramètres en vue d’optimiser les conditions de la réaction. Nous avons ainsi fait varier la température, le nombre d’équivalents d’alcyne, le pourcentage de RuCl₃·nH₂O et enfin le temps de réaction. Nous avons ainsi pu établir que les meilleures conditions étaient d’opérer avec 2 équivalents d’alcyne, 5% molaire de RuCl₃·nH₂O, à 50 °C pour une durée de deux heures. Dans ces conditions réactionnelles, le dérivé 65 a été isolé avec 72% de rendement.

Table R1. Optimisation des conditions de la réaction

<table>
<thead>
<tr>
<th>Entrée</th>
<th>17/51</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Conv. (%) b</th>
<th>Rdt (%) c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:6</td>
<td>110</td>
<td>18</td>
<td>&gt; 99</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>1:4</td>
<td>80</td>
<td>18</td>
<td>&gt; 99</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>1:3</td>
<td>80</td>
<td>18</td>
<td>&gt; 99</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>1:3</td>
<td>80</td>
<td>18</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>1:3</td>
<td>50</td>
<td>18</td>
<td>&gt; 99</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>1:2</td>
<td>50</td>
<td>18</td>
<td>&gt; 99</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>1:2</td>
<td>50</td>
<td>4</td>
<td>&gt; 99</td>
<td>73</td>
</tr>
<tr>
<td>8</td>
<td>1:2</td>
<td>50</td>
<td>2</td>
<td>&gt; 99</td>
<td>72</td>
</tr>
<tr>
<td>9</td>
<td>1:2</td>
<td>50</td>
<td>18</td>
<td>40</td>
<td>nd</td>
</tr>
</tbody>
</table>

a 2% mol RuCl₃·nH₂O (0.007 mmol) utilisés. b Sous atmosphère d’air.

Ayant établi les conditions optimales de la réaction, nous nous sommes intéressés à la généralisation, en particulier l’effet du substituant en position C7. Il ressort ainsi qu’un phényle
augmente la réactivité par rapport à un groupe alkyle (n-butyle). L’introduction de groupements donneur ou accepteur conduit à peu de changement, les rendements restant du même ordre. Un groupement silyl à la place du groupe phényl apporte peu de modification, et conduit aussi au produit attendu (Schéma R2). Ce résultat est intéressant car il permet d’envisager une post-fonctionnalisation. Le groupement protecteur des alcools a aussi été examiné et les groupes benzyle ou tert-butyle sont compatibles avec les conditions réactionnelles, et conduisent ainsi aux produits 76 et 77 (80 et 81%). La structure de la fluorénone 77 a pu être établie sans ambiguïté par une analyse de diffraction des rayons X (Schéma R3).

Schéma R2
Le pont reliant les deux fonctions diynes a ensuite été modifié: le groupe phenyle a ainsi été remplacé par un hétérocycle (furanyl, thiényle, cycle azoté); la cycloaddition se fait également pour conduire à des hétéro-fluorénones variées 83-87, 89 et 90 avec des rendements allant de 30 à 78 % (Schéma R4).

Cette réaction de cycloaddition ne se limite pas aux diynes symétriques internes, puisqu’une série de diynes terminaux a été utilisée. La réaction de ces derniers avec le diyne 17
est détaillée dans le Schéma R5. La faible régiosélectivité peut s’expliquer par un encombrement stérique proche des substituants présents.

Schéma R5

Pour valider l’intérêt synthétique de cette méthode catalytique, la réaction a été conduite sur une échelle d’un gramme dans les conditions pré-établies. La fluorénone 65 a pu être isolée avec un rendement de 71% (Schéma R6).

Schéma R6

Après avoir synthétisé une gamme de dérivés fluorénones, nous nous sommes tournés vers l’étude de la post-fonctionnalisation des composés 65, 69 et 76. En utilisant des protocoles décrits dans la littérature, nous avons pu accéder aux composés dihydrobenzo[b]furan 94, au diol 95, et au polycycle dibromé 96 avec de bons rendements (Schéma R7).
La fluorénone silylée 69 s’est également avérée un bon intermédiaire pour accéder, après iodation au composé 97, lui même précurseur de dérivés fonctionnalisés par un alcyne ou un ester boronique par des réactions de couplage de Sonogashira ou Suzuki-Miyaura (Schéma R8).
La fluorénone bromée 73 s’est également révélée un bon adduit, puisque après couplage de Suzuki-Miyaura, elle a été transformée en ester boronique 100 avec un rendement de 85% (Schéma R9).

Schéma R9

Une nouvelle approche directe et éco-compatible vers la synthèse de fluorétones hautement substituées ainsi que des analogues a été mise au point. Cette méthode fait intervenir une cycloaddition [2+2+2] semi-intramoléculaire de cétones possédant un motif 1,6-diyn avec un alcyne, initié par le complexe RuCl₃·nH₂O. Ce procédé économique est conduit sans solvant, ni aucun ligand ou additif, et ce dans des conditions douces. Cette réaction a permis l’obtention de fluorétones polycycliques complexes, d’aza-fluorétones, des benzo[b]furanones et également des thiophénones polycycliques, avec de bons rendements. Des études ultérieures ont montré que les fluorétones ainsi obtenues pouvaient être converties en molécules plus complexes.

Chapitre 3. Utilisation de la catalyse au ruthénium pour des cycloadditions [2+2+2] de diynes avec des cyanamides électronicement enrichis: un accès facile aux dérivés 2-aminopyridines

Dans la continuité de notre précédent travail relatif aux cycloadditions [2+2+2] catalysées par un métal de transition, nous avons décidé d’explorer, la réaction de cycloaddition [2+2+2] de α,ω-diynes et cyanamides dans le but de synthétiser des dérivés 2-aminopyridines.

a. Cycloaddition [2+2+2] d’α,ω-diynes avec des cyanamides catalysée par RuCl₃·nH₂O

Différent diynes et cyanamides ont été efficacement préparés. La diyne 101 et le diméthyl cyanamide 154 ont été choisis comme substrats modèles pour optimiser les conditions
Résumé

Nous avons commencé l’étude avec 5% molaire de RuCl₃·ₙH₂O, dans des conditions sans solvant. Un examen plus approfondi a montré qu’il fallait opérer à 110 °C pour une durée de 18 heures.

Table R2. Optimisation des conditions de la réaction

<table>
<thead>
<tr>
<th>Entrée</th>
<th>101/154</th>
<th>T (°C)</th>
<th>Conv. (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Rdt (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:6</td>
<td>110</td>
<td>&gt;99</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>1:3</td>
<td>110</td>
<td>&gt;99</td>
<td>76</td>
</tr>
<tr>
<td>3&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>1:3</td>
<td>110</td>
<td>50</td>
<td>nd</td>
</tr>
<tr>
<td>4</td>
<td>1:3</td>
<td>80</td>
<td>90</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>1:3</td>
<td>50</td>
<td>nr</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td>1:2</td>
<td>80</td>
<td>30</td>
<td>nd</td>
</tr>
<tr>
<td>7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1:2</td>
<td>90</td>
<td>70</td>
<td>nd</td>
</tr>
<tr>
<td>8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1:2</td>
<td>100</td>
<td>93</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>1:2</td>
<td>110</td>
<td>&gt;99</td>
<td>74</td>
</tr>
</tbody>
</table>

<sup>a</sup>0.02 mmol of RuCl₃·ₙH₂O (2% mol) utilisés. <sup>b</sup>24 heures de réaction.

Après avoir mis au point les conditions pour réactionnelles, nous avons évalué la réactivité de divers diynes et cyanamides. Les résultats sont regroupés dans le Schéma R10. Une série de cyanamides obtenus à partir d’amines secondaires ont été soumis à la réaction de cycloaddition pour conduire aux 2-aminopyridines correspondantes avec de bons rendements. Par exemple, des diynes symétriques portant diverses fonctions telles que des esters, cétones ou amides sont compatibles.
La régiosélectivité de la réaction de cycloaddition de diynes-1,6 non symétriques a aussi été étudiée, comme indiqué dans le Schéma R11. Les diynes-1,6 portant un substituant méthyle ou phényle ont été mis en réaction avec la 4-carbonitrile morpholine et ont conduit à 2 régioisomères avec une sélectivité réduite et un rendement global plus faible. Le ratio des deux régioisomères a été déterminé par analyse RMN $^1$H du brut réactionnel.
Un exemple de nitrile électro-déficient a également été considéré, plus précisément le malononitrile qui a été soumis à la cycloaddition avec le diyne 108 comportant un pont azoté, dans les conditions usuelles de 110 °C en présence de RuCl₃·nH₂O. Dans ce cas, le cycloadduit 195 est obtenu avec une conversion de 22%, malgré un taux de catalyseur de 10% molaire (Schéma R12). Ce résultat est nettement inférieur à ceux obtenus avec des nitriles enrichis.

Au cours du travail précédent faisant intervenir le ruthénium sous forme neutre (RuCl₃·nH₂O) pour la mise en œuvre de cycloaddition [2+2+2] d’α,ω-diynes et cyanamides, nous avions démontré que le ruthénium sous forme cationique était également très efficace pour cette réaction. Les essais initiaux ont porté sur l’utilisation du diyne 101 et du cyanamide 155, dans des conditions sans solvant à température ambiante. La réaction a été optimisée en faisant varier différents paramètres. Nous avons ainsi montré que la réaction pouvait être conduite...
Résumé

efficacement avec 2% molaire du complexe pentaméthylcyclopentadiényle (Cp*) Cp*Ru(CH₃CN)₃PF₆ pour fournir la 2-aminopyridine 169 avec un excellent rendement et un temps de réaction de 5 min. Par ailleurs, nous avons également découvert que lorsque la réaction était réalisée avec un petit volume de dichlorométhane, avec le diyne 109 comme modèle, il était possible de réduire à la fois le taux catalytique à 1% molaire et le nombre d’équivalents de cyanamide à 1.2 équivalents (entrée 8). L’utilité de cette méthode a été démontrée en conduisant la réaction sur une échelle d’un gramme, avec le diyne 109 comme modèle. La 2-aminopyridine 188 a ainsi été obtenue avec 82% de rendement (entrée 10).

Table R3. Optimisation des conditions de la réaction

Dans un second temps et comme précédemment, ayant établi les conditions optimales de la réaction, nous nous sommes intéressés à la généralisation de cette réaction en faisant intervenir divers diynes substitués et le cyanamide 155 comme partenaire (Schéma R13). Une grande variété de diynes symétriques, pontés avec un carbone quaternaire, un oxygène ou encore un azote protégé ont été soumis au cyanamide 155 pour donner les 2-aminopyridines correspondantes. L’introduction de groupements volumineux tels que le groupe tert-butyle ou iso-propyle conduit également à d’excellents rendements. De même, des groupes fonctionnels portés par le carbone quaternaire, tels que des diols, des nitriles, des diones ont également été

<table>
<thead>
<tr>
<th>Entrée</th>
<th>Diyne</th>
<th>Catalyst (x% mol)</th>
<th>t</th>
<th>Produit</th>
<th>Conv. (%)</th>
<th>Rdt (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>101</td>
<td>Ru(PPh₃)Cl₂ (5)</td>
<td>8 h</td>
<td>169</td>
<td>nr</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>101</td>
<td>[Ru(p-cymene)Cl₂]₂ (2.5)</td>
<td>8 h</td>
<td>169</td>
<td>nr</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>101</td>
<td>Cp*Ru(cod)Cl (2)</td>
<td>5 min</td>
<td>169 &gt;99</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>101</td>
<td>Cp*Ru(CH₃CN)₃PF₆ (5)</td>
<td>5 min</td>
<td>169 &gt;99</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>101</td>
<td>Cp*Ru(CH₃CN)₃PF₆ (2)</td>
<td>5 min</td>
<td>169 &gt;99</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>101</td>
<td>Cp*Ru(CH₃CN)₃PF₆ (1)</td>
<td>60 min</td>
<td>169</td>
<td>80 nd</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>109</td>
<td>Cp*Ru(CH₃CN)₃PF₆ (2)</td>
<td>3 min</td>
<td>188 &gt;99</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>8ᵃ</td>
<td>109</td>
<td>Cp*Ru(CH₃CN)₃PF₆ (1)</td>
<td>2 min</td>
<td>188 &gt;99</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>9ᵃ</td>
<td>109</td>
<td>Cp*Ru(CH₃CN)₃PF₆ (0.5)</td>
<td>18 h</td>
<td>188</td>
<td>90 82</td>
<td></td>
</tr>
<tr>
<td>10ᵇ</td>
<td>109</td>
<td>Cp*Ru(CH₃CN)₃PF₆ (2)</td>
<td>5 min</td>
<td>188 &gt;99</td>
<td>82</td>
<td></td>
</tr>
</tbody>
</table>

ᵃ 0.6 mmol de cyanamide 155 et 0.5 mL de dichlorométhane utilisés.ᵇ échelle d’un gramme
Résumé

utilisés avec succès. La formation des composés 186 et 187 montre aussi que la réaction est compatible avec des diynes internes (Schéma R13).

Schéma R13

Par la suite, dans le but d’examiner les limites de la réaction, un certain nombre d’amines secondaires portées sur le cyanamide a été testé. Comme indiqué dans le Schéma R14, les résultats se sont avérés très probants avec l’obtention d’un grand nombre de 2-aminopyridines.
Comme dans le cas du ruthénium neutre (RuCl₃·nH₂O), la régiosélectivité a été examinée. Dans ce cas, il a été observé que la régiosélectivité ainsi que le rendement étaient plus élevés. Notamment, le régioisomère ortho était formé majoritairement (Schéma R15). De plus, la réaction tolère un grand nombre de fonctions avec l’obtention des halopyridines, diaminopyridines, et vinylpyridines avec des rendements allant de 65 à 93%. La structure du produit 220 a été confirmée sans ambiguïté par une étude de diffraction des rayons X (Schéma R15).

Schéma R14
Résumé

Une étude ultérieure a par ailleurs montré que la réaction était possible avec les diynes-1,7 138 (lien oxygéné) et 139 (lien azoté). En présence de 5% molaire de Cp*Ru(CH₃CN)₃PF₆, ils conduisent aux pyridines bicycliques à 6 chaînons 230-233 avec des rendements de 34 à 86% et une excellente régiosélectivité (Schéma R16).
Le composé spirocyclique 237 a été isolé à partir d’un dérivé du mestranol avec 58% de rendement et une haute régiosélectivité. La structure de ce dernier a été précisément établie par diffraction des rayons X (Schéma R17).

Schéma R17

c. Obtention d’aza-fluorénols et aza-fluorénone par cycloaddition [2+2+2] catalysée par le complexe Cp*Ru(CH3CN)3PF6

En utilisant cette méthode catalytique et éco-compatible, une famille d’aza-fluorénols et aza-fluorénone a été préparée. Le choix de la position du substituant sur le diyne permet de contrôler la régiosélectivité du substituant sur le cycle pyridine. La structure de l’azafluorénone 248 a été formellement établie par diffraction des rayons X (Schéma R18).
En se basant sur les résultats obtenus, ainsi que sur ceux décrits dans la littérature, nous proposons le mécanisme ci-dessous afin d’expliquer la régiosélectivité observée (Schéma R19). La réaction passerait par un intermédiaire ruthénacyclopentadiène Ru-II, dont la formation serait suivie par l’insertion du cyanamide et l’élimination de l’espèce ruthénium, conduisant majoritairement à la pyridine ortho-substituée la moins encombrée.
La synthèse de composés à motif 2-aminopyridine hautement substitués par cycloaddition [2+2+2] de α,ω-diynes avec des cyanamides via une catalyse en présence de complexes de ruthénium aussi bien sous forme neutre (RuCl₃·nH₂O) que cationique (Cp*Ru(CH₃CN)₃PF₆), a donc été réalisée. Le complexe RuCl₃·nH₂O peu onéreux s’est révélé très efficace en tant que catalyseur pour la préparation de 2-aminopyridines substituées. La réaction se déroule en présence de 5% molaire de RuCl₃·nH₂O sans l’ajout de ligand ou autre additif, et en l’absence de solvant. Le ruthénium complexe cationique (Cp*Ru(CH₃CN)₃PF₆) s’est avéré très efficace pour ce type de cycloaddition aussi bien dans le cas des diynes-1,6 ou -1,7, en présence de cyanamides et dans des dans des conditions douces. Diverses diynes, terminaux ou internes possédant des groupes fonctionnels variés se sont révélés compatibles avec ce système catalytique. Une excellente régiosélectivité a été obtenue dans le cas de diynes dissymétriques. L’utilité de ce protocole a ensuite été démontrée avec la synthèse de molécules à haute valeur ajoutée telles que des halopyridines, des diaminopyridines ou encore des vinylpyridines en une seule étape. Cette réaction a pu conduire à des pyridines polycycliques incluant des hétéroatomes, à partir de diynes-1,7 et cyanamides. La fonctionnalisation du mestranol, molécule biologiquement active, a pu aussi valider le potentiel de cette méthodologie. Une famille d’aza-fluorénones et aza-fluorénols a également été préparée efficacement selon cette méthode éco-compatible et directe.
Chapitre 4. Synthèse asymétrique de 1,3-dihydroisobenzofuranes 1,1-disubstitués à partir de triynes prochiraux et des alcynes internes catalysée par des complexes de rhodium

Les 1,3-dihydroisobenzofuranes sont une classe de composés hétérocycliques oxygénés très présents dans les composés naturels biologiquement actifs ainsi que dans un certain nombre de médicaments. Plusieurs méthodes permettent d’accéder à ces structures, parmi lesquelles on peut citer la cyclotrimérisation [2+2+2] d’alcynes, les réactions de Diels-Alder, ou encore la transformation de phtalides. Parmi ces méthodes, la cycloaddition [2+2+2] catalysée par les métaux de transition constitue l’une des plus efficaces comme indiqué dans le chapitre I.

Concernant la préparation de 1,3-dihydroisobenzofuranes contenant un centre chiral en position $\alpha$, peu d’exemples ont été rapportés, c’est pourquoi leur accès constitue un défi.

La réaction de désymétrisation de composés prochiraux constitue un moyen efficace pour accéder à des molécules complexes possédant un centre stéréogène. C’est pourquoi nous avons envisagé que la construction de 1,3-dihydroisobenzofuranes optiquement actifs pouvait être accomplie via une cycloaddition [2+2+2] de triynes oxygénés avec un alcyne interne catalysée par un métal de transition comme indiqué dans le Schéma R20.

Les triynes de départs peuvent être facilement obtenus à partir de produits commerciaux selon la rétrosynthèse décrite dans le schéma R21.
Dans un premier temps, nous nous sommes intéressés à la préparation des produits de départ. Les triynes ont été préparés en deux étapes. Une condensation d’un acétylure sur un chlorure d’acide conduit à un alcool quaternaire, qui peut ensuite être condensé sur le bromure de propargyle ou le 1-bromo-but-2-yné pour conduire au triyne. Les alcynes internes ont été obtenus à partir du 2-butyl-1,4-diol dont les fonctions alcools ont été protégées par différents groupements (OAc, OMe, …).

**a. Optimisation des conditions de la réaction**

L’étude de la réaction de cycloaddition [2+2+2] a pu ainsi être menée, en utilisant le triyne 255 et le 1,4-diacétoxy-but-2-yné 262 comme modèles pour conduire au 1,3-dihydroisobenzofuranne 266. Différents catalyseurs de rhodium ont été évalués, en opérant dans le dichlorométhane à une température de 40°C, en présence de (R)-BINAP comme ligand. Les résultats sont regroupés dans le tableau R4, et montrent que la combinaison du catalyseur Rh(cod)2BF4 et du (R)-BINAP est la plus efficace pour mener la cycloaddition. Il est à noter que la réaction n’a pas lieu en absence de phosphine.

**Table R4. Optimisation des conditions de la réaction**

<table>
<thead>
<tr>
<th>Entrée</th>
<th>[Rh] catalyseur</th>
<th>Additif (x% mol)</th>
<th>Rendement (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh(cod)2BF4</td>
<td>/</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(hexadiene)Cl]2</td>
<td>AgSbF6 (5)</td>
<td>74</td>
<td>20</td>
</tr>
<tr>
<td>3a</td>
<td>[Rh(ethylene)Cl]2</td>
<td>NaBAR4 (10)</td>
<td>72</td>
<td>49</td>
</tr>
<tr>
<td>4b</td>
<td>Rh(cod)2BF4</td>
<td>/</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>5c</td>
<td>Rh(cod)2BF4</td>
<td>/</td>
<td>nr</td>
<td>/</td>
</tr>
<tr>
<td>6d</td>
<td>Rh(cod)2BF4</td>
<td>/</td>
<td>66</td>
<td>43</td>
</tr>
<tr>
<td>7e</td>
<td>Rh(cod)2BF4</td>
<td>/</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

*a ArF = 3,5-(CF3)3C6H2, b 10 % molaire de (R)-BINAP ont été utilisés, c Pas de ligand, d [Rh]/(R)-BINAP complexe hydrogéné au préalable (H2, 1 atm, rt, 1 h), e Addition lente du triyne 255 en 3 heures à l’aide d’une seringue munie d’une pompe.

**b. Influence de la phosphine chirale et du solvant**
Résumé

Ayant établi les conditions optimales pour mener la réaction de cycloaddition, nous avons examiné l’influence de différentes phosphines, comme le (R)-Xylyl-BINAP, le (R)-Difluorophos ou encore le (R)-MeOBiphep. Nous n’avons pas noté d’amélioration significative. De même, plusieurs solvants ont été testés, parmi lesquels le THF, le dichloroéthane, ou le xylène. Le toluène s’est avéré un bon candidat puisque il a donné un ee identique à celui obtenu avec le DCM, et avec un rendement supérieur (70%); toutefois cela nécessite d’opérer à une température de 100 °C.

c. Influence de l’alcyne interne symétrique

Par la suite, nous avons examiné l’influence de différents groupes protecteurs sur les fonctions alcools en utilisant les conditions mises au point, à savoir des groupements donneurs ou électroattracteurs. De même, les fonctions alcools ont été remplacées par des groupes alkyles ou esters. Il est à noter qu’aucune réaction n’a lieu avec deux groupements phényles (composé 272 voir Schéma R22). Les rendements varient entre 20% et 79%, tandis que les ee restent modérés à faibles (21-50%).
d. Influence du substituant porté par le carbone quaternaire du triyne

Pour compléter cette étude, nous nous sommes intéressés à l’influence stérique engendrée sur les triynes, en remplaçant le groupe méthyle par un groupement plus volumineux, comme le n-propyle ou tert-butyle ou encore un phényle. L’augmentation de l’encombrement stérique en position R’ ne conduit pas à une amélioration du rendement ni de l’excès énantiomérique (Schéma R23).

Schéma R22
Afin de rendre compte de la stéréosélectivité observée, nous nous sommes intéressés au cycle catalytique de la réaction. Un des mécanismes possible est développé dans le Schéma R24.

La réaction pourrait débuter par le couplage oxydatif de deux fonctions alcynes issues du triyne et de l’alcyne avec l’espèce rhodium pour conduire à l’intermédiaire rhodacyclopentadiène Rh-I. Une coordination intramoléculaire ultérieure avec l’une des fonctions alcynes portée par le carbone quaternaire fournirait l’intermédiaire Rh-II. Ceci pourrait être considéré comme l’étape stéréo déterminante pour expliquer l’énantiosélectivité observée en raison de la gêne stérique entre le groupe alcyne et le ligand chiral. L’insertion intramoléculaire de l’alcyne sur le rhodium de Rh-II délivrerait alors l’intermédiaire à 7 chainons Rh-III, qui subirait une élimination réductrice pour donner le 1,3-dihydroisobenzofurane avec un excès énantiomérique (Schéma R24).
Dans ce chapitre, nous avons donc démontré que la cycloaddition [2+2+2] conduite en présence d’un catalyseur au rhodium Rh(cod)$_2$BF$_4$, en présence d’une phosphine chirale, était un moyen d’accès rapide vers les 1,3-dihydroisobenzofuranes énantioméritiquement enrichis. Bien que les rendements et l’énantiosélectivité restent à améliorer, cette méthode est prometteuse.
Résumé
General introduction
General introduction

Heterocycles represent by far the largest of classical divisions in organic chemistry and are of great importance biologically and industrially. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic while several additives and modifiers used in industrial applications in the field of cosmetics, reprography, information storage and plastics are heterocyclic in nature. Over the past century, heterocycles have constituted one of the largest areas of research in organic chemistry. They have contributed to the development of humanity from a biological and industrial point of view as well as to the understanding of life processes and to the improvement of the quality of life.

In this context in the field of chemistry, efficient clean methods to access functionalized heterocycles are highly suitable. One of the key principles of “Green Chemistry”\(^1\) (Figure 1) is to limit the use of organic solvents in industrial processes. Indeed, these solvents are often toxic, expensive and generate difficulties in disposal and reprocessing. A major research effort in recent years is to develop new more environmentally friendly synthetic methods. Even if water seems to be the best choice because of its abundance and non-toxicity,\(^2\) the development of solvent-free processes during the reaction and purification, is undeniably the ideal solution.\(^3\) A solvent-free system is not only environmentally friendly but also provides effective, safer and more economical solutions for industrial partners (temperature and reaction time decreased, reducing the size of the reactors, process intensification, no extra costs incurred relating to the purchase and processing of solvents).


General introduction

Figure 1

Functionalization of aromatic or heteroaromatic compounds has been a major topic of study among organic chemists, and has been used both in industrial and academic laboratories. One of the best known and traditional methods to functionalize aromatic rings involves the stepwise addition of electrophilic substituents, using Friedel-Crafts alkylation or acylation. This method is very useful for the synthesis of polysubstituted benzene derivatives, but may cause problems in terms of regioselectivity (and therefore yield), which requires special attention in the choice of reagents and synthesis plan of the target compound (Scheme 1). Another method, transition-metal-catalyzed [2+2+2] cycloaddition reactions, involves the

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construction of aromatic rings in a single step, thereby obtaining highly functionalized aromatic rings in a one pot reaction (Scheme 1).

\[ \text{Friedel-Crafts alkylation or acylation} \]

Scheme 1

Since Berthelot’s pioneering thermal cyclization of three acetylene leading to benzene formation discovered in 1866, many advances have been reported in this field. The first metal-catalyzed [2+2+2] cycloaddition reaction was reported in 1948 by Reppe and Schweckendiek and involved Ni(CO)₂(PPh₃)₂ complex. This cyclotrimerization of monoalkynes occurred at 60-70 °C to provide 1,3,4- and 1,3,5-trisubstituted benzene derivatives in quantitative yield with no regioselectivity (Scheme 2). After this pioneering work, extensive studies have been conducted using cobalt, rhodium, nickel, ruthenium, and iridium.

First thermal [2+2+2] cyclotrimerization:

\[ \text{3} \quad \text{[2+2+2] cyclotrimerization} \]

First metal-catalyzed [2+2+2] cyclotrimerization:

\[ \text{OH} \quad \text{Ni(CO)₂(PPh₃)₂} \quad \text{60-70 °C} \quad \text{ratio} = 1:1, \text{quant.} \]

Scheme 2

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General introduction

In 1973, Yamazaki and Wakatsuki discovered that the substituted pyridines can be stepwise assembled from two acetylenes and one nitrile by using a catalytic amount of \( \pi \)-cyclopentadienyl(triphenylphosphine)cobalt complex (Scheme 3).\(^{10,11}\)

![Scheme 3](image)

Apart from the synthesis of benzenes and pyridines via cyclotrimerization of three alkynes or two alkynes with one nitrile, other unsaturated carbocyclic and heterocyclic compounds such as 1,3-cyclohexadienes, 1,2-dihydropyridines, thioxothiopyranes, 2-pyrones, 2-pyridones, and thiopyridones were also synthesized reacting two alkynes with the corresponding unsaturated alkenes, allenes, carbonyl compounds, imines, carbon disulfide, carbon dioxide, isocyanates, and thiocyanates (Scheme 4). The most commonly studied work is the synthesis of multiple substituted benzene and pyridine derivatives, which is the topic of this work.


Scheme 4
General introduction
Chapter I: Bibliography
Chapter I: Bibliography

The first chapter will present selected literature data concerning the formation of benzene via transition-metal-catalyzed [2+2+2] cycloaddition reactions. In each section, we will deliver the works based on three types of cycloaddition reactions (intermolecular, partially intramolecular, and totally intramolecular, Scheme 5). Practical and general catalyst, construction of novel scaffolds, recent advances in mechanistic insight, regioselectivity and chemoselectivity issues will also be described.

(1) Intermolecular:
(2) Partially intramolecular:
(3) Totally intramolecular:

Scheme 5

1. Intermolecular reactions

The intermolecular [2+2+2] alkyne cyclotrimerization is considered as one of the most efficient synthetic method to access benzene skeleton. Various types of transition metal complexes have been used for this transformation. However, the reaction is limited because of the low chemo- and regioselectivity. For example, as shown in Scheme 6, the homo-cyclotrimerization of a single symmetrical alkyne gives hexa-substituted benzenes (Eq. 1), the cycloaddition of unsymmetrical alkynes produces two regioisomers (Eq. 2), and the combination of two or three different alkynes leads to the formation of complex mixtures (Eq. 3).
1.1. Cyclotrimerization of one alkyne

In 1993, Rothwell and co-workers reported the first regioselective transition-metal-catalyzed [2+2+2] cycloaddition reactions, which selectively produced the symmetrical 1,3,5- and unsymmetrical 1,2,4-substituted benzene derivatives using a catalytic amount of titanium complex. It was demonstrated that the steric effects controlled the regioselectivity. For instance, in the presence of 0.004 mol % titanium catalyst, cyclotrimerization of phenylacetylene led to trisubstituted benzenes in quantitative yield, with 1,2,4-substituted regioisomer as the major product (ratio = 7:93). The more sterically hindered alkynes, such as trimethylsilyl acetylene and tert-butyl acetylene, afforded the 1,3,5-substituted products in high yields (ratio > 95:5), albeit with higher catalyst loading and prolonged reaction time (Scheme 7).

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12 Hill, J. E.; Balaich, G.; Fanwick, P. E.; Rothwell, I. P. *Organometallics* 1993, 12, 2911.
After this pioneering work, many late transition metals have been used for the regioselective synthesis of benzene derivatives. The most common employed metals were cobalt, rhodium, ruthenium, iridium, nickel, and iron. An interesting example was reported by Hess and co-workers, who described a solvent-dependent regioselective [2+2+2] cyclotrimerization of phenylacetylene using a cobalt complex catalyst containing a disulfide ligand (Scheme 8).\(^{13}\) Optimization of different disulfide ligands in various solvents was also studied in this reaction. The result indicates that the coordination ability of the solvent greatly influenced the regioselectivity of the cyclotrimerizations.

Sivasankar and co-workers reported a series of highly efficient pincer ligands stabilized Ni(II) complexes as catalyst to promote the regioselective [2+2+2] cyclotrimerization of various alkynes. The complex bearing di-tert-butyl groups on the phosphine ligand acts as the best catalyst in this reaction.\(^{14}\) They observed that the selectivity correlated well with the electronic feature of the alkynes, the electron-rich alkynes were trimerized to give 1,3,5-

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substituted benzenes as the major products, whereas the electron-deficient alkynes afforded the 1,2,4-substituted benzenes as the major products (Scheme 9).

![Scheme 9](image)

Transition-metal-catalyzed [2+2+2] cyclotrimerization of disubstituted acetylene is considered as an elegant and efficient method to access hexa-substituted benzene derivatives in a single synthetic operation. Many groups have reported such reactions, including Fréchet and co-workers for the convergent synthesis of dendrimers using a cobalt-catalyzed [2+2+2] cyclotrimerization of bisdendritic alkynes, affording the corresponding benzene-cored dendrimers in 36-83% yields (Scheme 10).\(^{15}\)

![Scheme 10](image)

Zhao and co-workers reported a facile and efficient method for the regioselective synthesis of polysubstituted benzenes via nickel-catalyzed [2+2+2] cyclotrimerization of simple unactivated alkyl(aryl)acetylenes and diarylacetylenes (Scheme 11).\(^{16}\) They found that the combination of Ni(acac)\(_2\), imidazolium salt (IBz·HBr) and Grignard reagent (\(n\)BuMgCl) at

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60 °C led exclusively to the formation of 1,2,4-substituted isomer in up to 98% yield. This method was also utilized to access hexa-substituted benzenes by using IBz-HCl as the imidazolium salt partner providing a convenient synthetic route to various π-conjugated systems.

![Scheme 11](image)

1.2. Cycloaddition between two different alkynes.

Takeuchi and Nakaya\textsuperscript{17} described the chemoselective iridium-catalyzed [2+2+2] cyclotrimerization of electron-deficient alkynes with electron-rich internal alkynes (Scheme 12). It was demonstrated that the chemoselectivity was controlled by the nature of the phosphine ligands. When 1,2-bis(diphenylphosphino)ethane (dppe) was used as a ligand, the electron-rich iridium/dppe complex coordinates with two electron-deficient alkynes to form iridacyclopentadiene Ir-I which undergoes coordination and insertion of another electron-rich alkyne to furnish the dicarbomethoxy-substituted product as a major product. On the other hand, when electron-deficient 1,2-bis(dipentafluorophenylphosphino)ethane (fdppe) was employed, the reaction proceeded via iridacyclopentadiene Ir-II as the intermediate, affording the tetracarbomethoxy-substituted compound as a major product. This reaction provided a useful and practical method for the synthesis of polycyclic substituted benzene derivatives.

\textsuperscript{17} Takeuchi, R.; Nakaya, Y. Org. Lett. 2003, 5, 3659.
The same group also described in 2008 an iridium-catalyzed chemo- and regioselective synthesis of 1,3,5-substituted benzene derivatives via [2+2+2] cyclotrimerization of two different terminal alkynes. In the presence of Ir/fdppe catalyst system, a variety of 1,3,5-substituted benzenes was obtained as a single regioisomer in 58-96% yields. However, this strategy required the combination of one strong electron-deficient alkyne and one electron-rich alkyne (Scheme 13).

Scheme 12

Scheme 13

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1.3. Cycloaddition of three different alkynes

The intermolecular [2+2+2] cyclotrimerization of three different alkynes is difficult to control. Early transition metals such as zirconium\(^\text{19}\) and titanium\(^\text{20}\) were used for such transformation. However, the use of stoichiometric catalyst and harsh reaction conditions were required in some cases.

In 2004, Yamamoto and co-workers developed a chemo- and regioselective intermolecular cyclotrimerization of three different unsymmetrical alkynes using Cp*Ru(cod)Cl as the catalyst.\(^\text{21}\) The reaction is initiated by the oxidative cyclization of an alkynylboronate and a propargyl alcohol to form the key ruthenacycle intermediate Ru-I, which undergoes insertion of the third alkyne to afford the intermediate arylboronate. The subsequent one-pot functionalization of these arylboronates could further be converted into several substituted aromatic compounds such as biaryls, boraphthalides, phthalides, and imidates (Scheme 14).

![Scheme 14](image-url)

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In 2005, Mitsudo and co-workers developed a ruthenium-catalyzed chemoselective [2+2+2] cycloaddition to form polysubstituted α-phthalates (Scheme 15). It was demonstrated that a high chemoselectivity and regioselectivity could be attained by controlling the molar ratio of the three substrates. The reaction is also influenced by the bulkiness of the two substituents on the internal and terminal alkynes. Mitsudo’s group proposed a plausible mechanism for the [2+2+2] cycloaddition. At the first step, the internal alkyne and DMAD react with the ruthenium to form the ruthenacyclopentadiene Ru-I intermediate, followed by an insertion of the terminal alkyne into the formed ruthenacycle. A subsequent reductive elimination would afford the final regioisomers and regenerate the ruthenium catalytic species. However, a large excess of internal alkyne was required to avoid the formation of side-products.

Scheme 15

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1.4. Cyclotrimerization of two alkynes with another unsaturated substrate

Tanaka and co-workers described a cationic rhodium-catalyzed intermolecular [2+2+2] cycloaddition reaction of a terminal alkyne, a dialkyl acetylenedicarboxylate, and an enol ester. A variety of tri- and tetra-substituted benzenes was obtained in 35-80% yields with complete regioselectivity. The proposed mechanism features the regioselective formation of the rhodacyclopentadiene Rh-I followed by the regioselective insertion of an enol acetate leading to the intermediate Rh-II, which is stabilized by the coordination of the carbonyl group with the cationic rhodium through a five-membered chelation. Finally, a subsequent reductive elimination affords the corresponding substituted benzenes and one equivalent of acetic acid (Scheme 16).

![Scheme 16](image)

Cheng and co-workers described a new and efficient Ni(dppe)Br₂/Zn catalytic system for the cross intermolecular [2+2+2] cyclotrimerization of two alkynes with an allene. A

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variety of polysubstituted benzene derivatives was obtained in complete regioselectivity and high chemoselectivity. According to the proposed mechanism, at the first step, two molecules of propiolate are consumed in the presence of the catalytic Ni(0) species to form the nickellacyclopentadiene intermediate Ni-I, coordination and subsequent insertion of allene into a Ni(II)-carbon bond gives nickellacyclopentadiene intermediate Ni-II. Subsequent reductive elimination and isomerization provide the aromatic product and regenerate the Ni(0) catalyst. Notably, the results indicated that the presence of a strong electron-withdrawing ester group in the alkyne moiety was necessary to ensure the success of the reactions. (Scheme 17)

\[
\begin{align*}
\text{Ni(dppe)Br}_2 & \quad 5 \text{ mol \%} \\
\text{CH}_3\text{CN, 80 °C, 8 h} & \\
& \quad \text{Zn 2.75 equiv}
\end{align*}
\]

\[
\begin{align*}
R^1 &= (\text{CH}_3)_2\text{CH}_2 \quad \text{cyclohexyl, cyclopentyl, Ph} \\
R^2 &= \text{CO}_2\text{Me, Me, (CH}_3)_2\text{CH}_2, \text{(CH}_3)_2\text{CH}_2, \text{(CH}_2)_3\text{C}_6
\end{align*}
\]

Notably, the results indicated that the presence of a strong electron-withdrawing ester group in the alkyne moiety was necessary to ensure the success of the reactions. (Scheme 17)

\[\text{Scheme 17}\]

2. Partially intramolecular reactions

2.1. Cobalt-catalyzed partially intramolecular [2+2+2] cycloadditions

In 2006, Okamoto and co-workers reported the first partially intramolecular cobalt-catalyzed [2+2+2] cycloaddition reaction of α,ω-diynes with alkynes by using a catalytic
system based on the combination of 2-(2,6-diisopropylphenyl)iminomethylpyridine (dipimp), CoCl$_2$•6H$_2$O, and Zn powder. This method is efficient with a variety of functional terminal or internal alkynes, such as alcohols, esters, alkenes and silyl-substituted alkynes (Scheme 18).

The use of Zn powder was required to promote the catalytic cycles, and the reaction was incompatible with aryl bromides, iodides, and nitro compounds because of the interaction with zinc and/or cobalt. Okamoto’s team also demonstrated that the addition of a silver salt, such as silver triflate (AgOTf) or silver hexafluoroantimonate (AgSbF$_6$), could accelerate the reaction to furnish sterically demanding benzene derivatives starting from unactivated simple internal alkynes.

Scheme 18

Doszczak and Tacke accomplished a one-step synthesis of hydroxyalkyl-substituted 1,3-disilaindanes, 1,4-disilatetralines, and 1,3-disila-1,3-dihydroisobenzofuranes via Co/Zn-catalyzed [2+2+2] cycloaddition of silicon-containing diynes and unprotected propargyl alcohols under mild conditions (Scheme 19).

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In 2011, Aubert, Gandon, and Malacria engaged a series of halogenated diynes with alkynes in the presence of CpCo(CO)(dimethylfumarate) and Cp*Ru(cod)Cl catalyst via [2+2+2] cycloaddition reactions. The studies confirmed that the ruthenium complex remains the best choice for the cycloaddition of all kind of alkynyl halides. The air-stable CpCo(CO)(dmfu) complex proved to be efficient with alkynyl bromides (Scheme 20).

### Scheme 19

### Scheme 20

#### 2.2. Rhodium-catalyzed partially intramolecular [2+2+2] cycloadditions

Since the first examples of partially intramolecular [2+2+2] cycloadditions of α,ω-diynes and alkynes using a stoichiometric amount of Wilkinson's catalyst (RhCl(PPh3)3)

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reported by Müller in 1974,\(^2^9\) the rhodium-catalyzed [2+2+2] cycloaddition of diynes and alkynes has been well studied over the past few decades. The most efficient and widely used rhodium catalysts were neutral \(\text{RhCl}(\text{PPh}_3)_3\) complex and cationic rhodium(I)/biaryl bisphosphine complex catalysts.

**Wilkinson’s catalyst:**

Grigg and co-workers described the first catalytic [2+2+2] cycloaddition of 1,6-diynes with alkynes under mild conditions in the presence of a catalytic amount of \(\text{RhCl}(\text{PPh}_3)_3\) catalyst.\(^3^0\) Various tethered diynes and monoalkynes could be employed under these reaction conditions to afford the cycloadducts in 3-99% yields (Scheme 21).\(^3^1\)

\[\begin{align*}
\text{R}_1^1 & \quad \text{R}_1^1 \\
\text{R}_2 & \quad \text{R}_3 \\
\text{X} = \text{C(}\text{Ac}_2, \text{CH}_2, \text{C(}\text{CO}_2\text{Me})_2, \text{C(}\text{CO}_2\text{Et})_2, \text{SO}, \text{SO}_2, \text{NAc, O} \\
\text{R}_1^1 = \text{H, Me} \\
\text{R}_2 = \text{H, nPr, nBu, (CH}_3)_2\text{C}^-=\text{CH, (CH}_2)_3\text{C}^-=\text{CH, CH}_2\text{OH, CH}_2\text{OMe} \\
\text{CH}_2\text{OAc, CH}_2\text{CH}_2\text{OH, C(Me)=CHPh, SiMe}_3 \\
\text{R}_3 = \text{H, CH}_2\text{OH}
\end{align*}\]

**Scheme 21**

The Wilkinson's catalyst could also be used in the regioselective cycloaddition of unsymmetrical diynes with alkynes. In 1995, McDonald and co-workers reported the \(\text{RhCl}(\text{PPh}_3)_3\)-catalyzed [2+2+2] cycloaddition of different substituted diynes with simple monosubstituted alkynes to afford functionalized dihydroisobenzofuran products in 35-61% yields.\(^3^2\) In most cases, the *meta*-substituted aromatic products were formed as major products because of the steric hindrance of the alkyne substituents (Scheme 22).

In contrast to the formation of five or six-membered bicyclic benzene derivatives, the [2+2+2] cycloadditions to form medium-sized ring systems remain a challenge. Wu and co-workers developed a Rh-catalyzed [2+2+2] cycloaddition reaction for the preparation of trifluoromethylated benzo-fused eight-membered rings. The Wilkinson’s catalyst was chosen for the reaction to deliver the expected products in 46-90% yields with good functional group tolerance (Scheme 23).\(^{33}\)

Cationic Rh(I)-biaryl bisphosphine complexes:

The cationic rhodium/biaryl bisphosphine catalysts are the most efficient catalysts and have been widely studied in partially intramolecular [2+2+2] cycloaddition reactions. In 2006, Tanaka and co-workers successfully employed a Rh(cod)\(_2\)BF\(_4\)/(S)-Xylyl-BINAP complex for the enantioselective [2+2+2] cycloaddition of \(\alpha,\omega\)-diynes with trimethylsilylnamides to furnish axially chiral anilides.\(^{34}\) The authors demonstrated that the substituted groups on the ynamides greatly influenced the yield of anilides. Indeed, the phenyl- and methoxycarbonyl-substituted trimethylsilylnamides showed high reactivity. According to the mechanism, the high enantioselectivity of the anilides could be explained by the formation of the key

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intermediate Rh-I, in which the rhodium center is coordinated to the carbonyl group of trimethylsilylnamidate and the bulky PAr2 group of (S)-Xylyl-BINAP which sterically interacts with the R3 of the trimethylsilylnamidate (Scheme 24).

Scheme 24

The same group applied the cationic rhodium(I)/H8-BINAP catalyst for the synthesis of substituted benzopicenes via [2+2+2] cycloaddition of binaphthyl-linked diynes with alkynes (Scheme 25).\(^\text{35}\) This method was further applied for the benzopicene-based long ladder and helical molecules synthesis.

Scheme 25

2.3. Nickel-catalyzed partially intramolecular \([2+2+2]\) cycloadditions

Since the first examples of cyclotrimerization of alkynes to form benzene derivatives reported by Reppe,\(^9\) the nickel-catalyzed \([2+2+2]\) cycloaddition reactions have been well studied because of several advantages such as a high reactivity, a broad functional groups tolerance, relatively cheaper price compared to other late transition metals.

Cheng and co-workers developed an efficient protocol for the synthesis of polysubstituted arylalkynes based on the nickel-catalyzed \([2+2+2]\) cycloaddition of non-conjugated diynes with 1,3-diynes in a single transformation (Scheme 26).\(^{36}\) The results showed that the electron-withdrawing ester groups substituted diynes are more reactive compared to the terminal diynes.

\[
\begin{align*}
\text{X} & = CH_3CH_2, CH_3, C(CO_2Et)_2, O \\
R^1 & = H, CO_2Me \\
R^2 & = nBu, Ph, 4-Ac-C_6H_4
\end{align*}
\]

Scheme 26

Under the optimized conditions, the reaction of unsymmetrical 1,6-diyynes with symmetrical 1,3-diynes afforded the products in 58-79% yields with excellent chemo- and regioselectivity. Phenyl-, \(n\)-butyl-, and trimethylsilyl-substituted 1,3-diynes reacted with 1,6-diyynes to afford highly functionalized arylalkynes. Interestingly, unsymmetrical 1,3-diynes reacted with di-ester-substituted symmetrical diynes at room temperature to give the cycloadduct with high regioselectivity (ratio = 19:1). The cycloaddition mainly occurred with the triple bond adjacent to the \(n\)-butyl group of the 1,3-diyne (Scheme 27).

---

Kotora and co-workers reported a nickel-catalyzed [2+2+2] cycloaddition of 6-alkynylpurines with α,ω-diynes to access biologically active 6-arylpurines. A variety of terminal diynes and substituted 6-alkynylpurines was examined to afford various functionalized 6-arylpurines. Several catalysts have been evaluated in this reaction, such as CoBr(PPh$_3$)$_3$, RhCl(PPh$_3$)$_3$, NiBr$_2$(dppe)/Zn, NiI$_2$(PPh$_3$)/Zn, and Ni(cod)$_2$/PPh$_3$. The results showed that Ni/phosphine complexes were the best catalysts for the cyclotrimerization of alkynes. For example, in the presence of 20 mol % of Ni(cod)$_2$/2PPh$_3$, different 1,6-diynes smoothly reacted with 6-alkynylpurine nucleosides at 20 °C to deliver the 6-arylpurine nucleosides in 48-81% yields (Scheme 28).

---

**Scheme 27**

---

**Scheme 28**

---

Deiters and co-workers described the microwave irradiation assisted nickel-catalyzed [2+2+2] cyclotrimerization reactions to quickly access highly substituted aromatic compounds. The application of microwave irradiation highly enhanced the reactivity of Ni(CO)$_2$(PPh$_3$)$_2$ catalyst, and enabled the reaction to produce highly substituted benzene derivatives in a short reaction time. A variety of diynes and alkynes were tolerated to afford various substituted indanes, isoindolines, and tetraline core structures in 50-98% yields. Notably, the developed protocols were used as a key step for the total synthesis of natural product Illudinone (Scheme 29).

Scheme 29

2.4. Iridium-catalyzed partially intramolecular [2+2+2] cycloadditions

In 2001, Takeuchi and co-workers described a simple and convenient protocol for the synthesis of polysubstituted benzene derivatives by using [Ir(cod)Cl]$_2$/dppe complex as a catalyst. A broad range of functional groups such as alcohols, amines, alkenes, ethers, halogens, and nitriles were tolerated to give various functionalized benzene derivatives. It was proposed that the reaction formed an iridacyclopentadiene intermediate Ir-1 by the oxidative cyclization of $\alpha$,$\omega$-diynes. The coordination of a monoyne would facilitate a Diels-Alder type

\[
\text{Ni(CO)}_2(P\text{Ph}_3)_2 \quad 10 \text{ mol }% \\
\text{W (300 w)} \\
\text{Toluene, 82 °C, 2 min} \\
21 \text{ examples} \quad 50-98\%
\]

Selected examples:

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{EtO}_2\text{C} \\
\text{R}_2 & \quad \text{R}_2 \\
\text{BocN} & \quad \text{BocN} \\
\text{CH}_2\text{NHBOc} & \quad \text{CH}_2\text{NHBOc} \\
79\% & \quad 0\% \text{ (conventional heating)} \\
80\% & \quad 84\%
\end{align*}
\]

5 steps

**Illudinone**

---


process to form an intermediate Ir-II, followed by reductive elimination to deliver the cycloadduct (Scheme 30).

\[
\begin{align*}
\text{Scheme 30} \\
\end{align*}
\]
In 2014, Takeuchi’s group expanded the scope of this reaction to the synthesis of carbonyl group functionalized benzene derivatives. Upon screening several iridium complexes and ligands, they found that the $[\text{Ir(cod)Cl}]_2$/($\text{rac}$)-BINAP was the best catalytic system for the reaction. A broad range of 2,7-diynes reacted with alkynyl ketones and alkynyl esters in the presence of $[\text{Ir(cod)Cl}]_2$/($\text{rac}$)-BINAP catalyst to provide the corresponding functionalized benzenes in 22-91% yields (Scheme 31).

Scheme 31

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Scheme 32

\[ R^1 = H, \text{Me, Et, Ph, 2-Py, 2-thienyl} \]
\[ R^2 = \text{nHex, nOct, 1-cyclohexenyl, Ph} \]
\[ R^3 = H, \text{Me, Et, iPr, nPent, CHCHCH}_3, \text{Ph, 2-thienyl} \]

Taking advantage of the triply iodo-bridged iridium(III) complexes, \([\{\text{Ir}(\text{H})[\text{rac-binap}]\}_2(\mu-I)_3]\), our group developed in 2012 a convenient and efficient protocol for the preparation of fused arenes. Isoindolines, indanes, and dihydroisobenzofurans bearing a wide range of substitution groups could be achieved through an iridium(III)-catalyzed [2+2+2] cycloaddition of \(\alpha,\omega\)-dienes with alkynes. The reaction proceeds with symmetrical and unsymmetrical diynes, which affords highly substituted benzene derivatives in up to 97% yields. This methodology can be applied to alkynylboronates, which is a convenient means to generate the challenging, highly functionalized borylated fused arenes that present great potential for further elaboration. Notably, these processes are extremely robust and simple to perform. The catalyst system is compatible with commercial grade non-degassed solvents, whereas the alkynes herein do not necessitate purification before use (Scheme 33).

\[X \equiv \text{RC(O)Me}_2, \text{NTs, NBoC, O R}^1, R^2 = \text{H, Me, Ph R}^3 = \text{nBu, cyclopropyl, CH}_2\text{OH, CH(Me)OH, (CH}_2\text{)}_2\text{OH, Ph, 4-Me-C}_6\text{H}_4, 4\text{-MeO-C}_6\text{H}_4 O\]

Selected examples:

<table>
<thead>
<tr>
<th>Structure</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BocN[O][OH</td>
<td>90%</td>
</tr>
<tr>
<td>BocN[O][Cl</td>
<td>61%</td>
</tr>
<tr>
<td>TsN[O][OH</td>
<td>76%</td>
</tr>
<tr>
<td>TsN[O][B ]</td>
<td>62%</td>
</tr>
</tbody>
</table>

Scheme 33

---


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In 2003, this atom-economical process has also been successfully performed under solvent-free conditions to access various fused arenes in 43-85% yields (Scheme 34). \(^{45}\)

![Scheme 34](image)

2.5. Ruthenium-catalyzed partially intramolecular [2+2+2] cycloadditions

Cp*Ru(cod)Cl catalyst:

In 2000, Itoh and Yamamoto described the first example of ruthenium-catalyzed [2+2+2] cycloaddition of \(\alpha,\alpha\)-diynes with monoalkynes using Cp*Ru(cod)Cl catalyst. \(^{46}\) Later, they extended the scope of this reaction, and found that a variety of tethered diynes including heteroatom tethered diynes, such as nitrogen, oxygen, sulfur, was compatible with these reaction conditions leading to the formation of the corresponding benzene derivatives in 64-96% yields. A self-dimerization or trimerization of diynes product have been detected in some cases as a competitive process (Scheme 35). \(^{47}\)

![Scheme 35](image)

---


The regioselectivity of the ruthenium-catalyzed cycloadditions was also studied by using unsymmetrical monosubstituted diynes. Treatment of the unsymmetrical diynes, bearing methyl, phenyl, and trimethylsilyl terminal substituents, with the Cp*Ru(cod)Cl catalyst, gave the corresponding cycloadducts in high yields with high regioselectivities, the meta selective product being formed as the major product. According to the mechanism, the coordination and oxidative coupling of diyne with ruthenium complex led to the ruthenacyclopentadiene intermediate Ru-I, followed by the selective insertion of the monoalkyne into the less substituted Ru–C single bond leading to the formation of the ruthenacycloheptatriene intermediates Ru-II or Ru-II’. The reductive elimination from Ru-II afforded meta-selective product, whereas Ru-II’ furnished ortho-selective isomer (Scheme 36).

Scheme 36

In 2004, Yamamoto’s group described the cycloaddition of unsymmetrical terminal diynes bearing amide, ester and ketone carbonyl tethered groups with terminal alkynes to afford the corresponding cycloadducts with unexpected regioselectivities. The observed results showed that the regioselectivity was directed by the electron effects of the internal conjugated carbonyl groups, and increased in the order of amide tether (X = NBn) ≈ ester tether (X = O)

---

< ketone (X = CH₂). The stronger electron-withdrawing ability of the carbonyl group allowed the highest regioselectivity (Scheme 37).

\[
\begin{array}{c}
\text{O} \\
\text{X} \\
\equiv \equiv \\
\text{O}
\end{array} + \begin{array}{c}
\text{rBu}
\end{array} \xrightarrow{\text{Cp}^*\text{Ru(cod)Cl}, 5 \text{ mol} \%} \begin{array}{c}
\text{meta} \\
\text{X} \\
\equiv \equiv \\
\text{O} \\
\text{rBu}
\end{array} \quad \begin{array}{c}
\text{ortho} \\
\text{X} \\
\equiv \equiv \\
\text{O} \\
\text{rBu}
\end{array}
\text{DCE, rt, 0.5-20 h}
\]

<table>
<thead>
<tr>
<th>X</th>
<th>Yield</th>
<th>meta:ortho</th>
</tr>
</thead>
<tbody>
<tr>
<td>NBn</td>
<td>76</td>
<td>63:37</td>
</tr>
<tr>
<td>O</td>
<td>93</td>
<td>70:30</td>
</tr>
<tr>
<td>CMe₂</td>
<td>70</td>
<td>78:22</td>
</tr>
</tbody>
</table>

**Scheme 37**

During the investigation of partially intramolecular [2+2+2] cycloaddition reactions, a bicyclic ruthenacyclopentatriene complex Ru-I was isolated by Yamamoto’s group. The internal diyne bearing two phenyl substituents slowly reacts with Cp*Ru(cod)Cl complex in CDCl₃ at room temperature to give the bis-carbene ruthenium complex in 51% yield, which could react in a stoichiometric way with acetylene to afford [2+2+2] cycloadduct. Another example of naphthoquinone-fused ruthenacyclopentatriene complex Ru-II was prepared from 1,2-bis(phenylpropiolyl)benzene and Cp*Ru(cod)Cl complex by the same group. The Ru-II complex could be isomerized to form cyclobutadiene complex Ru-III at room temperature in solution (Scheme 38).

**Scheme 38**

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Based on the observed results and DFT calculations, Yamamoto’s group proposed a mechanism for the cycloaddition of acetylene to form benzene on a CpRuCl fragment, as shown in Scheme 39. The coordination of two alkynes to the ruthenium center exchanges with the diene ligand to form species Ru-I, which undergoes oxidative cycloaddition to give ruthenacyclopentatriene Ru-II. Coordination of a third alkyne to the ruthenium center followed by a subsequent [2+2] cycloaddition between the Ru-C double bond with alkyne produces metallobicyclo[3.2.0]heptatriene Ru-IV, this intermediate rapidly undergoes ring-opening process resulting in the formation of ruthenacycloheptatetraene Ru-V. Finally, a ring-closing step occurs with the seven-membered ruthenacycle Ru-V via a carbene-carbene coupling delivering an η²-arene complex Ru-VI. A rapid exchange between arene and acetylene produces the cycloadduct and regenerates the starting ruthenium complex Ru-I.

Scheme 39

Taking advantage of this efficient catalyst, Nicolaou’s group accomplished the total synthesis of the highly oxygenated, marine-derived, natural product Sporolide B. The key intermediate indene structural motif was prepared by the partially intramolecular [2+2+2] cycloaddition of chloroacetylenic cyclopentenyne and propargylic alcohol in the presence of 7 mol % Cp*Ru(cod)Cl in dichloroethane at room temperature. The reaction provided the key
building block as a single regioisomer in 87% yield, which was finally converted to Sporolide B over 13 steps (Scheme 40).

**Scheme 40**

**Grubbs catalyst:**

Grubbs catalyst has also been used in partially intramolecular [2+2+2] cycloaddition reactions. In 2000, Witulski and co-workers employed Grubbs I (\([\text{RuCl}_2(\text{NCHPh})(\text{PCy}_3)_2]\)) for the regioselective synthesis of 4,6-substituted indolines. The reaction probably proceeds via a cascade metathesis mechanism to give the high regioselective formation of 2,4-substituted product. The catalytic cycle was shown in Scheme 41. The Grubbs I complex initially adds to the least substituted alkyne moiety of the 1,6-diyne leading to the formation of vinyl carbene complex Ru-I, which undergoes an intramolecular metathesis reaction to give the five-membered carbo- or heterocycle Ru-II. The coordination of another monoalkyne followed by an intermolecular metathesis insertion affords the highly conjugated carbene complex Ru-III, which undergoes the final ring-closing olefin metathesis step resulting in the regeneration of the ruthenium benzylidene catalyst and in the preferred formation of the corresponding meta-isomer (Scheme 41).


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3. Totally intramolecular reactions

Totally intramolecular cycloaddition reactions are considered as the most efficient method to solve the problem of the control of the chemo- and regioselectivity to access highly substituted benzenes. Three alkynes linked with two or three carbo- or hetero-tethers form a triyne which can be assembled via a cyclotrimerization to give a polycyclic aromatic compound with complete selectivity.

Malacria and Aubert reported in 2004 the first totally chemo- and regioselective formal intermolecular [2+2+2] cycloaddition of three different alkynes by using the CpCo(CO)₂ catalyst. A series of easily prepared silicon-tethered triynes successfully reacted with cobalt catalyst to furnish various benzene derivatives. Selective deprotection of the silylated group,

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52 Chouraqui, G.; Petit, M.; Aubert, C.; Malacria, M. *Org. Lett.* 2004, 6, 1519.
53 Petit, M.; Chouraqui, G.; Aubert, C.; Malacria, M. *Org. Lett.* 2003, 5, 2037.
resulted in the formation of functionalized arenes. This synthetically useful method avoided the formation of unexpected regioisomers in such cycloaddition reactions (Scheme 42).

Scheme 42

In 2009, Aubert, Gandon, and Malacria applied the new designed and synthesized CpCo(CO)dmfu catalyst for totally intramolecular [2+2+2] cycloaddition reactions. The air-stable cobalt catalyst efficiently catalyzed the cyclotrimerization of carbo- and hetero-tethered triynes, forming a variety of fused tricycle benzenes in 69-92% yields (Scheme 43). Notably, these reactions can be performed under both conventional heating and microwave irradiation heating conditions.

---

In contrast to the linear triynes, the macrocyclic triynes can also be employed in \([2+2+2]\) cycloaddition reactions. In 2004, Roglans and co-workers reported a totally intramolecular rhodium-catalyzed \([2+2+2]\) cycloaddition reaction of nitrogen-containing \(15\)-membered triacetylenic macrocycles.\(^{55}\) The nitrogen-tethered macrocyclic triynes smoothly reacted with 1-5 mol % of \(\text{RhCl(CO)(PPh}_3)_2\) in toluene to afford various multiple ring compounds in 80-96% yields (Scheme 44). Notably, this was the first example of \([2+2+2]\) cycloaddition reactions of macrocyclic triynes.

Scheme 43

Taking advantage of this strategy, Witulski and co-workers reported the first total synthesis of the sesquiterpenoid alcyopterosin E from simple starting materials. In this multi-step synthesis, the formation of the key precursor indeno[4,5-c]furan was achieved through a totally intramolecular cycloaddition of an enantiomerically pure triyne by using Wilkinson’s catalyst in dichloromethane at 40 °C. Subsequent transformation of the tosylate into a nitrate group completed the total synthesis (Scheme 45).\(^{56}\)

Scheme 44

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Scheme 45
Chapter II: Access toward fluorenone derivatives through solvent-free ruthenium trichloride mediated [2+2+2] cycloadditions
Chapter II: Access toward fluorenone derivatives through solvent-free ruthenium trichloride mediated [2+2+2] cycloadditions

1. Interest of fluorenones

Over the past few years, fluoren-9-one and its derivatives have attracted much attention from academia and industry regarding their frequent application in various fields.57

The fluorenone scaffolds and related chemicals are important structural moiety that constitute the central core of a variety of compounds, which are found in many natural products and bioactive molecules encompassing a wide range of biological properties (Scheme 46).58

For example, Dengibsin A and Dengibsinin B were the first natural fluorenone derivatives isolated from the Indian orchid Dendrobium gibsonii Lindl,58a 2,7-disubstituted amidofluorenone derivatives D exhibited a range of human telomerase inhibitory activities,58d tilorone dihydrochloride E has great potential for inducing interferon against pathogenic infection,58e indenone F showed anti-HIV-1 activity,58f dicationic 2-fluorenonylcarbapenems G were potent anti-MRS agents.58g


Additionally, because of their attractive luminescent properties, fluorenones could also be employed as organic and polymer light-emitting diodes, bulk heterojunction solar cells and photochemical sensitizers (Scheme 47).<sup>59</sup> For examples, bisindenofluorene H represented a novel building block class for n-type electronic materials,<sup>59a</sup> compounds I formed ferroelectric liquid crystals,<sup>59b</sup> 2,7-poly(9-fluorenone) J was a suitable candidate as an electron-injection material in multilayer LEDs,<sup>59</sup> and compound K was a stable fluorenone-based sensitizer dye for solar cell.<sup>59</sup>

Scheme 46

2. Preparation methods in the literature

2.1 Traditional methods for the preparation of fluorenones

Numerous synthetic methods have been developed for the synthesis of fluorenones. Traditional synthetic methods include Friedel-Crafts acylation,$^{60}$ remote metalation,$^{61}$ Diels-Alder reaction,$^{62}$ and oxidation of fluorenes or fluorenols.$^{63}$ (Scheme 48)
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2.2 Transition-metal-catalyzed synthesis of fluorenones

Over recent years, transition-metal-catalyzed functionalization has been recognized as a novel and efficient method to synthesize complex fluorenone derivatives that are not accessible by conventional methods. Palladium, rhodium, silver and copper complexes have been reported as catalysts to access fluorenones and derivatives. Synthetic methods for the preparation of fluorenone derivatives are summarized below and classified according to the metal.

2.2.1 Palladium-catalyzed synthesis of fluorenones

2.2.1.1 C-H functionalization of 2-haloarylketones

In 1984, Ames and Opalko disclosed a novel palladium-catalyzed dehydrohalogenation of 2-iodobenzophenone to provide fluorenone (Scheme 49). Various bases and solvents employed with Pd(OAc)$_2$ have been used in this reaction. When 2-iodobenzophenone was heated in N-methylimidazole in the presence of Pd(OAc)$_2$ at 190 °C, fluorenone product was obtained in 100% yield.

---

Scheme 48

Based on the previous results reported by Ames and Opalko, Jones and co-workers further optimized the reaction conditions, involving high-temperature with PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} and sodium acetate in dimethylacetamide (DMA) under microwave irradiation (Scheme 50).\textsuperscript{65} They successfully synthesized benzo[b]fluorenone in 53% yield, this derivative being considered as a key intermediate to access the natural products stealthin C\textsuperscript{66} and prekinamycin\textsuperscript{67}.

2.2.1.2 Directing-group-assisted C-H activation

In 2007, Larock’s research group reported an efficient synthesis of fluorenones using a Pd-catalyzed intramolecular C-H activation strategy involving an aryl to imidoyl palladium migration process (Scheme 51).\textsuperscript{68} Treatment of imines with 5 mol % of Pd(OAc)\textsubscript{2}, 5 mol % of bis(diphenylphosphino)methane (dpdm), and 2 equivalents of CsO\textsubscript{2}CCMe\textsubscript{3} (CsPiv) in DMF at 100 °C, followed by hydrolysis using aqueous HCl, afforded the desired fluorenones in 56-100% yields. Subsequent deuterium labeling experiments showed that the reaction involved both a palladium migration and a C-H activation process through an unprecedented organopalladium hydride intermediate Pd-I.

In 2008, Daugulis and co-workers reported a one-pot synthetic method for ortho-benzonitriles and fluorenone derivatives formation by the palladium-catalyzed C-H bond functionalization of simple benzamide and aryl halides (Scheme 52). Notably, the reaction could afford various desired products by tuning the alkyl substituent on the amide group. *N*-cyclohexyl benzamides led to the formation of benzonitrile derivatives, whereas *N*-propyl benzamides can be converted to fluorenones.

Beside imines, oximes can be also considered as directing groups in Pd-catalyzed C-H activation to synthesize fluorenone derivatives. In 2008, Cheng and co-workers reported a Pd-catalyzed synthesis of fluorenones from substituted aromatic aldoxime ethers and aryl iodides through a dual C-H activation and oxidative Heck cyclization (Scheme 53). A series of control

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experiments suggested that both palladium acetate and silver oxide are required for this transformation, allowing the facile synthesis of the desired fluorenones in 63-90% yields.

Scheme 53

Shi and co-workers described in 2010 a one-pot Pd-catalyzed ortho-directed C-H arylation of aromatic aldoxime ether and arylboronic acids for the synthesis of fluorenone derivatives (Scheme 54).71

Scheme 54

In 2011, the continuous work in Cheng’s group demonstrated that a Pd-catalyzed ortho-directed multiple C-H activation of aromatic aldoxime ether with arenes could proceed smoothly to give the corresponding substituted fluorenone derivatives in 42-91% yields (Scheme 55).72 Notably, this synthetic method for the preparation of fluorenones showed a significant improvement since it avoided the use of aryl halides, aryl boronic acids, and expensive metal oxidants.

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Scheme 55

Hsieh and co-workers developed in 2013 a method for the preparation of polysubstituted fluorenones via a Pd-catalyzed nitrile directed remote C-H and dual C-H bond activation with intramolecular 1,2-insertion of nitrile (Scheme 56). A wide range of functional groups were tolerated under the reaction conditions, providing various fluorenones in 17-91% yields.

Scheme 56

In addition, a Pd-catalyzed ortho C-H activation of benzylamines with iodo arenes to provide fluorenone derivatives has been explored. Satyanarayana and co-workers reported a one-pot domino Pd-catalyzed reaction proceeding through the formation of a five-membered Pd(II)-cycle and subsequent ortho C-H activation with iodoarenes to give fluorenones in 42-88% yields with high regioselectivities (Scheme 57). Notably, the reaction could further activate C(sp³)-H and C(sp²)-H bonds to afford the fused fluorenone derivatives.

Kumar, D. R.; Satyanarayana, G. Org. Lett. 2015, 17, 5894.
In 2014, Wang’s group described a Pd-catalyzed intramolecular C-C coupling reaction through a dual C-H bond activation directed by a removable carboxylate group.\textsuperscript{75} The reaction proceeds in the presence of Pd(OAc)\textsubscript{2} and Cu(OAc)\textsubscript{2}\cdot nH\textsubscript{2}O under air atmosphere, to provide various substituted fluorenones in 31-91% yields. According to the proposed mechanism, the intramolecular carboxylate-directed dual C-H activation generates a 9\textit{H}-fluorene-9-carboxylic acid (I) intermediate, a subsequent oxidative decarboxylation by the oxygen from the air in the presence of Pd(OAc)\textsubscript{2} and Cu(OAc)\textsubscript{2} and furnishes the cyclized product along with eliminating carbon dioxide and water (Scheme 58).

Another interesting example involving Pd-catalyzed carboxylic acid directed ortho-selective oxidative C-H/C-H cross-coupling of aromatic carboxylic acids with arenes followed by subsequent intramolecular Friedel-Crafts acylation for the construction of poly-substituted fluorenones was reported by You and co-workers. (Scheme 59). By following this strategy, a variety of commercially available aromatic carboxylic acids and arenes were successfully converted to substituted fluorenones in 53-82% yields.

---

Sorensen’s group reported in 2017 Pd-catalyzed C(sp$^2$)–H functionalization cascade reactions for the preparation of fluorenones from readily available benzaldehydes and aryl iodides using anthranilic acid as transient directing group.\textsuperscript{77} It is worthy to mention that the antiviral drug Tilorone was synthesized in 40% yield over three steps (Scheme 60).

\textbf{Scheme 59}

\textbf{Scheme 60}

\textbf{2.2.1.3 Dehydrogenative cyclization}

In 2012, Cheng’s group disclosed a novel synthetic method involving a dual C-H activation of diarylketones to form fluorenones by Pd-catalyzed oxidative dehydrogenative

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cyclization of benzophenones. This process provided a wide range of fluorenones in 36-94% yields (Scheme 61). A mechanistic study demonstrated that the first step was the coordination between the ketone group and Pd(II) followed by the consecutive ortho-C-H activation to form a palladacycle Pd-I, which was expected to be in equilibrium with its palladium aryl σ-complex Pd-II. Then the palladium complex Pd-II underwent the second C-H activation, lead to the six-membered palladium complex Pd-III and subsequent reductive elimination to produce the fluorenone product and Pd(0) species. Independently, Shi’s group reported similar conditions to access fluorenone derivatives through palladium-catalyzed dehydrogenative cyclization reactions.

Scheme 61

Kantam and co-workers reported in 2015 an efficient method for the synthesis of fluorenones by dehydrogenative cyclization of benzophenones using a palladium(II)/magnesium-lanthanum mixed oxide catalyst in TFA/H₂O solution system

Fluorenones were formed in 50-85% yields in the presence of reusable Pd(II)/Mg-La catalyst under heterogeneous reaction conditions.

**Scheme 62**

### 2.2.1.4 Cyclocarbonylation

The first practical method for the Pd-catalyzed cyclocarbonylation of ortho-halobiaryls to substituted fluorenone derivatives was developed by Larock’s group in 2000. Treatment of the ortho-halobiaryls with 5 mol % of Pd(PCy)_3 and 2 equivalents of anhydrous cesium pivalate in DMF solution under 1 atm of carbon monoxide atmosphere provided the expected fluorenones in 67-100% yield. This method has been successfully employed for the preparation of polycyclic and heterocyclic fluorenones (Scheme 63).

**Scheme 63**

A related study published in 2015 by Xie and co-workers demonstrated that the Pd-catalyzed carbonylative cross-coupling of aryl dihalides with arylboronic acids proceeded

---


smoothly under a carbon monoxide atmosphere, leading to the substituted fluorenones in 22-94% yields (Scheme 64). Notably, a series of more challenging fluorenones containing various substituents and π-conjugated extended systems was achieved.

\[
\text{Br} + \text{CO} \xrightarrow{(1 \text{ atm})} \text{Pd(OAc)}_2 5 \text{ mol } \% \text{ PCy}_3 10 \text{ mol } \% \text{ CaCO}_3 3 \text{ equiv} \xrightarrow{\text{PivOH } 1 \text{ equiv}} \text{Toluene, } 100 \degree \text{C} \xrightarrow{25 \text{ examples}} 22-94\%
\]

![Scheme 64](image)

Kakiuchi’s group described in 2016 a Pd-catalyzed cyclocarbonylation of 2-bromobiphenyls with formaldehyde through the cleavage of a C-H bond to afford the desired fluorenones in 45-75% yields (Scheme 65).\(^{83}\) The use of paraformaldehyde as a carbonyl surrogate resulted in a practical synthetic method and can be widely used.

\[
\text{Br} + (\text{CH}_2\text{O})_n \xrightarrow{(20 \text{ equiv})} \text{Pd(OAc)}_2 10 \text{ mol } \% \text{ PCy}_3 10 \text{ mol } \% \text{ Na}_2\text{CO}_3 2 \text{ equiv} \xrightarrow{\text{MgSO}_4 30 \text{ mol } \%} \text{Toluene, } 110 \degree \text{C} \xrightarrow{6 \text{ examples}} 45-75\%
\]

![Scheme 65](image)

---

2.2.1.5 Decarboxylative cyclization

With respect to carbonyl sources, several methods involving different carbonyl sources, such as carboxylic acids, nitriles, aldoximes, aldehydes, have been reported for the preparation of fluorenones. Jin and co-workers reported in 2016 a one-pot palladium-catalyzed decarboxylative cyclization of 2-phenylbenzoic acid to synthesize fluorenones by using tert-butyl isocyanide as a new carbonyl source (Scheme 66). Subsequent C-H activation and decarboxylation insertion of the isocyanide into 2-phenylbenzoic acid provided a six-membered intermediate that underwent elimination and hydrolysis to generate the cyclized product.

Scheme 66

2.2.1.6 Other methods for the preparation of fluorenones

In 2005, Larock’s group reported the synthesis of fluorenone derivatives via a palladium-catalyzed annulation of arynes with o-halobenzaldehydes. Later, they extended the scope of functionalized o-halobenzaldehydes and arynes. A variety of o-halobenzaldehydes and arynes has been examined, affording the substituted fluorenones in 33-82% yields (Scheme 67).

---

A rapid approach to access fluorenone derivatives via domino reactions using microwave as heating source has been reported by Lautens and co-workers. The aryl-palladium intermediate generated by a sequence of norbornene mediated C-H activation and subsequent ortho-arylation, underwent ester addition providing the corresponding fluorenone in 46-93% yields (Scheme 68). Several aldehydes were also subjected to this method affording the 9H-fluoren-9-one products in good yields. In the case of aldehydes, the reaction proceeded with triphenylphosphine as ligand under conventional heating at 90 °C for 24 h.

Scheme 67

Scheme 68

In 2010, Ray and co-workers disclosed an efficient method for the preparation of fluorenones through a palladium-catalyzed one-pot Suzuki-Miyaura coupling reaction followed by an intramolecular arylpalladation of 2-bromophenyl boronic acid with 2-bromocarboxaldehyde (Scheme 69). Various fluorenones and condensed fluorenone derivatives have been synthesized in 51-80% yields from readily available starting materials.

\[
\text{CHO} + \text{(HO)B} \xrightarrow{\text{Pd(OAc)}_2 \text{ 10 mol \% } \text{PPPh}_3 \text{ 0.5 equiv}} \xrightarrow{\text{NaOAc 4 equiv}} \xrightarrow{\text{DMF, 120 °C, 16-28 h}} \text{12 examples 51-80%}
\]

**Scheme 69**

The Dharmaraj’s group described in 2016 an efficient palladium-catalyzed domino reaction of benzoyl chloride with aryloboronic acid to synthesize substituted fluorenones (Scheme 70). A newly synthesized ONO pincer-type Pd\textsuperscript{II} complex has been used in this reaction and exhibited high catalytic efficiency (0.1 mol % catalyst-loading). Compared to other systems the catalyst could be reused over six consecutive runs.

\[
\text{Cl} + \text{B(OH)}_2 \xrightarrow{\text{Pd complex 0.1 mol \%}} \xrightarrow{\text{KOH 2 equiv}} \xrightarrow{\text{H}_2\text{O/MeOH (7:3)}} \xrightarrow{50 \degree C, air, 6-8 h} \text{25 examples 62-93%}
\]

**Scheme 70**

---


2.2.2 Rhodium-catalyzed synthesis of fluorenones

2.2.2.1 Conversion of benzoic anhydrides into fluorenones

Blum and co-workers reported in 1969 the first example of Rh-catalyzed transformation of benzoic anhydrides to fluorenones. Treatment of benzoic anhydride derivatives with chlorotris(triphenylphosphine)rhodium at high temperature led to the corresponding fluorenones in 5-72% yields. (Scheme 71).

![Scheme 71]

2.2.2.2 Partially intramolecular [2+2+2] cycloadditions

Considering the potential applications of optical and electronic functional materials, Tanaka and co-workers developed an efficient rhodium-catalyzed partially intramolecular double [2+2+2] cycloaddition to synthesize enantioenriched fluorenone-containing [9]-helicene-like derivatives and 1,1’-bistriphenylenes (Scheme 72).

---

2.2.2.3 Intramolecular acylation

Ryu and co-workers disclosed in 2014 the first catalytic preparation of fluorenone derivatives through Rh-catalyzed intramolecular acylation of biarylcarboxylic acids (Scheme 73).\(^3\) Screening of several reaction conditions led to the selection of [Rh(cod)Cl]\(_2\)/dppe system and potassium iodide/pivalic anhydride as catalyst and additives. Notably, the microwave irradiation promoted the reaction in a shorter reaction time.

---

Chapter II

2.2.3 Silver-catalyzed synthesis of fluorenones

2.2.3.1 Intramolecular radical cyclization

In 2011, Baran and co-workers developed a silver-catalyzed intramolecular radical cyclization of arylboronic acids and potassium aryltrifluoroborates, in the presence of silver nitrate and potassium persulfate, to access fluorenones through a ‘borono-Pschorr’ process (Scheme 74).\(^{94}\) The reaction was carried out under mild conditions and tolerated various functional groups, such as CO\(_2\)Me, CN, CF\(_3\). The aza-fluorenones were synthesized as a mixture with moderate regioselectivity.

![Scheme 74](image)

2.2.3.2 Decarboxylative radical cyclization

Greaney and co-workers reported in 2012 a similar study which involved Ag-catalyzed decarboxylative radical cyclization of arylbenzoic acids to afford fluorenones (Scheme 75).\(^{95}\) Notably, CD\(_3\)CN was unconventionally chosen as solvent, because of the stronger C-D bond that decreased hydrogen atom abstraction from the solvent. In addition, deuterated decarboxylation product was obtained as a side product which confirmed that the solvent was acting as a hydrogen atom donor.

---


2.2.4 Copper-catalyzed synthesis of fluorenones

A Cu-catalyzed simple construction of methoxy-substituted fluorenones from substituted 2-iodobenzophenones was reported by Haggam (Scheme 76). This study demonstrated that the intramolecular Cu-catalyzed cyclization of 2-iodobenzophenones afforded the corresponding fluorenones in 71-92% yields under conventional heating or under microwave conditions in a shorter reaction time.

Scheme 76

---

3. Objectives

As we detailed above, various fluorenones have been synthesized through transition-metal-catalyzed reactions. However, there are still important challenges to solve considering current limitations of these methods. Because of special structural features, the construction of the three single C-C bonds between the two six-membered rings has been generally privileged (Scheme 77). In contrast, only few examples focused on the construction of one of the two six-membered rings.

Scheme 77

Considering the results described in the literature, we envisioned that highly substituted fluorenones and related derivatives, such as azafluorenones, indenothiophenones, and benzo[b]furanones, could be successfully accessed using [2+2+2] cycloaddition of suitably substituted arylcarbamoyl bridged α,ω-diynes and monoalkynes. The retrosynthetic analysis is shown in Scheme 78.

Scheme 78
Chapter II

4. Results and discussion

4.1 Synthesis of starting materials: arylcarbamoyl bridged $\alpha,\omega$-diynes and internal alkynes

4.1.1. Synthesis of benzoyl bridged $\alpha,\omega$-diynes

The synthesis of benzoyl bridged diyynes could be accessed from the commercially available 2-bromobenzaldehydes via Sonogashira cross-coupling followed by condensation of the corresponding alkyl or phenyl substituted terminal alkyne to the carbonyl group, and final oxidation of the resulting secondary alcohol to ketone.

First, the substituted monoalkyne benzaldehyde derivatives 1-7 were prepared by a Sonogashira cross-coupling reaction. Under classical conditions, the reactions were conducted with 1.2 to 1.5 equivalents of the corresponding terminal alkynes and 2-bromobenzaldehyde in the presence of 5 mol % PdCl$_2$(PPh$_3$)$_2$ and 2.5 mol % CuI in a mixture of triethylamine and tetrahydrofuran (5.0 M, $v/v = 1/1$) at 50 °C. As shown in Scheme 79, various commercial substituted acetylenes were used, such as phenylacetylene, 1-hexyne, and trimethylsilylacetylene. In order to study the influence of the substituents on the phenyl ring at C7 position, electron-donating groups such as methyl (4) or tert-butyl (5) were introduced by using 4-ethynyltoluene or 4-(tert-butyl)phenylacetylene. In order to evaluate the effect on the tethered phenyl ring, the 2-bromoarylaldehydes having both electron-donating and electron-withdrawing substituents, such as methylenedioxy (6) and fluoride (7), were used for the cross-coupling reaction. All the desired compounds 1-7 were obtained in 70-87% yields (Scheme 79).
In the second step, derivatives 8-16 were synthesized by a lithium mediated nucleophilic addition of terminal alkynes with benzaldehyde derivatives 1-7, as shown in Scheme 80. The anion of terminal alkynes was formed by reacting \( n \)-butyl lithium with terminal alkyne at low temperature and was followed by the addition of the previously synthesized alkyny benzaldehyde derivatives 1-7 in THF, allowing the preparation of substituted diynes 8-16 in 50-96% yields. To maximize the yield of the reaction, 1.2 equivalents of \( n \)-butyllithium and 1.5 equivalents of terminal alkynes were used. Different functionalities at C8 position, such as \( n \)-butyl, cyclopropyl and phenyl, were introduced to study the influence of the substituents.
Compounds 8-16 were next converted to the corresponding benzoyl bridged $\alpha,\omega$-diynes 17-25 via oxidation reaction using Dess-Martin periodinane reagent (1.3 equivalents) (Scheme 81). After transformation of the secondary alcohols into ketones, symmetrically and unsymmetrically benzoyl bridged $\alpha,\omega$-diynes 17-25 were isolated in 74-94% yields.
Having in hand diyne 12, a standard deprotection with TBAF and oxidation reaction with Dess-Martin periodinane afforded substituted terminal phenylacetylene 29. The Sonogashira cross-coupling reaction was next envisaged for the preparation of electron-withdrawing group substituted diynes 26 and 27. Compound 29 reacted with a 1.5 equivalents of 4-iodobenzotrifluoride or 1-bromo-4-iodobenzene in the presence of 5 mol % of PdCl$_2$(PPh$_3$)$_2$ and 2.5 mol % of CuI in tetrahydrofuran/triethylamine at 50 °C. The reaction provided the desired products 26 and 27 in 65% and 48% yields, respectively (Scheme 82).
4.1.2. Synthesis of heteroaromatic bridged $\alpha,\omega$-diynes

Heteroaromatic compounds 30-36 were prepared following the same strategy by Sonogashira cross-coupling of the corresponding 2-bromo-heteroarylaldehydes with phenylacetylene. As shown in scheme 83, the coupling products 30-36 were obtained in 50-88% yields under the same conditions.

Next, aldehydes 30-36 reacted with terminal alkynes in the presence of $n$BuLi to provide the corresponding diynes 37-43 in yields ranging from 71% to 90% (Scheme 84).
Finally, oxidation of diynes 37-43 with Dess-Martin periodinane furnished the heteroaromatic carbonyl bridged diynes 44-50 in 40-94% yields. (Scheme 85).
4.1.3. Synthesis of internal alkynes

Alkynes 51-64 that were used in this chapter are shown in Scheme 86. Symmetrical alkynes 51-54 and unsymmetrical alkynes 58-64 were purchased, while ether-substituted monoalkynes 55, 56, and 57 were synthesized in agreement with the methods described in the literature.

Scheme 86

Alkyne 55 was prepared by reacting 2-butyne-1,4-diol 52 with a large excess of tert-butyl methyl ether (as solvent). The reaction was performed in the presence of two equivalents of sulfuric acid and molecular sieves at room temperature, providing 1,4-di-tert-butoxy-2-butyne 55 in 43% yield (Scheme 87).

Scheme 87

The nucleophilic substitution of 2-butyne-1,4-diol 52 with 2.2 equivalents of benzyl bromide in the presence of sodium hydride, afforded 1,4-dibenzylxyloxy-2-butyne 56 in 75% isolated yield (Scheme 88).

\[
\text{HO} \equiv \text{OH} + \text{Br} \quad \text{NaH 2.2 equiv} \quad \text{THF, 0 °C to rt, 48 h} \quad \text{75%} \\
\begin{align*}
\text{BnO} & \equiv \text{OBn} \\
52 & \quad 56
\end{align*}
\]

Scheme 88

Internal alkyne 57 was synthesized through the nucleophilic substitution of 2-butyne-1,4-diol 52 with 2.4 equivalents of tert-butyldimethylsilyl chloride at room temperature, using 2.4 equivalents of imidazole and a catalytic amount of DMAP, leading to 1,4-bis-tert-butyldimethylsilyloxy-2-butyne 57 in 80% yield (Scheme 89).

\[
\begin{align*}
\text{HO} & \equiv \text{OH} + \text{Me}_2\text{Si} - \text{Me}_2\text{Si} \text{Cl} \\
\text{DMAP 10 mol %} & \quad \text{Imidazole 2.4 equiv} \\
\text{DCM, rt, 1.5 h} & \quad \text{80%} \\
\text{Me}_2\text{BuSiO} & \equiv \text{OSiBuMe}_2 \\
52 & \quad 57
\end{align*}
\]

Scheme 89

### 4.2 Interest of RuCl₃·nH₂O complex

Since we synthesized a series of benzoyl bridged α,ω-diynes and internal alkynes, we therefore attempted to find a suitable catalytic system for the [2+2+2] cycloaddition reactions.

In this context, ruthenium trichloride is a stable salt which can be easily oxidized or reduced, and most commonly used in hydrated form (RuCl₃·nH₂O). As shown in Scheme 90, anhydrous ruthenium(III) chloride is usually prepared by heating powdered ruthenium metal with chlorine.¹⁰⁰

\[
\begin{align*}
\text{Ru(s)} & \quad + \quad \text{3/2 Cl}_2 (g) \quad \text{700 °C} \\
& \quad \rightarrow \text{RuCl}_3 (g)
\end{align*}
\]

Scheme 90

---

As the most commonly available ruthenium source, ruthenium trichloride was reported to be the best starting material for the synthesis of various ruthenium complexes (Scheme 91), with a wide range of oxidation states present in these complexes (Ru VIII to Ru II).

Scheme 91

Ruthenium trichloride was also reported as an efficient catalyst to promote C-C, C-H, C-O and C-N bond formations. Notable examples include many types of cyclization

---


reactions. For example, as shown in Scheme 92, Sames and co-workers demonstrated that RuCl\(_3\)/AgOTf was a mild and efficient catalyst for the intramolecular hydroarylation cyclization of a range of arene-ene substrates (Eq. a).\(^{102c}\) Liu and co-workers reported that the thermal cyclization of various 3,5-dien-1-ynes can be greatly enhanced by using RuCl\(_3\) as catalyst (Eq. b).\(^{102d}\) The group of Jia developed a series of RuCl\(_3\)-catalyzed intramolecular C-H amination reactions of organic azides, affording the corresponding indoles (Eq. c).\(^{102l}\) Rostamnia and co-workers described a RuCl\(_3\)-catalyzed solvent-free Ugi-type Groebke–Blackburn condensations of aldehydes and 2-aminopyridines with isocyanides in the presence of 5 mol % RuCl\(_3\)-\(n\)H\(_2\)O without any ligand or additive leading to the formation of aminomidazole heterocycles (Eq. d).\(^{102t}\)

Scheme 92

In the context of RuCl\(_3\)-catalyzed cycloaddition reactions, our group previously reported the first RuCl\(_3\)-\(n\)H\(_2\)O-promoted [2+2+2] cycloaddition reaction of \(\alpha,\alpha\)-diynes and alkynes to

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access highly substituted benzene derivatives (Scheme 93).\textsuperscript{103} We demonstrated that the cost-effectively available RuCl$_3$·nH$_2$O was an efficient catalyst to promote the cycloaddition reaction under solvent-free conditions affording fused functionalized arenes including dihydrobenzofurans, isoindolines, and indanes in 48-97% yields. Notably, this practical method used neither additional ligand nor additive.

![Scheme 93](image)

Encouraged by these results, we assumed that the RuCl$_3$·nH$_2$O complex might also be an efficient catalyst for solvent-free [2+2+2] cycloaddition of arylcarbamoyl bridged α,ω-diynes and monoalkynes to access fluorenone derivatives.

4.3 RuCl$_3$·nH$_2$O-mediated [2+2+2] cycloaddition of benzoyl bridged α,ω-diynes with symmetrical internal alkynes

With a series of diynes and alkynes in hand, we began our study by investigating the reaction of arylcarbamoyl bridged diyne 17 with 1,4-dimethoxy-2-butyne 51 which has often been reported as a good partner in transition-metal-catalyzed [2+2+2] cycloaddition reactions. The reaction was therefore initially performed in the presence of 5 mol % RuCl$_3$·nH$_2$O at 110 °C under previously described solvent-free conditions.\textsuperscript{103} Fortunately, the reaction gave the corresponding fluorenone 65 in complete conversion and isolated yield up to 86% (Entry 1, Table 1). It is noteworthy that the desired product could be isolated on silica column chromatography without any treatment after complete conversion (determined by TLC and crude $^1$H NMR). This result confirmed that RuCl$_3$·nH$_2$O is an efficient catalyst in [2+2+2] cycloaddition of α,ω-diynes with alkynes under solvent-free conditions. Based on such

encouraging result, we further optimized the reaction conditions. First, we studied the consumption of the monoalkyne 51, we were pleased to observe that when the amount of alkyne 51 was decreased from 6 to 2 equivalents, the reaction still provided the desired product 65 in satisfactory yields (Entries 2-6). In addition, decreasing the reaction temperature to 50 °C provided the cycloadduct in a similar yield (Entry 3, 73% and Entry 5, 75%, respectively). Lowering the catalyst loading from 5 to 2 mol %, led to a decrease of the conversion and isolated yield was observed in 18 hours at 80 °C (Entry 4, 60% conv. and 40% yield, respectively). Furthermore, we found that the reaction could be accomplished in 2 hours at 50 °C affording the desired cycloadduct 65 in satisfactory yield of 72% (Entries 6-8). When the reaction was placed under open-air condition, the conversion decreased significantly (Entry 9).

Table 1 Optimization of the reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>17/51</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Conv. (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
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</thead>
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<tr>
<td>1</td>
<td>1:6</td>
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<td>&gt; 99</td>
<td>86</td>
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<tr>
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<td>&gt; 99</td>
<td>74</td>
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<tr>
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<td>1:3</td>
<td>80</td>
<td>18</td>
<td>&gt; 99</td>
<td>73</td>
</tr>
<tr>
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<td>1:3</td>
<td>80</td>
<td>18</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>1:3</td>
<td>50</td>
<td>18</td>
<td>&gt; 99</td>
<td>75</td>
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<td>18</td>
<td>&gt; 99</td>
<td>72</td>
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<td>8</td>
<td>1:2</td>
<td>50</td>
<td>2</td>
<td>&gt; 99</td>
<td>72</td>
</tr>
<tr>
<td>9&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1:2</td>
<td>50</td>
<td>18</td>
<td>40</td>
<td>nd</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: RuCl₃·nH₂O (0.0175 mmol), diyne 17 (0.35 mmol), alkyne 51 (0.7 mmol) were heated in a screw-capped tube under free-solvent conditions and argon atmosphere. <sup>b</sup>Determined by ¹H NMR. <sup>c</sup>Isolated yields. <sup>d</sup>2 mol % RuCl₃·nH₂O (0.007 mmol) was used. <sup>e</sup>Under air atmosphere.

To investigate the synthetic utility of this catalytic method, the reaction was performed on one gram-scale under optimized conditions. Fluorenone 65 was efficiently isolated in 71% yield (Scheme 94).
Having established a set of optimal conditions, we examined the scope and limitations of the solvent-free RuCl$_3$·$n$H$_2$O-catalyzed [2+2+2] cycloaddition between diynes 18-27 and alkyne 51, as shown in Scheme 95. Initially, we observed that diyne 18 having two identical alkyl substituents at the C1 and C7 positions was less reactive compared to the unsymmetrical substituted diynes having a phenyl group at C7 position, the corresponding product 66 was obtained in 38% yield. The use of diyne 19 gave the desired product 67 in 43% yield. This result suggested that the unsymmetrical substituted diynes having a phenyl group at C7 positions was necessary. On the other hand, the reaction of diyne 20 with a cyclopropyl moiety delivered the cyclic product 68 in 63% yield. Interestingly, the cyclization of silyl-substituted diyne 21 with alkyne 51 provided the desired compounds 69 with 58% yield, which was used for further functionalization. Further experiments showed that diynes 22, 23, 26 and 27, having electron-donating or electron-withdrawing substituent on para position of phenyl ring at C7 could be successfully used in this reaction, leading to the targeted products 70-73 in 56-71% yields. To evaluate the influence of the tethered phenyl group, cycloaddition using diynes 24 and 25, bearing electron-donating or electron-withdrawing group, were accomplished smoothly to yield the desired products 74 and 75 in similar yields (68% and 65%, respectively). It is worth mentioning that these reactions were based on complete conversion even at elevated temperatures or prolonged reaction times.
To further investigate the generality of the [2+2+2] cyclization, the reactivity of various alkynes was examined (Scheme 96). Switching the methyl group to a bulkier group, such as tert-butyl and benzyl, allowed to access the corresponding functionalized fluorenones 76 and 77 in 80% and 81% yields, respectively. The structure of fluorenone 77 was unambiguously confirmed by single crystal X-ray diffraction as shown in Scheme 96. Furthermore, when the cycloaddition of diyne 17 with 3-hexyne 53 was carried out under the same conditions, cycloadduct 78 was obtained in 11% isolated yield. However, we did not observe the cyclized products 79 and 80 when the alkynes 54 and 57 were used in the reactions, these results could be explained by the steric effects and poor reactivity of these alkynes.
During our ongoing investigation on the scope of different substituted diynes and alkynes, we found that the reaction of diyne 8 with alkyne 51 did not afford cyclic product 81, most of starting material being decomposed under the reaction conditions (Eq. a, Scheme 97). To further evaluate the influence of free hydroxyl substituent, the reaction of diyne 17 with 2-butyne-1,4-diol 51 was studied. Unfortunately, we did not observe any desired product 82 (Eq. b, Scheme 97). This result suggested that free hydroxyl groups from both diyne or monoalkyne would greatly influence the formation of cycloadduct in this reaction.
Once the heteroaromatic carbonyl bridged diyne 44-50 were obtained, we examined their partially intramolecular [2+2+2] cycloaddition to provide the corresponding hetero-based fluorenones. A series of hetero-aromatic tethered diyynes has been studied.

First, the cycloaddition of furan-bridged diyne 44 with alkyne 51 in the presence of RuCl₃·nH₂O under the optimal conditions delivered the corresponding benzo[b]furanones 83 in 55% yield. Then, the thienyl-based fluorenones 84 and 85 were obtained in 71% and 62% isolated yields, respectively. Moreover, the cyclization of diyne 46, having a benzo[b]thiophene moiety as tether, produced the expected fused fluorenone 86 in 78% yield. When diyne 47 was used in the cycloaddition, the corresponding cyclic product 87 was obtained in 30% yield (Scheme 98).
On the other hand, it was found that the use of diyne 49 only gave the corresponding cycloadduct 89 in 6% yield, while cyclization of diyne 48 with alkyne 51 did not provide cyclized product 88. To explain these results, we speculate that the position of the nitrogen atom in pyridine would influence the course of the reaction toward the formation of an unactivated intermediate where the ruthenium is coordinated to the nitrogen atom. This could be confirmed by the preparation of aza-fluorenone 90, starting from the pyridine tethered diynes 50 and alkyne 51, 60% yield was obtained and a chlorine atom was compatible with this reaction. (Scheme 99).
4.5 Regioselective RuCl₃·nH₂O-mediated [2+2+2] cycloaddition of benzoyl bridged α,ω-diynes with unsymmetrical terminal and internal alkynes

The cycloaddition reaction was not limited to symmetrical internal alkynes, since a series of unsymmetrical terminal alkynes, such as cyclopropylacetylene 58, phenylacetylene 59, and 5-chloro-1-pentyne 60, were successfully reacted with phenylcarbamoyl bridged diyne 17 under optimized reaction conditions. The [2+2+2] cycloaddition reactions led to unseparable mixtures of regioisomers 91, 92, and 93 in 61–84% yields with regioselectivities from 55:45 to 73:27 ratio (Scheme 100).
Next, we turned our attention to the examination of unsymmetrical internal alkynes. Unfortunately, cycloaddition of methyl 3-phenylpropiolate 61, methyl 2-butynoate 62, phenylpropargyl aldehyde diethyl acetal 63, and 4-(3-phenylprop-2-yn-1-yl)-morpholine 64 failed to afford the desired fluorenone products (Scheme 101). Only degradation of starting diynes was observed. The control of the regioselectivity is therefore still a challenge for RuCl₃·nH₂O-catalyzed [2+2+2] cycloaddition of diynes with unsymmetrical alkynes.

4.6 Post-functionalization of fluorenone derivatives

With a set of substituted fluorenone derivatives in hand, we then turned our attention toward the investigation of post-functionalization reactions of fluorenone derivatives, including compounds 65 and 76, silylated derivative 69 and bromo-functionalized adduct 73.

First, we focused on the functionalization of cycloadducts 65 and 76, as shown in Scheme 102. When the dimethyl ether substituted fluorenone 65 was refluxed in the presence of concentrated trifluoroacetic acid, the reaction did not lead to the expected deprotected diol...
Chapter II

95: the substituted cyclized product dihydrobenzo[b]furan 94 was isolated as the main product in 85% yield. To achieve the deprotection of di-tert-butyl ether substituted fluorenone 76, the latter was subjected to classical deprotection conditions, yielding 75% of diol 95. On the other hand, the direct dibromination of compound 76 in the presence of refluxing mixture of HBr and Bu4NBr in chloroform provided the dibrominated 96 in 90% yield. The diol and dibrominated products were reported as key building blocks for the synthesis of OLEDs materials.59d

Scheme 102

The silyl-based fluorenone adduct 69 has been considered as a suitable substrate, since the reactivity of the substituted silyl group is expected to enable functionalization reactions, such as iodination reaction.104 The iodinated product could further allow the introduction of a variety of substituents using metal-catalyzed cross-coupling reactions.105 Starting from compound 69, the iodination by means of iodine monochloride afforded the iodinated product 97 in 84% yield. Consequently, a single Sonogashira cross-coupling reaction of compound 97 with phenylacetylene led to the desired alkyne 98 in 98% yield. Additionally, adduct 97 was

subjected to Suzuki-Miyaura cross-coupling reaction, leading to boronic ester 99 in 65% yield (scheme 103).

\[
\begin{align*}
\text{ICl} & \quad \text{1.05 equiv} \\
\text{DCM} & \quad \text{-78 °C, 30 min} \\
84\% \\
\end{align*}
\]

Scheme 103

To extend the applications of the functionalized fluorenones, additional Suzuki-Miyaura cross-coupling reaction was performed with bromo-substituted fluorenone 73. Boronic ester derivative 100 was obtained in 85% yield (Scheme 104).

\[
\begin{align*}
\text{Scheme 104}
\end{align*}
\]
5. Conclusion

In summary, we have developed a novel and eco-friendly straightforward access to highly substituted fluorenones and related analogues using RuCl$_3$·nH$_2$O-promoted partially intramolecular [2+2+2] cycloaddition of carbonyl bridged $\alpha,\omega$-diynes with alkynes. This economical process was performed without solvent, additional ligands or additives, and allowed the construction of complex polycyclic fluorenones, aza-fluorenones, benzo[b]furanones and indenothiophenones. This protocol offers several advantages: i) the stability and cost-effective RuCl$_3$·nH$_2$O used as catalyst, ii) prevention of pollution with no elimination of toxic or volatile solvents, iii) practical protocol without work up to access the targeted products.

A wide range of carbonyl bridged $\alpha,\omega$-diynes and alkynes containing different substituents was evaluated in this reaction. Unsymmetrical diynes bearing alkyl and phenyl substituents proved to be more active in the ruthenium-catalyzed [2+2+2] cycloaddition reaction. Both electron-donating and electron-withdrawing substituents on the phenyl ring and tether phenyl ring were tolerated in this reaction. Furthermore, heteroarene tethered carbonyl diynes, such as furanyl-, thienyl- and aza-based moieties, have been shown to be active in this cyclization and their cycloaddition proceeded efficiently to give the expected cycloadducts in 30-78\% yields. With regards to the scope of the alkynes, a wide range of substituted alkynes has been used for the [2+2+2] cycloaddition. It was found that symmetrical dialkoxy-substituted alkynes, such as methoxy, benzyloxy and tert-butoxy, could be engaged in the cyclization to deliver the desired product in 6-81\% yields. Unsymmetrical terminal alkynes also converted well to the expected cycloadducts, although 55:45 to73:27 regioselectivities were obtained.
Chapter III: Ruthenium-catalyzed [2+2+2] cycloaddition of diynes with electron-rich cyanamides: an easy access to 2-aminopyridine derivatives
Chapter III: Ruthenium-catalyzed [2+2+2] cycloaddition of diynes with electron-rich cyanamides: an easy access to 2-aminopyridine derivatives

1. Interest of 2-Aminopyridines

A recent report demonstrated that pyridine is the second most commonly used nitrogen heterocycle among all U.S. FDA approved pharmaceuticals (Figure 2). As analogues of pyridines, 2-aminopyridines represent one of the most important skeleton motifs which are widely present in many biologically active molecules as well as pharmaceuticals.

Figure 2

Chapter III

Compounds containing 2-aminopyridine ring scaffold exhibit an array of pharmacological properties such as antimicrobial,\textsuperscript{107} anti-inflammatory,\textsuperscript{108} anti-prion,\textsuperscript{109} anti-HBV,\textsuperscript{110} antithrombotic,\textsuperscript{111} antineoplastic,\textsuperscript{112} and antitumoral.\textsuperscript{113} Particularly, morpholine derived pyranopyridines (MBX2319) A is active against Gram-negative bacteria;\textsuperscript{107} piperazine derived pyranopyridine B is used as IDH1 mutants inhibitor for the treatment of cancer;\textsuperscript{113d} ethyl 6-aminonicotinate acyl sulfonamide C is potent antagonist of the P2Y\textsubscript{12} receptor;\textsuperscript{111} heterocycle D which exhibits potent γ-secretase modulator activity is expected for the treatment of Alzheimer’s disease;\textsuperscript{114} Crizotinib E is a commercially available anti-cancer drug, which has been approved for the treatment of lung cancer,\textsuperscript{113a-113c} α-carboline derivative (TAK-901) F is potent Aurora B kinase inhibitor with antineoplastic activity\textsuperscript{112a} (Scheme 105).

In addition to bioactive compounds, 2-aminopyridines are also synthetically useful compounds present in organometallic and material chemistry. The L-amino acid containing a 2-aminopyridine moiety G was used as highly efficient bidentate ligand for direct asymmetric


aldol reaction.\textsuperscript{115} Pyrido[2,3-\textit{b}]azepine \textbf{H}, a pH sensitive fluorescence dye, can be an ideal candidate for fluorescence label\textsuperscript{116} (Scheme 105).

\textbf{Scheme 105}

Amino-aza-fluorenones, containing 2-aminopyridine structural motif, have received increasing interest in recent years. Many of the synthetic and natural amino-aza-fluorenones displayed interesting properties and are present in a variety of pharmacophores\textsuperscript{117} and chromophores.\textsuperscript{118} As depicted in Scheme 106, 2-azafluorenone \textbf{I} is an antagonist of the

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Chapter III

Adenosine A2a receptor\textsuperscript{117a} piperazinyl derived compound J which exhibits inhibitory effect on topoisomerase I would be a potent anti-breast cancer candidate;\textsuperscript{117b} 2-azafluorenone K with typical aggregation-induced emission (AIE) properties can be used for lipid droplet-specific live cell imaging.\textsuperscript{118b}

\begin{center}
\begin{tabular}{c}
\includegraphics[width=0.3\textwidth]{figure1.png}
\end{tabular}
\end{center}

\textbf{Scheme 106}

2. Synthetic methods for the preparation of 2-aminopyridines

2.1 Traditional methods

The preparation of 2-aminopyridines has been reported with numerous strategies. For example, Chichibabin reactions start from pyridine and sodium amide,\textsuperscript{119} Buchwald-Hartwig amination\textsuperscript{120} and Ullmann coupling reactions\textsuperscript{121} of halopyridines with primary or secondary amines, one-pot three-component cascade reaction\textsuperscript{116} using N-tosyl propargyl amines, aryl halides, and N,S-ketene acetics, formal [2+2+1+1] cycloaddition reaction\textsuperscript{122} of aldehydes with ketones, and malononitrile (Scheme 107). However, these methods were efficient to access simple 2-aminopyridines, but for more complex substitution patterns, additional synthetic


manipulations were required. In addition, these reactions suffered more or less from some shortcomings such as harsh reaction conditions, multistep procedures, limited functionalities tolerance, etc.

Scheme 107

2.2 Transition-metal-catalyzed [2+2+2] cycloadditions of alkynes with cyanamides

Cyanamide derivatives moiety are widely present in pharmaceutical molecules and bioactive compounds.\(^\text{123}\) Owing to the high reactivity of the electron-rich nitrile triple bonds, bearing an amine group at the \(\alpha\)-position of nitrile (R\(_2\)N-CN), these privileged structures serve as versatile building blocks and have been widely used for the synthesis of various nitrogen-containing heterocycles,\(^\text{124}\) as shown in Scheme 108.

---


Particularly, cyanamides also proved to be good partners for the transition-metal-catalyzed [2+2+2] cycloaddition which has been reported as a powerful and atom-economical method for the construction of highly substituted 2-aminopyridines. The following discussion will focus on the [2+2+2] cycloaddition reactions involving the most common used cobalt, rhodium, nickel, iron, iridium and ruthenium complexes.

2.2.1. Cobalt-catalyzed [2+2+2] cycloadditions

In 1984, Bönnemann and co-workers disclosed the first cobalt-catalyzed [2+2+2] cycloaddition of acetylene and cyanamide to form 2-aminopyridine containing a free amino group using (η⁶-boranato) cobalt as catalyst. The reaction was successfully performed at 130 °C under 40 bar to afford 2-aminopyridine in 54% yield (Scheme 109).

\[
\text{Co cat. 0.47 mol %} \quad \text{DMF, 130 °C, 40 bar} \quad 54\%
\]

Scheme 109

---

After the pioneer work reported by Bönnemann, Heller and co-workers described the co-trimerization of acetylene with dimethyl-, pyrrolidinyl-, piperidinyl-substituted cyanamides in the presence of CpCo(cod) catalyst under photo-irradiation conditions at room temperature (Scheme 110). The reaction afforded the corresponding 2-aminopyridines respectively in 46%, 68%, and 75% yields. Notably, in this case, the acetylene gas was delivered at constant normal pressure.

**Scheme 110**

In 2000, Eaton and co-workers reported one example of cyclotrimerization of 2-butynediol with N-cyanopyrrolidine to afford a highly functionalized pyridine in 71% yield. This reaction presented many advantages including the use of a water-soluble cobalt(I) complex as catalyst, without the need of photochemical activation, only a stoichiometric amount of nitrile (alkyne:nitrile = 2:1) was required (Scheme 111).

**Scheme 111**

In 2004, Maryanoff’s group described the preparation of bicyclic 2-aminopyridine derivatives starting from α,ω-diynes and cyanamides. A variety of diynes and N-substituted cyanamides underwent cycloadditions in the presence of 15 mol % of CpCo(CO)$_2$ catalyst in

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refluxing dioxane, providing the corresponding bicyclic 2-aminopyridines in a range of 16% to 88% yield. Cyanamides disubstituted with alkyl, allyl, and aryl groups furnished the annulated compounds in 19-88% yields. The cyanamides possessing a large dibenzazepinyl group showed lower reactivity, and gave the cycloadduct in 19% yield. The cycloaddition of a bulky adamantyl-substituted cyanamide led to the corresponding 2-aminopyridine with a secondary amine group in 32% yield (Scheme 112).

\[
\text{X} = \text{C}(\text{CO}_2\text{OMe})_2, \text{CH}_2, (\text{CH}_2)_2, \text{O}.
\]

\[
\text{R}^1 = \text{H}, \text{Et}, \text{nBu}, \text{Ph}
\]

\[
\text{R}^2 = \text{H}, \text{Et}
\]

Selected examples:

<table>
<thead>
<tr>
<th>R^1</th>
<th>R^2</th>
<th>R^3</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>CN</td>
<td></td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>CN</td>
<td></td>
<td>88%</td>
</tr>
<tr>
<td></td>
<td>CN</td>
<td></td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td>CN</td>
<td></td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>CN</td>
<td></td>
<td>29%</td>
</tr>
<tr>
<td>N</td>
<td>CN</td>
<td></td>
<td>66%</td>
</tr>
<tr>
<td>N</td>
<td>CN</td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>CN</td>
<td></td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>NH</td>
<td></td>
<td>32%</td>
</tr>
</tbody>
</table>

**Scheme 112**

The same group also investigated in 2005 the formation of macrocycles from long-chain diynes and cyanamides in cobalt-mediated [2+2+2] cycloaddition reactions.\(^{129}\) The reaction of 1,15-diynes with cyanamides provided mainly the corresponding 16-membered para-pyridinophanes in 32-80% yields, whereas the reaction of 1,17-diyne furnished a mixture of both 17-membered meta- and 18-membered para-pyridinophanes in 64% yield. These results indicated that the regioselectivity of the reactions was affected by the length and the type of linker unit between the alkyne groups (Scheme 113).

In 2007, Maryanoff and co-workers applied this method employing CpCo(CO)$_2$ catalyst system for the synthesis of macrocyclic (17-20 members) bis(indolyl)maleimide pyridinophanes, although lower isolated yields (9-15%) were observed (Scheme 114). The biological results indicated that these macrocyclic heterophanes were potent and selective inhibitors of glycogen synthase kinase-3β.\textsuperscript{130}

One example of the synthesis of axially chiral biaryl containing 2-aminopyridine moiety was achieved.\textsuperscript{131} The use of chiral cobalt(I) catalyst for the enantioselective [2+2+2] cycloaddition of naphthyl-substituted 1,7-diyne with \textit{N}-cyanopiperidine gave the expected biaryl cycloadduct in 89% yield with 87% enantioselectivity (Scheme 115).

\begin{center}
\textbf{Scheme 115}
\end{center}

A quick access to allocolchicine analogues was developed by Schmalz and Nicolaus.\textsuperscript{132} In the presence of 20 mol \% CpCo(CO)\textsubscript{2} under microwave conditions at 150 °C, the 3,4,5-trimethoxybenzaldehyde and 3,4,5-trimethoxyacetophenone derived diyne reacted with morpholine-4-carbonitride to generate the desired products in a short reaction time with 27\% and 35\% yields, and regioselectivities up to >99:1 were obtained (Scheme 116).

\begin{center}
\textbf{Scheme 116}
\end{center}

Malacria, Aubert, Gandon and co-workers reported the CpCo(CO)(dmfu) complex-catalyzed [2+2+2] cycloaddition of yne-ynamides with cyanamides to provide 2,5-


\textsuperscript{132} Nicolaus, N.; Schmalz, H.-G. \textit{Synlett} \textbf{2010}, 2071.
diaminopyridine derivatives.\textsuperscript{133} Five-, six-, and seven-membered bicyclic compounds were synthesized in 20-85% yields with perfect regioselectivities (Scheme 117).

![Scheme 117](image)

**Scheme 117**

### 2.2.2. Rhodium-catalyzed [2+2+2] cycloadditions

As described in the first chapter, the cationic rhodium/bisphosphine complex is an efficient catalyst for [2+2+2] cycloaddition reactions (Schemes 24 and 25). However, only a single example was described for the synthesis of annulated 2-aminopyridine via a Rh(I)/H\textsubscript{8}-BINAP-catalyzed [2+2+2] cycloaddition of malonate-tethered diyne with morpholine-4-carbonitrile. The corresponding cycloadduct was obtained in 47% yield (Scheme 118).\textsuperscript{134}

![Scheme 118](image)

**Scheme 118**

\textsuperscript{133} (a) Garcia, P.; Evanno, Y.; George, P.; Sevrin, M.; Ricci, G.; Malacria, M.; Aubert, C.; Gandon, V. *Org. Lett.* \textbf{2011}, \textit{13}, 2030. (b) Garcia, P.; Evanno, Y.; George, P.; Sevrin, M.; Ricci, G.; Malacria, M.; Aubert, C.; Gandon, V. *Chem. - Eur. J.* \textbf{2012}, \textit{18}, 4337.

2.2.3. Nickel-catalyzed [2+2+2] cycloadditions

Louie and co-workers reported the nickel-catalyzed [2+2+2] cycloaddition of α,ω-diynes with cyanamides to form 2-aminopyridines.\textsuperscript{135} A variety of diynes reacted with different substituted cyanamides in the presence of Ni(cod)\textsubscript{2} catalyst in combination with a N-heterocyclic carbene (NHC) at room temperature. Various 2-aminopyridines were successfully obtained in 76-99% yields (Scheme 119). However, the nickel catalyst and NHC ligands required a pre-treatment in a glove box for at least 4 hours before introducing the two reactants.

![Scheme 119](image)

This Ni/NHC catalytic system was also applied for the totally intermolecular cyclotrimerization of two alkynes with cyanamides.\textsuperscript{136} Treatment of terminal alkynes and cyanamides with Ni(cod)\textsubscript{2}/SIPr (1:2) complex catalyst in toluene at room temperature for 4 h, provided the 3,5-disubstituted-2-aminopyridines as the major products (Scheme 120). However, this protocol was limited to the use of alkyl-alkynes, whereas the reaction of aryl-, ester-, or chloride-substituted alkynes failed to afford the desired 2-aminopyridines.


The same group also disclosed in 2011 the Ni/Xantphos-mediated cycloaddition of 1,6- and 2,7-diynes with $N$-cyanopyrrolidine, $N$-cyanomorpholine, $N,N$-diallylcyanamide at room temperature to access 6,6-fused cycloadducts in >99%, 75%, and 76% yields. Interestingly, unsymmetrical 1,6-diynes reacted with $N,N$-dimethylcyanamide leading to the formation of meta-substituted product as a single regioisomer. This result could be explained as follow: the reaction proceeded via the initial regioselective oxidative coupling to form azametallacycle followed by the intramolecular insertion of the less-sterically demanding terminal alkyne (Scheme 121).

Scheme 120

Scheme 121

Liu and co-workers successfully developed in 2017 the synthesis of α-carbolines via nickel-catalyzed [2+2+2] cycloaddition of functionalized alkyne-cyanamides with alkynes.\(^{138}\) Both internal and terminal alkynes successfully reacted with aryl- or alkyl substituted alkyne-cyanamides in the presence of NiCl\(_2\)(DME)/dppp/Zn catalytic system to provide α-carboline derivatives in 67-81% yields with moderate regioselectivities (Scheme 122). Interestingly, when phenyl- and TMS-substituted acetylenes were employed as the alkyne partners, the reaction resulted in the opposite regioselective formation of the cycloadduct, probably because of the difference of electronic effects between the two terminal alkynes.

\[
\begin{align*}
\text{NiCl}_2(\text{DME}) & \text{ 10 mol \%} \\
d\text{ppp} & \text{ 10 mol \%} \\
\text{Zn} & \text{ 1 equiv}
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 & = n\text{Bu, Ph} \\
\text{R}^2 & = H, \text{ Et, SiMe}_3 \\
\text{R}^3 & = H, \text{ Ph}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \text{ N - Et} \\
n\text{Bu} & \text{ N - Et} \\
\text{Ph} & \text{ N - Ph} \\
\text{Ph} & \text{ N - TMS}
\end{align*}
\]

\[
\begin{align*}
81\% & \\
81\% & \\
67\% (3:9:1) & \\
75\% (3:9:1)
\end{align*}
\]

\textbf{Scheme 122}

\textbf{2.2.4. Iron-catalyzed [2+2+2] cycloadditions}

Iron, the earth abundant and low cost metal, has rarely been used for the pyridines synthesis via [2+2+2] cycloadditions.\(^{139}\) Louie’s group described in 2012 the iron-catalyzed [2+2+2] cycloaddition of diynes with electron-rich cyanamides to form highly substituted 2-aminopyridines.\(^{140}\) The reaction proceeded in the presence of 5 mol % FeCl\(_2\) in combination with 10 mol % Mes-PDAI and Zn dust in benzene at 70 °C, various 2-aminopyridines were synthesized in 35-97% yields. The group of Wan reported in 2013 a similar work by using FeI\(_3\)/dppp/Zn catalytic system.\(^{141}\) Several examples have been described in 40-99% yields.


When comparing these works, Wan’s group used less toxic THF as solvent instead of benzene, and lower reaction temperature (Scheme 123). However, both conditions suffered from the moisture-sensitive iron salts as well as a slow-addition technique which was required in Louie’s work.

**Scheme 123**

With regard to the regioselectivity, the two reactions gave rise to an opposite selectivity of the regioisomers. In the case of Louie’s conditions, the reaction provided the sterically less demanding compound as the major product whereas the small substituent was placed in ortho to the nitrile substituent. In the case of Wan’s conditions, the regioselectivity trends led to the 2-aminopyridines with the small substituent placed in ortho to the nitrogen atom in the pyridine ring (Scheme 124). These two iron systems suggested that the regioselectivity may be controlled by the choice of the ligand.
Furthermore, Louie and co-workers also reported the totally intermolecular iron-catalyzed [2+2+2] cycloaddition of two alkynes with cyanamides. In contrast to the Ni(cod)$_2$/SIPr system (Scheme 120), in this case, the 2,4-disubstituted-2-aminopyridines were formed as major products with complete regioselectivity (Scheme 125).

**Scheme 124**

**2.2.5. Iridium-catalyzed [2+2+2] cycloadditions**

In 2015, Takeuchi and co-workers developed an efficient [Ir(cod)Cl]$_2$/dppf or BINAP catalyst system that was able to promote the [2+2+2] cycloaddition of α,ω-diynes and cyanamides in refluxing benzene. A wide range of secondary amines derived cyanamides was tolerated under these reaction conditions. Several examples have been studied by using

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symmetrical diynes with cyanamides to provide various 2-aminopyridines in 31-99% yields (Scheme 126). However, toxic and refluxing benzene was used as solvent.

Scheme 126

For the regioselectivity, as shown in Scheme 127, the methyl-/phenyl- or methyl-/2-pyridyl-substituted diynes reacted with N-cyanomorpholine, leading to the formation of less hindered product as a single product in which the phenyl and pyridyl groups were substituted at the \( \alpha \)-position. Interestingly, the methyl/TMS-substituted diyne underwent cycloaddition reaction and gave exclusively the more sterically hindered product in which the TMS group was substituted at the \( \beta \)-position. The authors therefore demonstrated that the regioselectivity was mainly controlled by the electronic effect of the substituent on the terminus of alkynes.

Scheme 127
Chapter III

2.2.6. Ruthenium-catalyzed [2+2+2] cycloadditions

During the publication process of our work, Goswami’s group reported a ruthenium-catalyzed [2+2+2] cycloaddition of N-cyanoindoles with α,ω-diynes to provide 1-(2-pyridyl)indole derivatives. In this work, the reaction was performed under solvent-free or with small amount of EtOH conditions with Cp*Ru(cod)Cl catalyst for a short reaction time, providing the desired product in 86-93% yields. Three examples have been studied using monosubstituted unsymmetrical oxygen tethered diynes to evaluate the regioselectivity. The less sterically hindered products were obtained as a single regioisomer in 86-89% yields (Scheme 128). However, the scope of diynes and cyanamides were limited to eight diynes and three 3-carbonyl indoles derived cyanamides.

![Scheme 128](image)

3. Objectives

Ruthenium complexes have been reported as highly efficient catalysts for the cycloaddition of α,ω-diynes with activated nitriles, such as electron-deficient nitriles, dicyanides, and α-halogen nitriles. However, there was no ruthenium-catalyzed synthesis of

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functionalized pyridines with electron-rich nitriles such as cyanamides that have been reported when we started this project (Scheme 129).

Scheme 129

Considering the rare reports on the transition-metal-catalyzed [2+2+2] cycloadditions of alkynes with cyanamides to access 2-aminopyridines, as well as the limitations of current methodologies, we decided to investigate the ruthenium-catalyzed [2+2+2] cycloaddition reaction to access highly substituted 2-aminopyridines and its derivatives.

4. Results and discussion

4.1 Synthesis of starting materials: diynes and cyanamides

We first decided to study the partially intramolecular [2+2+2] cycloadditions to access 2-aminopyridine derivatives using $\alpha,\omega$-diynes and cyanamides. Most of the starting diynes and cyanamides were not commercially available and were synthesized.

4.1.1. Synthesis of symmetrical diynes

Firstly, a series of symmetrical internal and terminal $\alpha,\omega$-diynes were prepared, as shown in Scheme 130. The diynes 101-110 and 121-124 were synthesized in accordance with the literature.\(^\text{145}\) Diynes 111-120 were produced based on laboratory’s work.

Diynes 101-103, 107, 109 and 123 were prepared through the nucleophilic substitution reaction of commercially available dimethyl malonate, 1,3-dimethylbarbituric acid, 2-butyne-1-ol, indene dione, and N-Boc-protected propargyl amine with 1.2-2.4 equivalents of propargyl bromide or 1-bromo-2-butyne in THF. The reaction used 1.5-2.4 equivalents of sodium hydride as base to afford the desired diynes in a range of 62-96% yields (Scheme 131). Notably, 1,3-dimethylbarbituric acid derived diyne 102 was a new substrate.
Treatment of diyne 101 with 6 equivalents of LiAlH₄ in THF solution afforded the diol-diyne 104 in 95% yield. The two hydroxyl groups of diyne 104 could be easily protected with acetyl and benzyl groups under basic conditions. In the presence of 4.4 equivalents of diisopropylethylamine in DCM, diyne 104 reacted with acetic anhydride to afford diacetyl-functionalized diyne 105 in 92% yield. The nucleophilic substitution of diol 105 with benzyl bromide using 2.5 equivalents of sodium hydride as base with 25 mol % n-tetrabutylammonium iodide as additive, gave dibenzyl protected diyne 106 in quantitative yield (Scheme 132).

The reaction of diol 120, in the presence of 2 equivalents of phosphorus pentoxide in dry acetone at room temperature, allowed a rapid access to diyne 121 in 80% isolated yield (Scheme 133).
Chapter III

The synthesis of nitrogen-tethered diynes 108 and 122 was based on the nucleophilic substitution of p-toluenesulfonamide with 1-bromo-2-butyne or propargyl bromide using 5 equivalents of potassium carbonate as base. The desired products could be easily synthesized in 70% and 91% yields, respectively (Scheme 134).

Scheme 134

The malonate derived diynes 110 and 124, bearing two functional groups on the terminal position of α,ω-diyn, have been synthesized (Scheme 135). Diyne 109 was treated with 2.2 equivalents of lithium bis(trimethylsilyl)amide in anhydrous THF at -78 °C, followed by the addition of an excess of trimethylsilyl chloride at the same temperature. After stirring for additional 1 h at room temperature, the reaction provided the disubstituted internal alkyne 110 in 45% yield (Eq. a). The low yield could be explained by the low reactivity of the terminal position of the alkyne as well as the formation of the monosubstituted side product. Dibromo-substituted diyne 124 was prepared through a classical bromination reaction using diyne 109 and NBS, in 98% yield (Eq. b).

Scheme 135
4.1.2. Synthesis of unsymmetrical diynes

To study the regioselective [2+2+2] cycloaddition reactions, we synthesized several unsymmetrical 1,6-, 1,7- and 1,8-diynes, as depicted in Scheme 136.

![Scheme 136](image)

The preparation of monosubstituted unsymmetrical diyne 125 started from malonate by stepwise alkylation reactions to introduce the internal and terminal alkyne motifs. Finally, the desired product was successfully isolated in 50% yield over two steps (Scheme 137).

![Scheme 137](image)

Compounds 138, 142, and 143 were prepared via nucleophilic substitution reactions. Starting from commercially available alcohols 3-butyn-1-ol, 4-pentyn-1-ol and Mestranol, the
oxygen tethered 1,6- 143, 1,7- 138 and 1,8-diynes 142 were respectively synthesized in 36%, 75%, and 79% yields (Scheme 138).

**Scheme 138**

To prepare the unsymmetrical oxygen tethered diynes 127, 131 and 140 containing a propargyl motif, the nucleophilic substitution reaction was performed using potassium hydroxide as the base in a mixed solution of water and DMSO, affording 127, 131 and 140 in respectively 79%, 50%, and 84% yields (Scheme 139).

**Scheme 139**

Upon treatment with $N$-bromosuccinimide (NBS) in the presence of 10 mol % AgNO$_3$ in dry acetone at room temperature, the corresponding terminal alkynes were converted to bromo-substituted diynes 129, 130, 132 and 141 in 65-98% yields. The iodo-substituted diyne 133 was prepared via the silver-catalyzed C$_{sp}$-H halogenation reaction using 10 mol % AgNO$_3$ in $N,N$-dimethylformamide (DMF), with 98% yield. In addition, starting from propargyl alcohol, the useful intermediate bromo-substituted propargyl alcohol 145 was prepared in 65% yield (Scheme 140).
The diyne 134 containing an ynamide moiety was obtained using a copper-catalyzed aerobic oxidative coupling reaction\textsuperscript{146} of terminal alkyne 127 with 2-oxazolidinone. The reaction proceeded efficiently in the presence of 20 mol % CuCl\textsubscript{2} and 2 equivalents of Na\textsubscript{2}CO\textsubscript{3} and pyridine under 1 atm of O\textsubscript{2}, providing the corresponding ynamide in 60\% yield (Scheme 141).

\begin{scheme}
\textbf{Scheme 140}

\begin{center}
\begin{tikzpicture}

\node (a) at (0,0) {\text{MeO}_2\text{C}};
\node (b) at (2,0) {\text{MeO}_2\text{C}};
\node[circle,fill,inner sep=1pt] (c) at (1,0) {};
\node (d) at (0,1) {\text{Me}};
\node (e) at (2,1) {\text{Me}};
\node (f) at (1,1) {};
\node (g) at (0,2) {\text{Br}};
\node (h) at (2,2) {\text{Br}};
\node (i) at (1,2) {};
\node (j) at (0,3) {129, 98\%};
\node (k) at (2,3) {130, 97\%};
\node (l) at (1,3) {132, 96\%};
\node (m) at (0,4) {MeO2C}
\node (n) at (2,4) {MeO2C}
\node (o) at (1,4) {MeO2C}
\node (p) at (0,5) {125, 127, 128, 140}
\node (q) at (2,5) {NXS}
\node (r) at (1,5) {131}
\node (s) at (0,6) {AgNO\textsubscript{3} 10 mol \%}
\node (t) at (2,6) {dry Acetone, rt, 3 h}
\node (u) at (1,6) {129, 130, 132, 133, 141, 145}
\node (v) at (0,7) {R=---X (X = Br or I)}
\node (w) at (2,7) {R=---X}
\node (x) at (1,7) {133, 98\%}
\node (y) at (0,8) {MeO2C}
\node (z) at (2,8) {MeO2C}
\node (aa) at (1,8) {MeO2C}
\node (bb) at (0,9) {141, 75\%}
\node (cc) at (2,9) {114, 65\%}
\node (dd) at (1,9) {145}
\end{tikzpicture}
\end{center}

\textbf{Scheme 141}

To study the tolerance ability of the [2+2+2] cycloaddition reactions, other examples were evaluated. For this purpose, the synthesis of diyne 135 containing a vinyl group was envisaged. Starting from dimethyl malonate, a mono-alkylation with 0.85 equivalents of propargyl bromide followed by a Sonogashira cross-coupling reaction with 1.2 equivalents vinyl bromide provided the malonate-derived enyne 147. Subsequent nucleophilic substitution of the latter with 1.2 equivalents propargyl bromide in the presence of sodium hydride afforded the desired diyne 135 (Scheme 142).

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Scheme 142

The unsymmetrical diyne 137 was prepared through a Sonogashira reaction of diyne 125 with 1.2 equivalents of 2-bromopyridine using 2 mol % PdCl$_2$(PPh$_3$)$_2$ and 1 mol % CuI, and was obtained in 60% yield (Scheme 143).

Scheme 143

4.1.3. Synthesis of benzoyl bridged $\alpha,\omega$-diynes

With the aim to synthesize amino-aza-fluorenones, the preparation of benzoyl or benzyl bridged $\alpha,\omega$-diynes 17, 28, 29, 149, 152, and 153 were envisaged, as shown in Scheme 144. The synthesis of diynes 17, 28, and 29 has been described in chapter II. Diynes 149, 152, and 153 were synthesized in accordance with the previously described protocols for diyne 29.

Scheme 144
The preparation of diyne 149 followed a two-steps procedure. The previously prepared monoalkyne 2 was treated with a lithium TMS-acetylide, which was prepared in situ from trimethylsilylacetylene and n-butyllithium, affording the product 148 in 78% yield. The resulting silylated alcohol 148 was subjected to deprotection using 1 equivalent of TBAF. The desired compound 149 was isolated in 81% yield (Scheme 145).

\[
\begin{align*}
\text{CHO} & \quad \xrightarrow{nBuLi, 1.2 \text{ equiv}} \quad \text{CHO} \\
\text{Br} & \quad \xrightarrow{\text{PdCl}_2(\text{PPh}_3)_2, 5 \text{ mol\%}, \text{CuI, 2.5 mol\%}, \text{Cyclopropyl acetylene, 1.2 equiv}} \quad \text{CHO} \\
\text{SiMe}_3 & \quad \xrightarrow{TBAF, 1.0 \text{ equiv}} \quad \text{OH}
\end{align*}
\]

**Scheme 145**

The synthetic methods for preparation of 2, 148, and 149 were used for the preparation of compounds 150-152, as shown in Scheme 146. Finally, treatment of the resulting diyne 152 with 1.2 equivalents of Dess-martin periodinane in dichloromethane solution, furnished the terminal diyne 153 in 82% yield.

\[
\begin{align*}
\text{CHO} & \quad \xrightarrow{\text{PdCl}_2(\text{PPh}_3)_2, 5 \text{ mol\%}, \text{CuI, 2.5 mol\%}, \text{Cyclopropyl acetylene, 1.2 equiv}} \quad \text{CHO} \\
\text{Br} & \quad \xrightarrow{nBuLi, 1.5 \text{ equiv}} \quad \text{CHO} \\
\text{SiMe}_3 & \quad \xrightarrow{TBAF, 1.0 \text{ equiv}} \quad \text{OH}
\end{align*}
\]

**Scheme 146**

4.1.4. Synthesis of cyanamides

Cyanamides 154-167 that were used in this chapter are depicted in Scheme 147. The cyanamides 154-156 and 160 were commercially available. The other different N-substituted
cyanamides 157-159 and 161-167 were prepared according previously reported procedures,\textsuperscript{147} most commonly via the electrophilic $N$-cyanation of amines using cyanogen bromide.

![Chemical structures of cyanamides 154-160 and 161-167](image)

**Scheme 147**

The synthesis of cyanamides 157, 158, and 161-163 was achieved by the $N$-cyanation of piperidine, $N$-methylbenzylamine, $N$-methylaniline, and $n$-butylamine with cyanogen bromide in a mixture solution of diethyl ether and THF (1:1) at 0 °C. Two equivalents of amines were required to promote the reaction furnishing the desired compounds in 82-96% yields. In the case of $n$-butylamine, pure diethyl ether was used as solvent, the reaction was complete in 1 hour (Scheme 148).

![Chemical structures of cyanamides 157, 158, 161-163](image)

**Scheme 148**

Another similar protocol was used for the preparation of cyanamides 159, 164, 166, and 167. Dibenzylamine, diallylamine, $N$-methylpiperazine and $N$-methylbutylamine were treated with cyanogen bromide in a mixture solution of water and dichloromethane (1:1) at 0 °C. In this case, 2 equivalents of sodium bicarbonate were used as the base, with 1.05 equivalents of

\textsuperscript{147}(a) For cyanamide 161-165, see: ref 130a. (b) For cyanamide 159, see: Goldberg, K.; Clarke, D. S.; Scott, J. S. *Tetrahedron Lett.* 2014, 55, 4433.
cyanogen bromide. After 3 hours stirring at room temperature, the reaction afforded the desired products in 86-99% yields. (Scheme 149).

Scheme 149

The cyanamide 164 containing a secondary amine group could easily undergo the acetylation by using 1.2 equivalents of sodium hydride and acetyl chloride to give the acetyl-protected cyanamide 165 in 80% yield (Scheme 150).

Scheme 150

4.2 RuCl$_3$·nH$_2$O-mediated [2+2+2] cycloaddition of $\alpha,\omega$-diynes with cyanamides

With a series of $\alpha,\omega$-diynes and cyanamides in hand, we evaluated the RuCl$_3$·nH$_2$O-mediated [2+2+2] cycloaddition reactions. Based on the previous work, we used 5 mol % RuCl$_3$·nH$_2$O as catalyst to conduct the reaction under solvent-free conditions. Diyne 101 and dimethyl cyanamide 154 were chosen as model substrates to optimize the reaction conditions.

Firstly, we examined the reaction of diyne 101 with a large excess of cyanamide 154 (6 equivalents) in the presence of 5 mol % RuCl$_3$·nH$_2$O at 110 °C affording the highly substituted 2-aminopyridine 168 in 75% yield (Entry 1, Table 2). Subsequently, we decreased the amount of cyanamide from 6 to 3 equivalents. To our delight, the reaction gave almost the same isolated yield of product 168 (Entry 2). Attempt to decrease the catalyst loading to 2 mol % caused a significant decrease of the conversion (50%, Entry 3). We also evaluated the temperature effect
on the reaction. Incomplete conversion of the benzannulation was observed when the reaction was carried out at 80 °C, 50 °C, 90 °C, 100 °C (Entries 4-8). Finally, we found that the diyne 101 was fully converted to pyridine 168 in 74% yield when the amount of cyanamide 154 was further reduced to 2 equivalents (Entry 9).

Table 2 Optimization of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>101/154</th>
<th>T (°C)</th>
<th>Conv. (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:6</td>
<td>110</td>
<td>&gt;99</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>1:3</td>
<td>110</td>
<td>&gt;99</td>
<td>76</td>
</tr>
<tr>
<td>3&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>1:3</td>
<td>110</td>
<td>50</td>
<td>nd</td>
</tr>
<tr>
<td>4</td>
<td>1:3</td>
<td>80</td>
<td>90</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>1:3</td>
<td>50</td>
<td>nr</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td>1:2</td>
<td>80</td>
<td>30</td>
<td>nd</td>
</tr>
<tr>
<td>7&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1:2</td>
<td>90</td>
<td>70</td>
<td>nd</td>
</tr>
<tr>
<td>8&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1:2</td>
<td>100</td>
<td>93</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>1:2</td>
<td>110</td>
<td>&gt;99</td>
<td>74</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: RuCl₃·nH₂O (0.05 mmol), diyne 101 (1.0 mmol), cyanamides 154 (2.0 mmol) were heated in a screw-capped tube under free-solvent conditions and an argon atmosphere. <sup>b</sup> Determined by crude ¹H NMR, nr = no reaction. <sup>c</sup> Isolated yields, nd = not detected. <sup>d</sup> 0.02 mmol of RuCl₃·nH₂O (2 mol %) was used. <sup>e</sup> The reaction was stirred for 24 hours.

With a set of optimized reaction conditions in hand, we next evaluated the reactivity of various secondary or primary amines derived cyanamides 155-163 and 165-167 with diyne 101, as shown in Table 3. We found that the [2+2+2] cycloaddition of diyne 101 with morpholine-functionalized cyanamide 155 furnished the desired pyridine 169 in excellent 95% yield, the reaction being carried out at 80 °C under solvent-free conditions (Entry 1). However, attempts to further decrease the reaction temperature to 70 °C and 60 °C, led to a decreased conversion or no reaction (Entries 2 and 3). Cyclic cyanamides N-cyanopyrrolidine 156 and N-cyanopiperidine 157 successfully reacted with diyne 101 to give the targeted heterocycles 170 and 171 in 86% and 78% yields, respectively (Entries 4 and 5). The N-methylbenzylcyanamide 158 reacted with diyne 101 at 80 °C to provide 2-aminopyridine 172 in 81% yield (Entry 6),
whereas the dibenzyl-substituted cyanamides 159 showed less reactivity than cyanamide 158, despite higher temperature, furnishing the corresponding product 173 in 90% conversion and 75% isolated yield (Entry 7).

**Table 3 Scope of different substituted cyanamides**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyanamides</th>
<th>T (°C)</th>
<th>Product</th>
<th>Conv. (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>155</td>
<td>80</td>
<td>169</td>
<td>&gt;99</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>155</td>
<td>70</td>
<td>169</td>
<td>95</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>156</td>
<td>60</td>
<td>169</td>
<td>nr</td>
<td>nd</td>
</tr>
<tr>
<td>4</td>
<td>157</td>
<td>80</td>
<td>170</td>
<td>96</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>158</td>
<td>110</td>
<td>171</td>
<td>&gt;99</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>159</td>
<td>80</td>
<td>172</td>
<td>&gt;99</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>159</td>
<td>110</td>
<td>173</td>
<td>90</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>160</td>
<td>80</td>
<td>174</td>
<td>26</td>
<td>nd</td>
</tr>
<tr>
<td>9</td>
<td>161</td>
<td>110</td>
<td>175</td>
<td>20</td>
<td>nd</td>
</tr>
<tr>
<td>10</td>
<td>162</td>
<td>80</td>
<td>176</td>
<td>22</td>
<td>nd</td>
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<tr>
<td>11</td>
<td>163</td>
<td>110</td>
<td>177</td>
<td>nr</td>
<td>nd</td>
</tr>
<tr>
<td>12</td>
<td>165</td>
<td>110</td>
<td>178</td>
<td>nr</td>
<td>nd</td>
</tr>
<tr>
<td>13</td>
<td>166</td>
<td>110</td>
<td>179</td>
<td>decomposed</td>
<td>nd</td>
</tr>
<tr>
<td>14</td>
<td>167</td>
<td>110</td>
<td>180</td>
<td>nr</td>
<td>nd</td>
</tr>
</tbody>
</table>

*a Reaction conditions: RuCl₃·nH₂O (0.05 mmol), diyne 101 (1.0 mmol), cyanamides 155-163 and 165-167 (2.0 mmol) were heated in a screw-capped tube under free-solvent conditions and an argon atmosphere. <sup>b</sup>Determined by crude <sup>1</sup>H NMR, nr = no reaction. <sup>c</sup>Isolated yields, nd = not detected.*
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The cyanamides 160-163 and 165-167 seemed incompatible with the RuCl₃·nH₂O-mediated [2+2+2] cycloaddition reaction, despite a higher temperature in some cases. Low conversion of cycloadducts was observed in the case of N,N-diethylcyanamide 160, N,N-dipropylcyanamide 161, and N-methyl-N-phenylcyanamide 162, because of the lower reactivity of the alkyl substituted cyanamides (Entries 8-10, Table 3). The reaction did not occur with both unprotected N-butylcyanamide 163 and acetyl-protected N-butyl-N-cyanoacetamide 165 (Entries 11 and 12). N,N-diallylcyanamide 166, containing two alkenes, was also evaluated and gave decomposed reaction mixtures (Entry 13), which could be explained by the competitive reaction between the activated alkenes and alkynes. N-methylpiperazine-derived cyanamide 167 was also employed but no reaction took place in these conditions (Entry 14).

Having evaluated the reactivity of several cyanamides, we then turned our attention to explore the scope and limitations of the reaction conditions by using the prepared symmetrical diyne 102-113 (Scheme 151), the highest reactive morpholine-4-carbonitrile 155 was chosen as the nitrile partner. The 1,3-dimethylbarbituric acid-derived diyne 102 and indene-1,3-dione-derived diyne 103 were successfully reacted with cyanamide 155 to access functionalized 2-aminopyridines 181 and 182 in good yields. The diyne 104 containing two hydroxyl groups was employed in the reaction, however, only 10% of the expected product 183 was isolated from the crude reaction mixture. Interestingly, the reaction of acetyl- (105) and benzyl-functionalized diyne 106 with cyanamide 155 furnished at 80 °C the corresponding 2-aminopyridines 184 and 185 in respectively 68% and 83% yields. The reaction was not limited to a quaternary-carbon tethered diyne since both oxygen- and nitrogen-tethered diyne were successfully used. The oxygen-tethered diyne 107 was converted to the corresponding oxygen fused bicyclic pyridines 186 in 64% yield. The cycloaddition of N-tosyl-tethered diyne 108 performed at 110 °C provided the heterocycle 187 in 72% yield. Meanwhile, we observed that the reaction was not feasible with terminal or TMS- and phenyl-substituted diyne 109-111, despite a higher reaction temperature. The diyne 112 and 113 bearing electron-donating or electron-withdrawing aryl moieties were also unreactive under these reaction conditions, afforded only traces of 191 and 192.
Next, the regioselective of the RuCl₃·nH₂O-mediated [2+2+2] cycloaddition using unsymmetrical 1,6-diyne was examined. As shown in Scheme 152, the reaction of methyl-substituted unsymmetrical 1,6-diyne proceeded to give (major, 43%) and (minor, 5%) in 48% combined yield with 87:13 regioselectivity. The reaction of phenyl-substituted unsymmetrical 1,6-diyne with cyanamide also proceeded under the same conditions. However, only the major isomer 194 was isolated in 16% yield, despite a 90:10 ratio of the two regioisomers detected by crude ^1H NMR.
Compared to electron-rich cyanamides, the reaction of symmetrical diyne 108 with electron-deficient nitrile such as malononitrile was also performed in the presence of RuCl$_3$·nH$_2$O catalyst at 110 °C to afford cycloadduct 195 with 22% conversion, although with increased catalyst loading and prolonged reaction time (Scheme 153). This result indicated that the electron-rich nitriles are more suitable with the RuCl$_3$·nH$_2$O complex catalytic system.

**Scheme 153**

The neutral RuCl$_3$·nH$_2$O has therefore been successfully used for the synthesis of highly substituted 2-aminopyridine derivatives via [2+2+2] cycloaddition of α,ω-diynes with electron-rich cyanamides. A range of 2-aminopyridines has been successfully synthesized in 10-95% yields. However, the regioselective synthesis of 2-aminopyridines still remains a challenge. To address this issue, encouraged by our results with RuCl$_3$·nH$_2$O, we decided to investigate the ruthenium-catalyzed [2+2+2] cycloadditions by using cationic ruthenium complex as catalyst.
4.3 Cp*Ru(CH\textsubscript{3}CN)\textsubscript{3}PF\textsubscript{6}-catalyzed [2+2+2] cycloaddition of \(\alpha,\omega\)-diynes with cyanamides

Encouraged by the results obtained using the neutral \(\text{RuCl}_3 \cdot n\text{H}_2\text{O}\) complex for the [2+2+2] cycloaddition reaction of \(\alpha,\omega\)-diynes with cyanamides, and since the cationic ruthenium complex is known to be an efficient catalyst for [2+2+2] cycloaddition reactions\textsuperscript{46-50}, we anticipated that the cationic ruthenium complex would be a good alternative for conducting this reaction.

Initial studies were focused on the ruthenium-catalyzed [2+2+2] cycloaddition reactions between dimethyl substituted internal diyne \textit{101} and cyanamide \textit{155} using ruthenium complex catalyst under solvent-free conditions at room temperature. The reaction was optimized with respect to the different type of ruthenium complexes and catalyst loading, as shown in Table 4. Several ruthenium complexes were evaluated. When \(\text{Ru(PPh}_3)_3\text{Cl}_2\) and \([\text{Ru(p-cymene)}\text{Cl}_2]\) were used as catalyst, no desired products were observed (Entries 1 and 2). We found that the presence of both pentamethylcyclopentadienyl (Cp\textsuperscript{*}) complexes \(\text{Cp*Ru(cod)}\text{Cl}\) and \(\text{Cp*Ru(CH}_3\text{CN)}\text{3PF}_6\), allowed to access the desired 2-aminopyridine \textit{169} in respectively 85\% and 93\% yields in a short reaction time of 5 min (Entries 3 and 4). The catalyst loading could be efficiently reduced to 2 mol \% when using \(\text{Cp*Ru(CH}_3\text{CN)}\text{3PF}_6\) as catalyst. The reaction effectively provided the cycloadduct in 91\% yield within 5 min (Entry 5). We showed that the conversion of the benzannulation was significantly diminished by lowering the catalyst loading to 1 mol \% (Entry 6). In addition to the internal diyne, terminal 1,6-diyne \textit{109} was examined under these reaction conditions. Treatment of diyne \textit{109} with cyanamide \textit{155} in the presence of 2 mol \% \(\text{Cp*Ru(CH}_3\text{CN)}\text{3PF}_6\) under solvent-free conditions at room temperature provided the cycloadduct \textit{188} in 94\% yield (Entry 7). Interestingly, we found that when the reaction was conducted with a small amount of dichloromethane as solvent, the catalyst loading (1 mol \%) and consumption of cyanamide (1.2 equivalents) were further reduced (Entries 7 and 8). However, lowering the catalyst loading to 0.5 mol \% led to lower conversion and yield, despite longer reaction time (Entry 9). Finally, to demonstrate the applicability of our method, we performed the Ru-catalyzed cycloaddition on one-gram of 1,6-diyne \textit{109} (Entry 10). Under the optimized solvent-free conditions in the presence of 2 mol \% of \(\text{Cp*Ru(CH}_3\text{CN)}\text{3PF}_6\) catalyst, the corresponding 2-aminopyridine \textit{188} was isolated in 82\% yield.
With a set of optimal conditions in hand, we investigated the scope and limitations of the cycloaddition using different substituted diynes and cyanamide 155 as partner (Scheme 154). A variety of symmetrical diynes with a quaternary-carbon tether reacted with cyanamide 155 to give various 2-aminopyridines in high yields. The 2-aminopyridine cycloadducts 196-199 bearing bulkier tert-butyl, isopropyl, and methyl ester moieties were obtained in 81-98% yields from the corresponding diynes. Notably, a nitrile group substituted on the quaternary-carbon of diyne 117 was compatible with the reaction conditions. However, the malononitrile-derived diyne 118 provided the desired product 200 in relatively lower yield (50%), because the competitive reaction of the activated nitrile substituents. The spirocyclic derivative 201 was synthesized in 97% yield, starting from the indene-1,3-dione-derived diyne 119. Interestingly, diyne 120 possessing two hydroxyl groups reacted nicely with cyanamide 155 under solvent-free conditions at room temperature to give the diol-derived 2-aminopyridine 202 in 87% yield. The diyne 121 containing a ketal moiety was also reactive to afford the corresponding product 203 in 87% yield. The reaction was not limited to a quaternary-carbon tethered diyne since the heteroatom-tethered diynes were successfully used, leading to the formation of various

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diyne</th>
<th>Catalyst (x mol %)</th>
<th>t</th>
<th>Product</th>
<th>Conv. (%)b</th>
<th>Yield (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>101</td>
<td>Ru(PPh₃)₂Cl₂ (5)</td>
<td>8 h</td>
<td>169</td>
<td>nr</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>101</td>
<td>[Ru(p-cymene)Cl₂] (2.5)</td>
<td>8 h</td>
<td>169</td>
<td>nr</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>101</td>
<td>Cp*Ru(cod)Cl (2)</td>
<td>5 min</td>
<td>169</td>
<td>&gt;99</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>101</td>
<td>Cp*Ru(CH₃CN)₃PF₆ (5)</td>
<td>5 min</td>
<td>169</td>
<td>&gt;99</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>101</td>
<td>Cp*Ru(CH₃CN)₃PF₆ (2)</td>
<td>5 min</td>
<td>169</td>
<td>&gt;99</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>101</td>
<td>Cp*Ru(CH₃CN)₃PF₆ (1)</td>
<td>60 min</td>
<td>169</td>
<td>80</td>
<td>nd</td>
</tr>
<tr>
<td>7</td>
<td>109</td>
<td>Cp*Ru(CH₃CN)₃PF₆ (2)</td>
<td>3 min</td>
<td>188</td>
<td>&gt;99</td>
<td>94</td>
</tr>
<tr>
<td>8d</td>
<td>109</td>
<td>Cp*Ru(CH₃CN)₃PF₆ (1)</td>
<td>2 min</td>
<td>188</td>
<td>&gt;99</td>
<td>95</td>
</tr>
<tr>
<td>9d</td>
<td>109</td>
<td>Cp*Ru(CH₃CN)₃PF₆ (0.5)</td>
<td>18 h</td>
<td>188</td>
<td>90</td>
<td>82</td>
</tr>
<tr>
<td>10e</td>
<td>109</td>
<td>Cp*Ru(CH₃CN)₃PF₆ (2)</td>
<td>5 min</td>
<td>188</td>
<td>&gt;99</td>
<td>82</td>
</tr>
</tbody>
</table>

a Reaction conditions: Ru complex (0.5-5 mol %), diyne 101 or 109 (0.5 mmol), cyanamides 155 (1.0 mmol) were stirred in a screw-capped tube under solvent-free conditions and an argon atmosphere. b Determined by crude 'H NMR, nr = no reaction. c Isolated yields, nd = not detected. d With 0.6 mmol of cyanamide 155 was used and 0.5 mL of dichloromethane as solvent. e One gram-scale.
pyridine-based fused heterocycles (186, 187, 204, and 205) within a range of 80-99% yields. The formation of compounds 186 and 187 demonstrated that the cycloaddition was not limited to terminal diynes but also worked well with internal diynes. However, more sterically hindered internal diynes, such as di-TMS, diaryl, and dibromo-substituted diynes (110, 113 and 124) did not afford the desired cycloadducts, despite increased reaction temperature (Scheme 154).

Scheme 154

Next, an evaluation of the reactivity of the cyanamide substrates was examined. As shown in Scheme 155, various secondary amine derived cyanamides smoothly underwent the cycloaddition reactions to produce the corresponding 2-aminopyridines in 76-97% yields. The
reaction of N-cyanopyrrolidine 156 with diynes 101 and 109 delivered the cycloadducts 170 and 207 in 81% and 90% yields, respectively. The cyanamides 159-161 and 164, bearing dibenzyl, diethyl, di-n-propyl, and methyl/n-butyl groups, were engaged in the cycloaddition to provide the 2-aminopyridines 208-211 in 76%-86% yields, albeit with increased catalyst loading. High yields (90-97%) were obtained for 2-aminopyridines bearing a phenyl group (212) and a monobenzyl group (213 and 214) in the presence of 1-2 mol % ruthenium catalyst. Similarly, as previously observed, no desired products 215 and 216 were obtained by using N-butyl-N-cyanoacetamide 165 and N,N-diallylcyanamide 166.

Scheme 155

With respect to the regioselectivity, we previously studied the reaction of unsymmetrical diynes 125 with cyanamides 155 in the presence of neutral RuCl₃·nH₂O catalyst. However, moderate yield and regioselectivity (48%, 88:12) were obtained. In contrast, when the reaction...
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was run using the cationic ruthenium complex, \( \text{Cp}^*\text{Ru(CH}_3\text{CN)}_3\text{PF}_6 \), the yield and regioselectivity were significantly increased (91\%, 98:2) and the \textit{ortho}-substituted regioisomer 193 was formed as the major product (Scheme 156). In addition, other unsymmetrical diynes were employed to explore the regioselectivity of the cycloaddition reactions. The reaction of phenyl-substituted diyne 126 exclusively furnished the biaryl compound 194 in excellent 96\% yield. Unsymmetrical 1,6-diynes tethered by either oxygen or nitrogen atom, possessing a terminal alkyne and a methyl internal alkyne moiety, were compatible with the cycloadditions and afforded the corresponding bicyclic compounds 217 and 218 as a single regioisomer, in 86\% and 90\% yields. However, the methyl/2-pyridyl-substituted diyne 137 did not undergo the cycloaddition to give the bipyridine 219, although the reaction was heated at 50 °C for 2 hours.

Encouraged by these promising results, we extended this study to develop a feasible synthetic route for the preparation of pyridine derivatives possessing various functional groups. To our delight, the challenging halogen-substituted diynes were all tolerated to deliver the synthetic useful halopyridines in 65-85\% yields with up to 99:1 regioselectivities (Scheme 157). Treatment of malonate-derived bromodiyne 129 and cyanamide 155 under the standard solvent-free conditions at room temperature, generated the less sterically hindered \textit{ortho}-bromopyridine
as the major product, in 80% yield and high regioselectivity (96:4). The structure of the product 220 was unambiguously determined by the basis of 2D-NMR analysis and X-ray crystallographic analysis. Bromodiynes 130-132 reacted nicely with cyanamide 155 to provide the corresponding bromopyridines 221-223 in 65-85% yields with 98:2 regioselectivities. The iodo-substituted 2-amimopyridine 224 was isolated as a single regioisomer in 83% yield.

Scheme 157

Inspired by the success of halogen substituted diyne to yield the halopyridines, we next examined whether the ynamide and enyne, could be suitable for the synthesis of the corresponding functionalized pyridines under the same conditions (Scheme 157). Gratifyingly, the cycloaddition of ynamide 134 with cyclic cyanamides 155 and 156 gave rise to pyridines 225 and 226 with excellent regioselectivities, in 79% and 93% yields, respectively.
Additionally, the regioselectivity was still controlled by the steric effect of the substituents, affording less sterically hindered ortho-substituted pyridines as the major product. More interestingly, we successfully employed enyne 135 with 1.2 equivalents of cyanamides 155 and 158 in the presence of 5 mol % Cp*Ru(CH₃CN)₃PF₆ combined with dichloromethane as solvent to afford the malonate-derived vinylpyridines 227 and 228 in 90% and 92% yields with complete regioselectivities. The N-tosyl-tethered enyne 136 was also subjected to standard solvent-free conditions, the corresponding vinylpyridine 229 was obtained as a single regioisomer in 75% yield. It is worthwhile to mention that the cycloaddition exclusively took place at the triple bond to form pyridines, no side-product from the double bond reactivity was detected.

To further demonstrate the synthetic utility of this method, the reaction of the challenging linear 1,7-diynes and 1,8-diynes was examined (Scheme 158). Oxygen-tethered 1,7-diyne 138 and cyanamide 155 were treated with 5 mol % Cp*Ru(CH₃CN)₃PF₆ in dichloromethane at 50 °C, affording the six-membered bicyclic pyridine 230 in 81% yield with excellent regioselectivity. Cyanamides 156 and 158, containing pyrrolidyl and methyl/benzyl moieties, provided 2-aminopyridines 231 and 232 in diminished yields (46% and 34%, respectively), despite with a total regioselectivity. Replacing the oxygen tether by a N-tosyl tether, the diyne 139 allowed rapidly an access to nitrogen-fused pyridine 233 in 86% yield with complete regioselectivity. Notably, compounds containing the pyrano-pyridine and piperidine-pyridine moieties are known to exhibit interesting pharmacological properties such as antibacterial and anticancer activities. Moreover, further studies showed that diynes 140-142 were not compatible with the reaction conditions. Diyne 140 having a propargyl motif failed to deliver the desired product. No reaction took place with both bromo-substituted 1,7-diyne 141 and terminal 1,8-diyne 142, probably because of the lack of a Thorpe-Ingold effect.148

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Finally, we consider the feasibility of the late-stage functionalization of potential drug or bioactive compounds. As an example, the diyne 143, derived from biologically active compounds mestranol\textsuperscript{149} was employed to deliver the spirocyclic framework having a 2-aminopyridine moiety 237 in 51\% isolated yield with 10:1 regioselectivity. The structure of the polycyclic product 237 was unambiguously confirmed by single crystal X-ray diffraction (Scheme 159).


\[ \text{Scheme 158} \]
Mechanistically, the metal-catalyzed [2+2+2] cycloaddition has been thoroughly studied in the presence of several metals. Nevertheless, as described in Scheme 160, one important feature concerns the regioselectivity of the ruthenium-catalyzed process, e.g., the formation of the major isomer versus the minor isomer. Following in situ ligand decoordination and coordination of 1,6-diyne, the oxidative coupling of the two alkyne units leads to a ruthenacyclopentadiene Ru-II in equilibrium with the bis-carbenic intermediate Ru-I. The next elemental step determines the regioselectivity of the reaction. Indeed, coordination of cyanamide gives intermediates Ru-III or Ru-III'. The origin of the observed regiochemistry can be reasonably explained by the steric hindrance of the amino part of the cyanamide leading to the favourable formation of Ru-III. Insertion of cyanamide gives rise to azaruthenacyclopentadiene intermediate Ru-IV, which upon reductive elimination subsequently affords the ortho-substituted product. When the 1,6-diyne is substituted by two very hindered groups (diynes 110 and 124), no reaction is observed. A hydrogen atom and/or methyl group as substituent of the alkynes are fully compatible with the cycloaddition process and favor the formation of the major intermediate Ru-III. This mechanism is therefore in agreement with the experimental data.

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4.4 Cp*Ru(CH$_3$CN)$_3$PF$_6$-catalyzed [2+2+2] cycloadditions to access aza-fluorenols and aza-fluorenone

Aza-fluorenones represent a privileged scaffold in material and medicinal chemistry. We hypothesized that by using benzoyl bridged α,ω-diynes and cyanamides, it should be possible to access amino-aza-fluorenones via the regioselective ruthenium-catalyzed [2+2+2] cycloaddition reaction. A retrosynthesis was proposed in Scheme 161.

Therefore, the benzoyl bridged internal diyne 17 was reacted with dimethylcyanamide under the optimized conditions using 5 mol % RuCl$_3$·nH$_2$O under solvent-free conditions at 80 °C. Unfortunately, no desired product 238 was obtained and only decomposition of diyne 17 was detected (Eq. a, Scheme 162). The same result was also observed by using

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**Scheme 160**

**Scheme 161**
Cp*Ru(CH$_3$CN)$_3$PF$_6$ as catalyst for the cycloaddition of diyne 17 and cyanamide 155 (Eq. b, Scheme 162). The results could be explained by the lower reactivity of the diyne which bears both phenyl and n-butyl groups on the terminal positions.

Scheme 162

To address this issue, we reasoned that a less sterically demanding diynes possessing a terminal alkyne moiety would be more reactive in the presence of Cp*Ru(CH$_3$CN)$_3$PF$_6$ catalytic system. Indeed, as shown in Scheme 163, when the benzoyl bridged diyne 29 was reacted with morpholine-4-carbonitrile 155 in the presence of 2 mol % Cp*Ru(CH$_3$CN)$_3$PF$_6$ at room temperature under solvent-free conditions, the 2-azafuorenone 240 was formed as a single regioisomer in 92% yield. Different cyanamides were next screened, such as N-cyanopyrrolidine 156, N-cyanopiperidine 157 and N,N-methylbenzyl cyanamide 158, and the desired 2-azafuorenones 241-243 were synthesized as a single isomer in 78-87% yields. In addition, the reaction of benzyl-bridged diyne 28 bearing an unprotected hydroxyl group could also be performed smoothly and exclusively to give rise to 2-azafluorenols 244 and 245 in 84% and 81% yields, respectively. Interestingly, in parallel to the synthesis of 2-azafluorenol 245, exchanging the terminal position of the starting diyne, allowed the formation of the 3-azafluorenol 247 in 71% yield with 99:1 regioselectivity. Moreover, switching to a cyclopropyl group instead of n-butyl group promoted the formation of 3-azafluorenol 247 in 78% yield with the same regioselectivity. The cycloaddition of benzoyl bridged diyne 153 was performed under the optimized reaction conditions, 3-azafluorenone 248 was formed as the major product in 89% isolated yield, with a decreased regioselectivity (94:6). The structure of 248 was unambiguously confirmed by single crystal X-ray diffraction (Scheme 163). These results illustrated that the regioselectivity allows the formation of less sterically hindered regioisomer.
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It is important to highlight that all the reactions occurred in a short reaction time using traces of dichloromethane or solvent-free conditions.

![Chemical structures and reactions](image)

Scheme 163

5. Conclusion

To conclude, we have demonstrated that highly substituted 2-aminopyridine derivatives can be efficiently synthesized by ruthenium-catalyzed [2+2+2] cycloaddition of 1,6-diynes and 1,7-diynes with cyanamides using both neutral RuCl₃·nH₂O and cationic Cp*Ru(CH₃CN)_3PF₆ complex as catalyst.
Firstly, the easy to handle and cost-effective RuCl$_3\cdot$nH$_2$O complex has been successfully employed for the synthesis of highly substituted 2-aminopyridines. The reaction proceeded in the presence of 5 mol % RuCl$_3\cdot$nH$_2$O, with neither additional ligands nor additives under solvent-free conditions, affording a range of different 2-aminopyridines in 10-95% yields.

Secondly, we established that a cationic Cp*Ru(CH$_3$CN)$_3$PF$_6$ complex is a highly efficient catalyst for the cycloaddition of both 1,6- and 1,7-diynes with cyanamides under mild conditions. Various symmetrical terminal or internal diynes possessing different functional groups were compatible with the catalytic system. High regioselectivity was obtained when unsymmetrical diynes were employed. The practicability and utility of this protocol were demonstrated with the preparation of high valuable halopyridines, diaminopyridines, and vinylpyridines in one-step synthesis. The reaction also provided synthetic useful six-membered heteroatom-fused pyridines starting from unsymmetrical 1,7-diynes and cyanamides. The late-stage functionalization of biologically active mestranol further improved the facile and usefulness of the present method.

Finally, a family of aza-fluorenones and aza-fluorenols were synthesized via eco-friendly and straightforward approaches. Controlling the terminal position of the benzoyl- or benzyl-bridged diyne allowed the synthesis of 2- or 3-azafluorenone(ol) with high regioselectivities.
Chapter IV: Rhodium-catalyzed asymmetric synthesis of 1,1-disubstituted 1,3-dihydroisobenzofurans from prochiral triynes and internal alkynes
Chapter IV: Rhodium-catalyzed asymmetric synthesis of 1,1-disubstituted 1,3-dihydroisobenzofurans from prochiral triynes and internal alkynes

The transition-metal-catalyzed enantioselective [2+2+2] cycloaddition reactions are extremely important tools in modern synthetic organic chemistry, because they serve as a powerful and atom-economical straightforward approach for the rapid construction of chiral polycyclic carbocycles and heterocycles in a single step. Since the first example of enantioselective [2+2+2] cycloaddition discovered in 1994 with the work of Sato, Mori, and Nishimata, catalytic asymmetric [2+2+2] cycloaddition reactions using a transition metal catalyst, such as rhodium, cobalt, nickel, and iridium, in the presence of a chiral ligand have been widely reported for the construction of various chiral molecules associated with central, axial, planar, helical chirality (Figure 3).

Figure 3

1. Enantioselective [2+2+2] cycloaddition reactions

1.1. Construction of central chirality

The transition-metal-catalyzed [2+2+2] cycloadditions of alkynes with unsaturated partners, such as olefins, imines, aldehydes, are of great interest given that they allow the construction of a six-membered ring containing one or more chiral carbon center. These processes proceed via a widely known reactive metallocyclopentene or metallocyclopentadiene intermediate, which is generated from the oxidative coupling of two unsaturated carbon-carbon bonds to the chiral metal catalytic species. The insertion and reductive elimination steps then provide the cyclic compound with chiral carbon center(s) on the six-membered ring (Scheme 164).

![Scheme 164](image)

In 2006, Shibata reported the first rhodium-catalyzed enantioselective [2+2+2] cycloaddition of diynes and alkenes. In the presence of a preliminary isolated chiral rhodium(I) complex, various exo-methylene cyclic lactones and ketones could undergo the cycloaddition with 1,6-diynes to give a family of chiral spirocyclic compounds possessing a quaternary carbon stereocenter, with 62-94% yields and 80-99% enantioselectivities (Scheme 165).

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The enantioselective [2+2+2] cycloaddition involving two alkene units allowed to introduce two new stereogenic centers in a single step in the resulting cycloadduct. The first report was described by Tanaka and co-workers in 2012.\textsuperscript{153} They demonstrated that the successful construction of annulated cyclohexene relies on the use of reactive acrylamides as alkene partners (Scheme 166). The high regioselective and diastereoselective formation of the cycloadduct could be explained by the regioselective insertion of the acrylamide into a rhodacyclopentene intermediate.

The unsaturated imine was also a good partner for these cycloadditions. The first asymmetric transition-metal-catalyzed [2+2+2] cycloaddition of diynes with sulfonimines was reported by Aubert, Gandon, Malacria and co-workers,\textsuperscript{154} and provided a new and efficient


method for the synthesis of enantioenriched 1,2-dihydropyridines. The combination of \([\text{Rh(hexadiene)Cl}]_2/\text{AgSbF}_6/(\text{R})\text{-ditBu-MeOBiphep (or (R)-Tol-BINAP)}\) was found to be the best catalytic system to promote the access to various heterocycles with good enantioselectivities (Scheme 167).

\[ \text{X = C(CO}_2\text{Me})_2, \text{CH}_2, \text{O} \]

Selected examples:

- 77% yield, 92% ee
- 75% yield, 95% ee
- 68% yield, 92% ee

1.2. Construction of axial chirality

Axially chiral biaryl compounds are widely found as a key structural motif in many chiral ligands, catalysts as well as biologically active compounds.\(^\text{155}\) The catalytic enantioselective synthesis of axially chiral biaryls via transition-metal-catalyzed [2+2+2] cycloadditions have been proved to be a straightforward and efficient method. The sterically demanding prochiral substrates and a chiral catalyst were commonly used for the formation of chiral biaryl compounds (Scheme 168).

\[ \text{ML}^* \rightarrow \text{R}^1 \text{R}^2 \text{R}^3 \text{R}^1 \text{R}^2 \text{R}^3 \text{R}^1 \text{R}^2 \text{R}^3 \text{ML}^* \]

Scheme 168

In 2004, Gutnov, Heller and co-workers reported the first example of direct synthesis of enantioenriched axially biaryls via a chiral cobalt(I) complex-catalyzed [2+2+2] cycloaddition of alkynes with nitriles. The reaction was performed under mild conditions using visible light or sunlight as the energy source (Scheme 169).

\[
\begin{align*}
\text{Scheme 169} \\
\end{align*}
\]

Shibata and co-workers reported the first example of iridium-catalyzed [2+2+2] cycloaddition of \(\alpha,\omega\)-diynes with alkynes. The combination of \([\text{Ir}(\text{cod})\text{Cl}]_2\) and \((S,S)-\text{Me-Duphos}\) promoted the high enantio- and diastereoselective synthesis of axially chiral 1,4-teraryls (Scheme 170).

\[
\begin{align*}
\text{Scheme 170} \\
\end{align*}
\]

Tanaka and co-workers also employed the cationic rhodium(I)/bisphosphine catalytic system to the asymmetric synthesis of axially chiral biaryls. In the presence of cationic rhodium(I)/(S)-H8-BINAP complex, various unsymmetrical diynes and internal alkynes were

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converted to axially chiral phthalides. Functional groups, such as trifluoromethyl and chloride were tolerated using these conditions (Scheme 171).

Scheme 171

1.3. Construction of planar chirality

The transition-metal-catalyzed intramolecular [2+2+2] cycloaddition of triynes, possessing a short ansa chain, could be possible to form a planar chirality cyclophanes in which the ansa chain cannot flip around the benzene ring (Scheme 172).

Scheme 172

In 2007, the group of Tanaka first reported that the planar-chiral metacyclophanes could be synthesized by transition-metal-catalyzed [2+2+2] cycloaddition reactions. The intramolecular cyclotrimerization of linear triynes, bearing ester or ether-linked 1,6-diyne moieties, proceeded in the presence of rhodium(I)/(R)-H8-BINAP complex furnishing the [7]-[10]metacyclophanes with high enantioselectivities (Scheme 173). This method opened a new way to synthesize these compounds.

1.4. Construction of helical chirality

The combination of transition metals with chiral ligands to catalyze [2+2+2] cyclotrimerization of alkynes is considered as one of the most efficient methods for the synthesis of helically chiral π-electron systems, although most examples are diastereoselective cycloadditions (Scheme 174).

Stará, Starý and co-workers reported a rapid approach for the synthesis of dibenzohelicenes based on a nickel-catalyzed cycloaddition reaction. A series of orthophenylene-tethered triynes were employed under the Ni(cod)$_2$(R)-Quinap catalytic system and

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gave rise to various dibenzo[5]-dibenzo[6]- and dibenzo[7]helicenes. Notably, a high catalyst loading (20 mol %) was required to give a higher enantioselectivity (Scheme 175).

![Scheme 175](image)

2. Desymmetric transition-metal-catalyzed \([2+2+2]\) cycloaddition reactions

Although many methods have been developed on enantioselective transition-metal-catalyzed \([2+2+2]\) cycloadditions for the synthesis of useful chiral compounds, new strategies to access challenging targets are still desirable.

The construction of all-carbon quaternary stereogenic centers via catalytic enantioselective desymmetrization\(^\text{161}\) of prochiral substrate is an ideal method which exhibits many advantages over conventional strategies (Figure 4). For example, the quaternary carbon stereocenter is formed, no matter what kind of reaction occurred at one of the two identical functional groups attached to the quaternary carbon; the functional groups could previously be introduced to the quaternary carbon; the theoretical yield of the desymmetrization reaction is 100%, while the yield of the kinetic resolution reaction cannot exceed 50%.

---

Taking advantage of the powerful and practical transition-metal-catalyzed [2+2+2] cycloadditions, and based on the principles of desymmetrization reactions, the synthesis of chiral compounds in term of desymmetric enantioselective [2+2+2] cycloaddition reactions were designed but scarcely reported (Scheme 176).

The first example was reported by Sato, Mori and Nishimata using a nickel(0)-catalyzed enantioselective [2+2+2] cycloaddition of prochiral triynes with gaseous acetylene in the presence of chiral phosphine ligands under mild conditions (Scheme 177).\textsuperscript{151,162} The combination of Ni(cod)$_2$ and (R,S)-BPPFA promoted the reaction of prochiral triynes with acetylene affording the isoindoline derivatives in 52% yield and 73% enantioselectivity.

whereas the cycloaddition of 1,7-diyynes and acetylene by using (S)-MOP as ligand led to isoquinoline in 62% yield and 54% enantioselectivity. Notably, this new method opened a novel route for the construction of benzylic chiral carbon centers, although the enantioselectivities were moderate.

Scheme 177

Since this pioneering work, the desymmetric [2+2+2] cycloadditions of prochiral substrates received more attention. Taking advantage of cationic rhodium(I)/phosphine catalytic systems, the group of Tanaka reported several examples by using these strategies. In 2006, they described two examples of enantioselective desymmetrization of substituted malononitriles. Using cationic [Rh(cod)2]BF4/(R)-Xylyl-Solphos (or (R)-BINAP) complex catalyst, the reaction afforded enantioenriched bicyclic pyridines in 75-91% yields with moderate enantioselectivities (33% and 64%, respectively, Scheme 178).

Scheme 178

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In 2007, the same group described the synthesis of enantioenriched tricyclic 3,3-disubstituted phthalides involving a cationic rhodium-catalyzed desymmetric [2+2+2] cycloaddition reaction. The reaction proceeded via an initial oxidative coupling of 1,6-diyne bearing a carbomethoxy group and simultaneously a transesterification with a symmetrical bispropargylic alcohol to form the rhodacyclopentadiene reactive species, followed by desymmetric insertion of one of the two alkynes to give the phthalide derivatives, which bear a chiral quaternary carbon center at the benzylic position (Scheme 179). The high regio- and enantioselectivity strongly relied on the presence of both methoxycarbonyl group and propargylic hydroxyl group.

The $C_2$-symmetric spirobipyridine structures were also prepared via the rhodium/bisphosphine-catalyzed enantioselective intramolecular double [2+2+2] cycloadditions of bis-diynenitriles. A wide range of substrates were examined to produce various $C_2$-symmetric spirobipyridine ligands in 70-99% yields with 18-71% enantioselectivities (Scheme 180).

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The aromatics containing a chiral center at $\beta$-position are more challenging to synthesize. Thus, Shibata and co-workers recently developed a rhodium-catalyzed intramolecular enantioselective [2+2+2] cycloaddition of amino-acid-tethered triynes for the preparation of the chiral center of tethered Aic derivatives (Scheme 181).\textsuperscript{166}

\begin{equation}
\text{Scheme 180}
\end{equation}

\begin{equation}
\text{Scheme 181}
\end{equation}

Not only quaternary-carbon-stereogenic centers but also other hetero-stereogenic centers, such as phosphorus and silicon, can be constructed through desymmetric enantioselective [2+2+2] cycloaddition reactions.

In 2008, Tanaka and co-workers successfully synthesized a family of phosphorus-stereogenic alkynylphosphine oxides by using cationic rhodium(I)/bisphosphine complex-catalyzed [2+2+2] cycloadditions of symmetrical dialkynylphosphine oxides with 1,6-diynes. The desymmetric formation of a phosphorus-stereogenic center could be explained by the steric effect between the coordinated dialkynylphosphine oxide and the chiral phosphine ligand in the formed rhodium intermediate (Scheme 1).

Nozaki and co-workers reported in 2015 a facile and efficient method for the preparation of silicon-stereogenic dibenzosiloles through enantioselective rhodium-catalyzed [2+2+2] cycloaddition of silicon-containing prochiral triynes with internal alkynes. In the presence of [RhCl(C₂H₅)₂]/monophosphine catalytic system, by exchange of the different tethers and unsaturated partners, enantioenriched germanium-stereogenic dibenzogermoles, silicon-stereogenic silicon-bridged arylpyridinones and arylpyridines were successfully obtained with good to high chemo-, regio- and enantioselectivities (Scheme 1).

\[ \text{Scheme 182} \]

\[ \text{NOZAKI and co-workers reported in 2015 a facile and efficient method for the preparation of silicon-stereogenic dibenzosiloles through enantioselective rhodium-catalyzed [2+2+2] cycloaddition of silicon-containing prochiral triynes with internal alkynes. In the presence of [RhCl(C₂H₅)₂]/monophosphine catalytic system, by exchange of the different tethers and unsaturated partners, enantioenriched germanium-stereogenic dibenzogermoles, silicon-stereogenic silicon-bridged arylpyridinones and arylpyridines were successfully obtained with good to high chemo-, regio- and enantioselectivities (Scheme 183). A drawback of this method was the difficult multiple-step synthesis of starting prochiral triynes.} \]

\[ \text{169 Shintani, R.; Takano, R.; Nozaki, K. Chem. Sci.} \text{ 2016, 7, 1205.} \]
3. Interest and synthesis of 1,3-dihydroisobenzofurans

1,3-dihydroisobenzofurans (phthalanes)\[^{171}\] constitute an important class of oxygenated heterocycles, which are widely present in many bioactive natural products\[^{172}\] and pharmaceuticals\[^{173}\]. For examples, as shown in Scheme 184, Flavimycin A (A) was isolated as inhibitor of peptide deformylase from cultures of \textit{Aspergillus flavipes}.\[^{172b}\] Citalopram (B) is a widely used antidepressant drug for the treatment of major depressive and general anxiety disorders in adults.\[^{172c}\] Further investigation indicated that the pharmaceutical activity of citalopram almost resided in the (S)-enantiomer, Escitalopram (C).\[^{173d}\] Pestacin (D) isolated from microorganism \textit{Pestalotiopsis microspora} exhibits antifungal, antimycotic, and potent


antioxidant activities.\textsuperscript{173e} Conformationally constrained miconazole analogues (E) containing a 1,3-dihydroisobenzofuran motif have improved antifungal potency compared to miconazole.\textsuperscript{173f} 3-Deoxyisoochracinic acid (F), the most abundant polyketide-derived metabolites of \textit{Cladosporium sp}, showed antibacterial activity and inhibits the growth of \textit{B. subtilis}.\textsuperscript{173g}

Many synthetic approaches have been reported in the literature for the synthesis of these structurally diverse 1,3-dihydroisobenzofurans including cycloetherification of the ortho-substituted aromatics,\textsuperscript{174} [2+2+2] cycotrimerization of alkynes,\textsuperscript{7} Diels–Alder reaction,\textsuperscript{175} and transformation of phthalides\textsuperscript{176} (Scheme 185). Among them, the preparation of this scaffold by transition-metal-catalyzed [2+2+2] cycloaddition reaction may be considered as one of the most efficient method, as described in chapter I.

Scheme 184


4. Objectives

Considering the literature, the enantioselective synthesis of 1,3-dihydroisobenzofurans containing a stereogenic center at the $\alpha$-position has rarely been reported and remains a challenge.\textsuperscript{177}

Desymmetrization of prochiral compounds serves as an efficient method to prepare complex molecules with a stereogenic chiral center. Therefore, we anticipated that the construction of 1,3-dihydroisobenzofurans could be achieved via the transition-metal-catalyzed [2+2+2] cycloaddition of prochiral oxygen-tethered triynes with internal alkynes. The proposed synthetic route is shown in Scheme 186.

5. Results and discussion

5.1 Synthesis of starting materials: prochiral triynes and internal alkynes

5.1.1. Synthesis of prochiral triynes

The prochiral oxygen-tethered triynes having an \( \alpha,\omega \)-diyne motif could be prepared from commercially available reagents, the retrosynthetic route is depicted in Scheme 187.

![Scheme 187]

The symmetrical bispropargylic alcohols 249-253 were prepared through the lithium mediated nucleophilic addition of terminal alkynes with acyl chlorides. As shown in Scheme 188, a series of acyl chlorides reacted with 2 equivalents of lithium acetylide, prepared \textit{in situ} from the corresponding alkynes and \textit{n}-butyllithium, affording the bispropargylic alcohols 249-253 in 70-99% yields. Both aryl and alkyl groups could be introduced to the quaternary carbon atom by using different acyl chlorides.

![Scheme 188]
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The oxygen-tethered triynes 254-259 were successfully synthesized via the nucleophilic substitution of the alcohols 249-253 with 1.3 equivalents of propargyl bromide or 1-bromo-but-2-yne. The reaction was performed in the presence 1.3 equivalents of sodium hydride in THF, and afforded the desired triynes 254-259 in 70-90% yields (Scheme 189).

\[
\begin{align*}
249-253 & \quad + \quad \text{Br} \quad \text{R}^3 \quad \text{NaH 1.3 equiv} \quad \text{THF, 0 °C to rt, 18 h} \quad \text{254-259} \\
249, \text{R}_1 = \text{Me}, \text{R}_2 = \text{Ph} & \quad 252, \text{R}_1 = \text{Ph}, \text{R}_2 = \text{Ph} \\
250, \text{R}_1 = \text{nPr}, \text{R}_2 = \text{Ph} & \quad 253, \text{R}_1 = \text{Ph}, \text{R}_2 = \text{nBu} \\
251, \text{R}_1 = \text{nBu}, \text{R}_2 = \text{Ph} & \quad \text{R}_3 = \text{H, Me} \\

\text{254, 87%} & \quad \text{255, 76%} & \quad \text{256, 74%} \\
\text{257, 70%} & \quad \text{258, 90%} & \quad \text{259, 88%}
\end{align*}
\]

Scheme 189

Treatment of terminal triyne 254 with 1.1 equivalents of nbutyllithium in THF at -70 °C, followed by subsequent silylation with 1.1 equivalents of trimethylsilyl chloride, delivered the TMS-substituted triyne 260 in 93% yield (Scheme 190).

\[
\begin{align*}
254 & \quad \text{nBuLi 1.1 equiv} \quad \text{TMSCl 1.1 equiv} \quad \text{THF, -70 °C, 2 h} \quad \text{260} \\
\text{Me} & \quad \text{SiMe}_3
\end{align*}
\]

Scheme 190
5.1.2. Synthesis of internal monoalkynes

To study the steric influence of the alkynes, different internal alkynes were prepared (Scheme 191). Diynes 51, 53, 54 and 261 were purchased from commercial sources, diynes 262-265 were prepared in the laboratory following the procedures described in the literature.\textsuperscript{178}

![Alkyne structures](image)

**Scheme 191**

The reaction of 2-butyl-1,4-diol 52 with 3 equivalents of acyl chlorides, such as acetyl chloride and benzoyl chloride, in the presence of 2.5 equivalents of pyridine provided the corresponding alkynes 262 and 264 in 96% and 95% yields, respectively (Scheme 192).

![Reaction mechanism](image)

**Scheme 192**

Alkyne 263 could be prepared by the reaction of 2-butyl-1,4-diol 52 with 3 equivalents of pivaloyl chloride using 5 mol % DMAP as catalyst and 4 equivalents of ethyldiisopropylamine as base, 98% of the desired product was obtained (Scheme 193).

![Reaction mechanism](image)

**Scheme 193**

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Treatment of the 2-butyl-1,4-diol 52 with 3.5 equivalents of sodium hydroxide in a mixture solution of water and THF at 0 °C with 2.2 equivalents of tosyl chloride furnished the tosyl protected internal alkyne 265 in 83% yield (Scheme 194).

![Scheme 194](image)

5.2 Rhodium-catalyzed desymmetric [2+2+2] cycloaddition of prochiral triynes with internal alkynes

With a series of alkynes in hand, we then attempted to synthesize 1,3-dihydroisobenzofuran 266 from prochiral triyne 255 and 1,4-diacetoxy-2-butyne 262 through an enantioselective rhodium-catalyzed [2+2+2] cycloaddition reaction. As shown in Table 5, we began our studies by investigating the reactivity of different cationic rhodium catalysts, such as Rh(cod)_2BF_4, [Rh(hexadiene)Cl]_2/AgSbF_6, [Rh(ethylene)Cl]_2/NaBArF_4, which proved to be efficient catalysts in related enantioselective [2+2+2] cycloadditions (Entries 1-3). The results showed that the use of Rh(cod)_2BF_4 in combination with (R)-BINAP was the best choice for the transformation. Using 5 mol % of cationic Rh(cod)_2BF_4/(R)-BINAP complex in dichloromethane at 40 °C lead to 50% yield and 50% ee of the desired product 266 by using 1:2 ratio of triyne 255 and alkyne 262 (Entry 1). Further evaluation of the ratio of [Rh]/ligand showed that an increase of the amount of (R)-BINAP (10 mol %, Entry 4) gave no improvement (yield and enantioselectivity). The reaction did not take place in the absence of phosphine ligand (Entry 5). Hydrogenation of the rhodium complex under 1 atm H_2 for 1 hour to remove the cod ligand allowed the formation of cycloadduct 266 in 66% isolated yield, but with a lower enantiomeric excess of 43% (Entry 6). Moreover, slow-addition technique was used to introduce triyne 255 in 3 h to a DCM solution of alkyne 262 and Rh(cod)_2BF_4/(R)-BINAP complex using a syringe pump (Entry 7). However, the formation of unclear side products was observed, due to the homo-cyclization of triyne and totally intramolecular cycloaddition of triyne with alkyne.
Table 5 Optimization of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Rh] catalyst</th>
<th>Additive (mol %)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh(cod)BF4</td>
<td>/</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(hexadiene)Cl]2</td>
<td>AgSbF6 (5)</td>
<td>74</td>
<td>20</td>
</tr>
<tr>
<td>3d</td>
<td>[Rh(ethylene)Cl]2</td>
<td>NaBAR4 (10)</td>
<td>72</td>
<td>49</td>
</tr>
<tr>
<td>4e</td>
<td>Rh(cod)BF4</td>
<td>/</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>5f</td>
<td>Rh(cod)BF4</td>
<td>/</td>
<td>nr</td>
<td>/</td>
</tr>
<tr>
<td>6g</td>
<td>Rh(cod)BF4</td>
<td>/</td>
<td>66</td>
<td>43</td>
</tr>
<tr>
<td>7h</td>
<td>Rh(cod)BF4</td>
<td>/</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

*a Reaction conditions: [Rh] catalyst (5 mol %), (R)-BINAP (5 mol %), triyne 255 (0.3 mmol), alkyne 262 (0.6 mmol) were heated at 40 °C in a sealed Schlenk tube in DCM (3 mL) under an argon atmosphere for 20-24 h. b Isolated yield, nr = no reaction. c Determined by SFC analysis. d ArF = 3,5-(CF3)2C6H3. e 10 mol % of (R)-BINAP was used. f No ligand. g [Rh]/(R)-BINAP complex with previous hydrogenation (H2, 1 atm, rt, 1 h). h Slow addition of triyne 255 in 3 hours using a syringe pump.

To further optimize the reaction conditions, a variety of bisphosphine and monophosphine ligands has been examined (Table 6). The influence of the chiral ligand was explored, (S)-Tol-BINAP, (R)-Xylyl-BINAP and (R)-H8-BINAP gave slight decreased enantiomeric excesses. The combination of Rh(cod)BF4 with axially chiral monophosphine (R)-MOP, which previously demonstrated high reactivity and selectivity for the desymmetrization of silicon-containing prochiral triynes with internal alkyne, afforded the cycloadduct in 70% yield with 7% ee. Oxygen fused electron-rich and electron-poor bidentate ligands, such as (R)-SegPhos, (R)-DifluorPhos, (R)-SynPhos and (R)-(4-CF3)-SynPhos, showed higher reactivity to access compound 266 (60-81% yields), but lower enantioselectivities were obtained (16-30% ee). Phosphine ligands bearing sterically hindered PAR2 moiety, such as (R)-dtbm-SegPhos and (R)-dtbm-MeOBiphep, did not provide the desired product. In contrast to the axially chiral phosphine ligands, (S)-Tol-BDP, (S)-PHANELOS, (R,S)-Josiphos and (R,R)-Me-DuPhos, showed poor enantioselectivities and low reactivities under these reaction conditions.
Table 6 Screening of chiral phosphine ligands

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R)-BINAP</td>
<td>50%</td>
<td>50% ee</td>
</tr>
<tr>
<td>(S)-Tol-BINAP</td>
<td>57%</td>
<td>47% ee</td>
</tr>
<tr>
<td>(R)-Xylyl-BINAP</td>
<td>71%</td>
<td>40% ee</td>
</tr>
<tr>
<td>(R)-H₂-BINAP</td>
<td>50%</td>
<td>42% ee</td>
</tr>
<tr>
<td>(R)-MOP</td>
<td>70%</td>
<td>7% ee</td>
</tr>
<tr>
<td>(R)-SegPhos</td>
<td>71%</td>
<td>30% ee</td>
</tr>
<tr>
<td>(R)-dtbm-SegPhos</td>
<td>81%</td>
<td>27% ee</td>
</tr>
<tr>
<td>(R)-SynPhos</td>
<td>60%</td>
<td>26% ee</td>
</tr>
<tr>
<td>(R)-(4-CF₃) SynPhos</td>
<td>70%</td>
<td>16% ee</td>
</tr>
<tr>
<td>(R)-MeOBiphep</td>
<td>54%</td>
<td>34% ee</td>
</tr>
<tr>
<td>(R)-dtbm-MeO Biphep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(S)-Tol-BDP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(S)-PHANEPHOS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(R,S)-Josiphos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(R,R)-Me-DuPhos</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Toluene was used as solvent.
We also evaluated a series of monodentate phosphoramidite ligands.\textsuperscript{179} However, no improvement of enantioselectivity of compound 267 was obtained (5-40\%, Scheme 195).

These results demonstrated that the chiral phosphine ligands play an important role to promote the desymmetric [2+2+2] cycloadditions, although moderate enantioselectivities were obtained. In this context, the Rh(cod)\textsubscript{2}BF\textsubscript{4}/(R)-BINAP complex was selected for the [2+2+2] cycloaddition reactions.

To improve the yield and enantiomeric excess, we next screened different organic solvents (Table 7). First, polar solvents were examined. The reaction was carried out in dichloroethane and tetrahydrofuran at 40 °C, in the presence of 5 mol % Rh(cod)\textsubscript{2}BF\textsubscript{4}/(R)-BINAP complex to deliver the desired 1,3-dihydroisobenzofuran 266 in 61\% and 72\% yields, respectively, with 37\% and 47\% ee, respectively (Entries 2 and 3). The non-polar solvents such as toluene, xylene, chlorobenzene have also been evaluated (Entries 4-6). Slight increased yields of cycloadducts were observed, with moderate enantioselectivity. Performing the cycloaddition in toluene at 100 °C did not significantly improve the course of the cycloaddition (70\% yield, 50\% ee, Entry 4). The reaction was performed in the presence of 5 mol % Rh(cod)\textsubscript{2}BF\textsubscript{4}/(R)-BINAP complex in 3 mL dichloromethane at 40 °C to evaluate the scope of the [2+2+2] cycloaddition.

Chapter IV

Table 7 The effect of solvent

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCM</td>
<td>40</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>DCE</td>
<td>40</td>
<td>61</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>40</td>
<td>72</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>100</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>Xylene</td>
<td>100</td>
<td>60</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>Chlorobenzene</td>
<td>100</td>
<td>54</td>
<td>42</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: Rh(cod)2BF4 (5 mol %), (R)-BINAP (5 mol %), triyne 255 (0.3 mmol), alkyne 262 (0.6 mmol) were heated at 40 °C or 100 °C in a sealed Schlenk tube under an argon atmosphere for 20 h. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by SFC analysis.

With the optimized reaction conditions in hand, we then investigated the generality and limitations of the synthetic protocol. A series of symmetrical internal alkynes with different substituents were engaged with triyne 255 under the optimized reaction conditions (Scheme 196). Switching to the more sterically hindered 2,2-dimethylpropanoate 263 and benzoate 264 allowed to promote the reaction to form cycloadducts 267 and 268 in respective 20% and 28% yields, and 36% and 46% ee. The use of 3-hexyne 53 gave the desired product 269 in 79% yield and 21% ee. The reaction of more electron-rich alkyne such as 1,4-dimethoxy-2-butene 51 with triyne 255 afforded the cycloadduct 270 in 63% yield with 32% ee. In addition, the electron-deficient alkyne dimethyl acetylenedicarboxylate 261 can also be employed to provide the corresponding cyclized product 271 in 51% yield and 47% ee. On the other hand, we observed that the reaction was not compatible with diphenylacetylene 54, probably because of the steric effect of the two phenyl groups. It was also found that no reaction occurred with the tosyl group protected 2-butene 265.
With respect to the prochiral triynes, different substituents on the triynes were evaluated (Scheme 197). Replacement of methyl group on the quaternary carbon atom by \( n \)-propyl group provided the corresponding product 274 with similar 46% yield and 51% enantiomeric excess. The reaction of sterically demanding tert-butyl- and phenyl-substituted triynes 257 and 258 with internal alkyne 262 were inefficient for the enhancement of the enantioselectivity, leading to cycloadducts 275 and 276 with slightly lower 38% and 41% ee. The reaction also proceeded smoothly with the prochiral triyne 259 affording the cycloadduct 277 in 54% yield with 24% ee. The reaction was also applicable to the trimethylsilyl-substituted triyne 260, which successfully reacted with alkyne 262 to deliver the corresponding product 278 with 52% enantioselectivity in 26% yield. Finally, the reactivity of the triyne 254 having a terminal alkyne moiety was examined. However, no desired product 279 was formed under these reaction conditions, only the decomposition of the starting triyne was observed.
To rationalize the moderate enantioselectivities, two plausible reaction pathways for the formation of chiral 1,3-dihydroisobenzofurans could be considered, A and B (Scheme 198). Reaction pathway A would comply a catalytic cycle starting from the intermolecular oxidative coupling of two alkyne motifs from both triyne and alkyne with rhodium species to afford the rhodacyclopentadiene intermediate Rh-I. Subsequent intramolecular selective coordination of one of the two alkynes substituted on the quaternary carbon atom to rhodium would lead to the intermediate Rh-II. This step could be considered as the enantioselective determining step affording higher enantioselective excess because of the steric interaction between the uncoordinated alkynyl group and the chiral ligand. The intramolecular insertion of the alkyne to the rhodium-carbon bond of Rh-II would deliver the seven-membered rhodacyle intermediate Rh-III, and the final reductive elimination would provide the 1,3-dihydroisobenzofuran with high ee.

On the other hand, pathway B would involve the rhodacyclopentadiene intermediate Rh-I’ initially formed by the fast intramolecular oxidative coupling of the triyne with rhodium species. The low enantioselectivities would be explained by the position of the quaternary center located “far” from the metal center. Coordination and insertion of the monoalkyne would
also lead to the rhodacycle intermediate Rh-III. Reductive elimination would regenerate the rhodium species, and deliver the cycloadduct with lower ee. Considering the moderate enantioselectivities observed, we hypothesized that these two reaction pathways would occur at the same time.

![Scheme 198]

**6. Conclusion**

In summary, we have developed a new route for the synthesis of enantioenriched 1,3-dihydroisobenzofuran derivatives via an enantioselective rhodium-catalyzed [2+2+2] cycloaddition of prochiral triynes and monoalkynes. The reaction proceeded in the presence of a cationic Rh(cod)\(_2\)BF\(_4/(R)\)-BINAP complex in DCM. This desymmetrization strategy allowed the formation of 1,1-disubstituted 1,3-dihydroisobenzofurans containing a quaternary carbon stereocenter in up to 79% yield and up to 52% ee. Two plausible reaction pathways were proposed to rationalize the moderate enantioselectivities.
Chapter IV
General conclusion
General conclusion

With the aim of the PhD project to develop environmentally friendly and atom-economical processes to access biologically interesting polycyclic and heterocyclic aromatic compounds via transition-metal-catalyzed [2+2+2] cycloaddition reactions, we successfully accessed relevant building blocks including fluorenones, 2-aminopyridines and enantioenriched 1,3-dihydroisobenzofurans.

This work was first dedicated to the development of an efficient and practical route for the preparation of highly substituted fluorenones and analogues via solvent-free RuCl$_3$·nH$_2$O-mediated [2+2+2] cycloaddition of α,ω-diyynes and alkynes. This green approach involves a solvent-free and atom-economical catalytic process to generate densely functionalized fluorenones and related derivatives of high synthetic utility (Scheme 199).

![Scheme 199](image)

We also developed a convenient access to functionalized 2-aminopyridines via a solvent-free RuCl$_3$·nH$_2$O-promoted [2+2+2] cycloaddition reaction of α,ω-diyynes and cyanamides. This transformation efficiently proceeds in the presence of a stable, easy to handle, and cost-effective RuCl$_3$·nH$_2$O complex, leading to various 2-aminopyridines in moderate to high yields following an eco-friendly straightforward approach. During the course of the studies, we found that the cationic ruthenium complex, Cp*Ru(CH$_3$CN)$_3$PF$_6$, could also be an efficient catalyst to promote the [2+2+2] cycloadditions of 1,6- and 1,7-diyynes with cyanamides to prepare 2-aminopyridines. Mild reaction conditions were developed for this transformation. Notably, this atom-economical catalytic process demonstrated remarkable

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regioselectivities to access highly substituted pyridine derivatives of high synthetic utility (Scheme 200).

**Scheme 200**

Taking advantage of the cationic \( \text{Cp}^*\text{Ru(CH_3CN)}_3\text{PF_6} \) catalytic system, we also synthesized a family of aza-fluorenones and aza-fluorenes with high regioselectivities (Scheme 201).

**Scheme 201**

Finally, we focused on the enantioselective synthesis of substituted 1,3-dihydroisobenzofurans, containing a quaternary carbon stereogenic center, through a [2+2+2] cycloaddition of prochiral triynes with internal alkynes using a cationic rhodium complex incorporating BINAP ligand. Moderate yields and enantioselectivities were obtained (Scheme 202). Further investigations of this method are underway in the laboratory.

**Scheme 202**
Experimental part
Experimental part

1. General informations

1.1. Analysis

$^1$H NMR and $^{13}$C NMR were recorded on Bruker AV300 or AV400 instruments. All signals are expressed as ppm ($\delta$) and are referenced to the non-deuterated solvent peak CHCl$_3$ (7.26 ppm for $^1$H and 77.16 ppm for $^{13}$C) or Methanol-D$_4$ (3.31 ppm for $^1$H and 49.00 ppm for $^{13}$C). Coupling constants ($J$) are given in Hz and refer to apparent peak multiplicities. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

Melting points were determined with a Kofler Heizbank 7841 apparatus and are uncorrected.

Enantiomeric excesses were determined by SFC using stationary phase columns: Daicel Chiralpak OD-H.

Mass spectrometry analyses (direct introduction by chemical ionization with ammoniac or electrospray) were performed at the Ecole Nationale Supérieure de Chimie de Paris (ENSCP). High resolution mass spectra were performed at the University Pierre and Marie Curie (Paris).

X-ray diffraction was made at Pierre et Marie Curie University (UPMC).

1.2. Chromatography

Sigma-Aldrich Silica gel (high-purity grade, pore size 60 Å, 230-400 mesh particle size, 40-63 μm particle size) was employed for flash column chromatography. Analytical thin layer chromatography (TLC) was carried out using commercial silica-gel plates (Merck 60 F254), spots were detected with UV light (254 nm) and revealed with a KMnO$_4$ or para-anisaldehyde stain solution.
Experimental part

1.3. Purification of solvents and reagents

All reactions were performed under an atmosphere of argon. Toluene, THF, CH$_2$H$_2$, DMF, Et$_2$O were dried over alumina columns in an Innovative Technologies apparatus. Acetone was distilled over K$_2$CO$_3$, and water was distilled. All the solvents for catalysis were degassed prior to use.

All reagents were used as received from commercial sources, unless specified otherwise, or prepared as described in the literature. Every reagent was either purified following the methods described in the literature or used without further purification.

2. Formation of fluorenone and related derivatives

2.1. Synthesis of benzoyl bridged $\alpha,\omega$-diynes

**General procedure A:**

$$
R^1\text{-}X + 
\begin{array}{c}
\equiv
\end{array}
R^2 \xrightarrow[	ext{(1.2-1.5 equiv)}]{	ext{PdCl}_2(\text{PPh}_3)_2 \text{ 2-5 mol %}} \xrightarrow[	ext{Cu 1-2.5 mol %}]{\text{Et}_3N/\text{THF}(1:1)} 
\begin{array}{c}
R^1
\equiv
R^2
\end{array}
50^\circ C, 3-12 h
$$

PdCl$_2$(PPh$_3$)$_2$ (2-5 mol %) and CuI (1-2.5 mol %) were added to a NEt$_3$/THF (1:1, 5.0 M) solution containing aryl halide (1.0 equiv), alkyne (1.2-1.5 equiv). The mixture was stirred at 50 °C for 3-5 h. When the reaction was complete (TLC monitoring), the mixture was cooled to room temperature. A saturated aqueous solution of ammonium chloride was added and the mixture was stirred for 5 minutes. The organic layer was extracted with ethyl acetate ($\times$3), washed with brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desire compound.

**General procedure B:**

$$
R^1\text{-}CHO + 
\begin{array}{c}
\equiv
\end{array}
R^2 \xrightarrow[	ext{(1.5 equiv)}]{\text{nBuLi 1.2 equiv}} \xrightarrow[	ext{THF, -70 °C to rt, 3-4 h}]{\text{OH}}
\begin{array}{c}
R^1
\equiv
R^2
\end{array}
$$

To a THF solution of alkyne (1.2 equiv, 5.0 M) was added nBuLi (1.3 equiv) at -70 °C. The mixture was warmed to 0 °C and stirred for 1 h. The resulting mixture was then cooled to
Experimental part

-70 °C again and a solution of aldehyde (1.0 equiv) in THF was added over 10 min. Then the mixture was warmed to room temperature and stirred for 2-3 h before addition of a saturated aqueous ammonium chloride solution. The organic layer was extracted with ethyl acetate (×3), washed with water and brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desired compound.

**General procedure C:**

Dess-Martin periodinane (1.3 equiv) was added to a solution of corresponding alcohol (1 equiv) in anhydrous CH₂Cl₂ (5 M) at 0 °C and the resulting mixture was stirred at room temperature for 4-12 h. When the reaction was complete (TLC monitoring), the reaction mixture was filtered through a pad of celite. A saturated aqueous solution of NaHCO₃ was added to the organic layer and stirred for 20 minutes. The organic layer was washed with water and brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desired compound.

**General procedure D:**

TBAF (1 M in THF, 1.0 equiv) was added to a solution of TMS-protected product (1 equiv) in THF (5 M) at 0 °C and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with water and the product was extracted with DCM (×3). The organic layer washed with saturated aqueous solution of NaHCO₃, water and brine, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to afford the desired product.

| 2-(Phenylethynyl)benzaldehyde (1) |
Experimental part

This compound was prepared using procedure A. Starting from 2-bromobenzaldehyde (1.0 g, 5.4 mmol) and phenylacetylene (0.71 mL, 6.5 mmol, 1.2 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 100/0 to 98/2) afforded 1 (0.85 g, 76%) as an orange oil. The analytical data were identical to the literature.\textsuperscript{183}

\[ R_f = 0.6 \] (Cyclohexane/Ethyl acetate; 95/5, KMnO\textsubscript{4}, UV).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}), \[ \delta 10.66 \text{ (d, } J = 0.8 \text{ Hz, 1H)}, 7.97 - 7.94 \text{ (m, 1H)}, 7.66 - 7.54 \text{ (m, 4H)}, 7.47 - 7.37 \text{ (m, 4H)}. \]

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}), \[ \delta 191.8, 135.9, 133.9, 133.3, 131.8, 129.2, 128.7, 128.6, 127.4, 127.0, 122.4, 96.4, 85.0. \]

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{2-(Hex-1-yn-1-yl)-benzaldehyde (2)} & \\
\hline
\end{tabular}
\end{table}

This compound was prepared using procedure A. Starting from 2-bromobenzaldehyde (2.5 g, 13.5 mmol) and 1-hexyne (2.0 mL, 17.5 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 99/1 to 95/5) afforded 2 (1.95 g, 79%) as a brown oil. The analytical data were identical to the literature.\textsuperscript{183}

\[ R_f = 0.8 \] (Cyclohexane/Ethyl acetate; 90/10, KMnO\textsubscript{4}, UV).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}), \[ \delta 10.53 \text{ (d, } J = 0.7 \text{ Hz, 1H)}, 7.87 \text{ (dd, } J = 4.8, 4.0 \text{ Hz, 1H)}, 7.53 - 7.47 \text{ (m, 2H)}, 7.41 - 7.30 \text{ (m, 1H)}, 2.48 \text{ (t, } J = 7.0 \text{ Hz, 2H)}, 1.68 - 1.55 \text{ (m, 2H)}, 1.55 - 1.40 \text{ (m, 2H)}, 0.95 \text{ (t, } J = 7.2 \text{ Hz, 3H)}. \]

\begin{flushright}
\end{flushright}
\( ^{13} \text{C NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) 192.3, 136.2, 133.8, 133.4, 128.1, 128.0, 127.0, 98.3, 76.5, 30.7, 22.2, 19.4, 13.7.

**MS (CI, NH\(_3\))**: \( m/z = 187 \) [M + H] \(^+\).

### 2-(((Trimethylsilyl)ethynyl)benzaldehyde (3)

This compound was prepared using procedure A. Starting from 2-bromobenzaldehyde (3.68 g, 20.0 mmol) and trimethylsilylacetylene (3.3 mL, 24.0 mmol, 1.2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 90/10) afforded 3 (3.5 g, 87%) as a white solid. m.p. 56 – 58 °C.

**\( R_f \) = 0.62** (Cyclohexane/Ethyl acetate; 95/5, KMnO\(_4\), UV).

\( ^1 \text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 10.37 (d, \( J = 0.8 \) Hz, 1H), 7.74 – 7.68 (m, 1H), 7.41 – 7.29 (m, 2H), 7.26-7.19 (m, 1H), 0.10 (s, 9H).

\( ^{13} \text{C NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) 191.8, 136.3, 133.7, 133.6, 128.9, 127.0, 126.9, 102.5, 100.2, -0.1.

**MS (CI, NH\(_3\))**: \( m/z = 203 \) [M + H] \(^+\).

### 2-(p-Tolyethynyl)benzaldehyde (4)

This compound was prepared using procedure A. Starting from 2-bromobenzaldehyde (2.5 g, 13.5 mmol) and 4-ethynyltoluene (1.88 mL, 16.2 mmol, 1.2 equiv). Purification on silica gel
Experimental part

(Cyclohexane/Ethyl acetate gradient from 99/1 to 98/2) afforded 4 (2.3 g, 80%) as a white solid. m.p. 32 – 34 °C. The analytical data were identical to the literature.184

Rt = 0.62 (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

**1H NMR** (300 MHz, CDCl₃), δ 10.66 (d, J = 0.9 Hz, 1H), 7.97 – 7.92 (m, 1H), 7.68 – 7.53 (m, 2H), 7.49 – 7.41 (m, 3H), 7.23– 7.16 (m, 2H), 2.39 (s, 3H).

**13C NMR** (75 MHz, CDCl₃), δ 191.9, 139.5, 136.0, 133.9, 133.3, 131.7, 129.4, 128.5, 127.4, 119.4, 96.8, 84.5, 21.7.

**MS** (Cl, NH₃): m/z = 221 [M + H]⁺.

---

<table>
<thead>
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<th>2-((4-(tert-Butyl)phenyl)-ethynyl)-benzaldehyde (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C₁₉₂₅H₂₅O</td>
</tr>
<tr>
<td>Exact Mass: 262.1358</td>
</tr>
</tbody>
</table>

This compound was prepared using procedure A. Starting from 2-bromobenzaldehyde (2.5 g, 13.5 mmol) and 4-(tert-butyl)phenylacetylene (2.56 g, 16.2 mmol, 1.2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 99/1 to 98/2) afforded 5 (2.4 g, 70%) as a brown solid. m.p. 50 – 52 °C. The analytical data were identical to the literature.185

Rt = 0.7 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

**1H NMR** (300 MHz, CDCl₃), δ 10.66 (s, 1H), 7.95 (dd, J = 7.8, 0.8 Hz, 1H), 7.68 – 7.54 (m, 2H), 7.54 – 7.35 (m, 5H), 1.34 (s, 9H).

**13C NMR** (75 MHz, CDCl₃), δ 192.0, 152.7, 136.0, 133.9, 133.3, 131.6, 130.2, 128.6, 127.3, 125.7, 119.5, 96.8, 84.5, 35.1, 31.3.

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| 6-(Phenylethynyl)benzo[d][1,3]dioxole-5-carbaldehyde (6) |

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This compound was prepared using procedure A. Starting from 2-bromo-4,5-methylenedioxybenzaldehyde (2.3 g, 10.0 mmol) and phenylacetylene (1.2 mL, 11.2 mmol, 1.1 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 99/1 to 98/2) afforded 6 (1.8 g, 72%) as a white solid. m.p. 118 – 120 °C. The analytical data were identical to the literature.\textsuperscript{186}

R\textsubscript{f} = 0.6 (Cyclohexane/Ethyl acetate; 95/5, KMnO\textsubscript{4}, UV).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 10.49 (s, 1H), 7.58-7.49 (m, 2H), 7.41-7.34 (m, 4H), 7.03 (s, 1H), 6.09 (s, 2H).

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 190.1, 152.5, 148.9, 132.3, 131.7, 129.1, 128.7, 123.8, 122.5, 112.2, 106.3, 102.5, 95.3, 84.9.

MS (Cl, NH\textsubscript{3}): m/z = 251 [M + H]\textsuperscript{+}.

### 5-Fluoro-2-(phenylethynyl)benzaldehyde (7)

This compound was prepared using procedure A. Starting from 2-bromo-5-fluorobenzaldehyde (2.0 g, 10.0 mmol) and phenylacetylene (1.23 g, 12.0 mmol, 1.2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded 7 (1.55 g, 70%) as a pale yellow solid. m.p. 54 – 56 °C. The analytical data were identical to the literature.\textsuperscript{187}


Experimental part

**R**\textsubscript{f} = 0.62 (Cyclohexane/Ethyl acetate; 95/5, KMnO\textsubscript{4}, UV).

**\textsuperscript{1}H NMR** (300 MHz, CDCl\textsubscript{3}) \(\delta\) 10.60 (d, \(J = 3.0\) Hz, 1H), 7.68-7.59 (m, 2H), 7.58-7.52 (m, 2H), 7.43-7.36 (m, 3H), 7.34-7.26 (m, 1H).

**\textsuperscript{13}C NMR** (75 MHz, CDCl\textsubscript{3}) \(\delta\) 190.5, 162.6 (d, \(J = 215.6\) Hz), 138.0 (d, \(J = 6.6\) Hz), 135.4 (d, \(J = 7.7\) Hz), 131.8, 129.3, 128.7, 123.1 (d, \(J = 3.3\) Hz), 122.3, 121.5 (d, \(J = 22.6\) Hz), 113.9 (d, \(J = 22.6\) Hz), 96.2, 84.0.

**\textsuperscript{19}F NMR** (282 MHz, (CDCl\textsubscript{3}): -109.94 (t, \(J = 2.8\) Hz).

**MS** (Cl, NH\textsubscript{3}): m/z = 242 [M + NH\textsubscript{4}]\(^+\).

This compound was prepared using procedure B. Starting from 2-(phenylethynyl)benzaldehyde 1 (2.6 g, 12.6 mmol) and 1-hexyne (2.16 mL, 18.0 mmol, 1.5 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded 8 (3.3 g, 92%) as a pale orange oil. The analytical data were identical to the literature.\textsuperscript{188}

**R**\textsubscript{f} = 0.34 (Cyclohexane/Ethyl acetate; 90/10, KMnO\textsubscript{4}, UV).

**\textsuperscript{1}H NMR** (300 MHz, CDCl\textsubscript{3}), \(\delta\) 7.74 (dd, \(J = 7.7, 1.3\) Hz, 1H), 7.58 – 7.54 (m, 3H), 7.42 – 7.28 (m, 5H), 5.96 (s, 1H), 2.70 (s, 1H), 2.30 – 2.25 (m, 2H), 1.51 – 1.39 (m, 4H), 0.88 (t, \(J = 7.2\) Hz, 3H).

**\textsuperscript{13}C NMR** (75 MHz, CDCl\textsubscript{3}), \(\delta\) 143.0, 132.5, 131.7, 128.9, 128.7, 128.5, 128.2, 126.7, 123.0, 121.4, 94.9, 87.7, 86.8, 79.4, 63.5, 30.7, 22.1, 18.7, 13.7.

1-(2-(Hex-1-yn-1-yl)-phenyl)hept-2-yn-1-ol (9)

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This compound was prepared using procedure B. Starting from 2-(hex-1-yn-1-yl)benzaldehyde 2 (0.91 g, 4.9 mmol) and 1-hexyne (0.73 mL, 6.4 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate 95/5) afforded 9 (0.68 g, 50%) as a pale orange oil.

\( \text{Rf} = 0.38 \) (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

\( ^{1}H \text{ NMR} \) (300 MHz, CDCl₃) \( \delta 7.66 \) (dd, \( J = 7.6, 1.4 \text{ Hz}, 1\text{H} \)), 7.41 (dd, \( J = 7.5, 1.4 \text{ Hz}, 1\text{H} \)), 7.34 – 7.20 (m, 2H), 5.88 – 5.79 (m, 1H), 2.64 (d, \( J = 5.5 \text{ Hz}, 1\text{H} \)), 2.46 (t, \( J = 7.0 \text{ Hz}, 2\text{H} \)), 2.28 (t, \( J = 7.0 \text{ Hz}, 2\text{H} \)), 1.65 – 1.52 (m, 4H), 1.49 – 1.37 (m, 4H), 0.96 (t, \( J = 7.1 \text{ Hz}, 3\text{H} \)), 0.91 (t, \( J = 7.1 \text{ Hz}, 3\text{H} \)).

\( ^{13}C \text{ NMR} \) (75 MHz, CDCl₃) \( \delta 142.9, 132.6, 128.2, 128.1, 126.7, 122.3, 96.3, 87.6, 79.4, 78.1, 63.7, 30.9, 30.8, 22.2, 22.1, 19.4, 18.7, 13.7.

\( \text{MS} \) (CI, NH₃): m/z = 251 [M + H - H₂O]⁺.

<table>
<thead>
<tr>
<th>1-(2-(Hex-1-yn-1-yl)phenyl)-3-phenylprop-2-yn-1-ol (10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="" alt="Chemical structure" /></td>
</tr>
<tr>
<td><strong>Exact Mass:</strong> 288.1514</td>
</tr>
</tbody>
</table>

This compound was prepared using procedure B. Starting from 2-(hex-1-yn-1-yl)-benzaldehyde 2 (1 g, 5.4 mmol) and phenylacetylene (0.77 mL, 7.0 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded 10 (1.25 g, 81%) as a pale yellow oil.

\( \text{Rf} = 0.4 \) (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).
Experimental part

\[^{1}\text{H\ NMR}\ (300\ \text{MHz, CDCl}\text{$_3$})\ \delta\ 7.73\ (dd,\ J = 7.6, 1.6\ \text{Hz, 1H}), 7.52 – 7.41\ (m,\ 3H), 7.37 – 7.23\ (m,\ 5H), 6.06\ (s,\ 1H), 2.80\ (br,\ 1H), 2.49\ (t,\ J = 7.0\ \text{Hz, 2H}), 1.69 – 1.56\ (m,\ 2H), 1.56 – 1.44\ (m,\ 2H), 0.94\ (t,\ J = 7.3\ \text{Hz, 3H}).\]

\[^{13}\text{C\ NMR}\ (75\ \text{MHz, CDCl}\text{$_3$})\ \delta\ 142.3, 132.7, 131.9, 128.6, 128.4, 128.3, 128.3, 126.8, 122.8, 122.4, 96.7, 88.5, 86.6, 78.1, 64.1, 30.9, 22.2, 19.5, 13.8.\]

\[^{\text{MS\ (CI, NH}}\text{$_3$)}: m/z = 271\ [M + H - H$_2$O]^+.\]

\begin{center}
\textbf{3-Cyclopropyl-1-(2-(phenylethynyl)phenyl)prop-2-yn-1-ol (11)}
\end{center}

This compound was prepared using procedure B. Starting from 2-(phenylethynyl)benzaldehyde 1 (1.1 g, 5.3 mmol) and cyclopropylacetylene (0.58 mL, 7.0 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded 11 (1.2 g, 92%) as a pale yellow oil. The analytical data were identical to the literature.\(^{188}\)

\[^{\text{Rf} = 0.38\ (\text{Cyclohexane/Ethyl acetate; 90/10, KMnO}_4, UV).}\]

\[^{1}\text{H\ NMR\ (300\ MHz, CDCl}\text{$_3$})\ \delta\ 7.70\ (dd,\ J = 7.6, 1.4\ \text{Hz, 1H}), 7.60 – 7.51\ (m,\ 3H), 7.42 – 7.34\ (m,\ 4H), 7.34 – 7.30\ (m, 1H), 5.90\ (dd,\ J = 5.5, 1.6\ \text{Hz, 1H}), 2.62\ (d,\ J = 5.6\ \text{Hz, 1H}), 1.38 – 1.23\ (m,\ 1H), 0.79 – 0.69\ (m,\ 4H).\]

\[^{13}\text{C\ NMR\ (75\ MHz, CDCl}\text{$_3$})\ \delta\ 142.9, 132.5, 131.7, 129.0, 128.7, 128.5, 128.2, 126.8, 123.0, 121.4, 94.9, 90.7, 86.8, 74.7, 63.6, 8.4, -0.3.\]

\[^{\text{MS\ (CI, NH}}\text{$_3$)}: m/z = 255\ [M + H - H$_2$O]^+.\]

\begin{center}
\textbf{1-(2-((Trimethylsilyl)ethynyl)phenyl)hept-2-yn-1-ol (12)}
\end{center}
This compound was prepared using procedure B. Starting from 2-((trimethylsilyl)ethynyl)benzaldehyde 3 (1.5 g, 7.4 mmol) and 1-hexyne (1.1 mL, 9.6 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 12 (1.7 g, 80%) as a colorless oil. The analytical data were identical to the literature.\textsuperscript{189}

$$\text{R}_f = 0.44 \text{ (Cyclohexane/Ethyl acetate; 90/10, KMnO}_4, \text{ UV).}$$

\textbf{\textsuperscript{1}H NMR} (300 MHz, CDCl\textsubscript{3}) \(\delta\) 7.71 – 7.63 (m, 1H), 7.47 (dd, \(J = 7.6, 1.2\) Hz, 1H), 7.35 (td, \(J = 7.6, 1.4\) Hz, 1H), 7.28 – 7.21 (m, 1H), 5.87 – 5.80 (m, 1H), 2.77 (d, \(J = 5.4\) Hz, 1H), 2.27 (td, \(J = 7.0, 2.0\) Hz, 2H), 1.59 – 1.35 (m, 4H), 0.91 (t, \(J = 7.2\) Hz, 3H), 0.28 (s, 9H).

\textbf{\textsuperscript{13}C NMR} (75 MHz, CDCl\textsubscript{3}) \(\delta\) 143.7, 132.9, 129.2, 128.1, 120.3, 120.1, 121.3, 100.5, 100.5, 87.8, 79.2, 63.6, 30.8, 22.1, 18.7, 13.7, -0.02.

\textbf{MS} (CI, NH\textsubscript{3}): m/z = 267 [M + H - H\textsubscript{2}O]\textsuperscript{+}.

\begin{center}
\textbf{1-(2-(p-Tolylethynyl)phenyl)hept-2-yn-1-ol (13)}
\end{center}

This compound was prepared using procedure B. Starting from 2-(p-tolylethynyl)benzaldehyde 4 (1.0 g, 4.6 mmol) and 1-hexyne (0.68 mL, 5.9 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 13 (1.19 g, 87%) as a pale oil. The analytical data were identical to the literature.\textsuperscript{190}

\textsuperscript{189} Schmittel, M.; Strittmatter, M.; Mahajan, A. A.; Vavilala, C.; Cinar, M. E.; Maywald, M. \textit{Arkivoc} 2007, 66.

Experimental part

**R**<sub>f</sub> = 0.43 (Cyclohexane/Ethyl acetate; 90/10, KMnO<sub>4</sub>, UV).

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.78-7.70 (m, 1H), 7.58-7.51 (m, 1H), 7.51-7.43 (m, 2H), 7.41-7.27 (m, 2H), 7.22-7.14 (m, 2H), 5.96 (s, 1H), 2.81 (d, <i>J</i> = 4.8 Hz, 1H), 2.38 (s, 3H), 2.33-2.24 (m, 2H), 1.59-1.35 (m, 4H), 0.90 (t, <i>J</i> = 7.2 Hz, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 143.0, 138.8, 132.3, 131.5, 129.2, 128.7, 128.1, 126.6, 121.6, 119.9, 95.1, 87.5, 86.2, 79.5, 63.5, 30.7, 22.0, 21.6, 18.6, 13.6.

**MS** (Cl, NH<sub>3</sub>): m/z = 285 [M + H - H<sub>2</sub>O]<sup>+</sup>.

1-(2-((4-(<i>tert</i>-Butyl)phenyl)-ethynyl)-phenyl)-hept-2-yn-1-ol (14)

![Chemical structure of compound 14](image)

This compound was prepared using procedure B. Starting from 2-((4-(<i>tert</i>-butyl)phenyl)-ethynyl)-benzaldehyde 5 (0.92 g, 3.5 mmol) and 1-hexyne (0.52 mL, 4.5 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 14 (1.0 g, 83%) as a pale oil.

**R**<sub>f</sub> = 0.42 (Cyclohexane/Ethyl acetate; 90/10, KMnO<sub>4</sub>, UV).

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.72 (dd, <i>J</i> = 7.6, 1.4 Hz, 1H), 7.54 (dd, <i>J</i> = 7.5, 1.3 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.43 – 7.34 (m, 3H), 7.30 (td, <i>J</i> = 7.5, 1.5 Hz, 1H), 5.91 – 5.96 (m, 1H), 2.48 (br, 1H), 2.28 (td, <i>J</i> = 7.0, 2.0 Hz, 2H), 1.56 – 1.35 (m, 4H), 1.33 (s, 9H), 0.88 (t, <i>J</i> = 7.2 Hz, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 152.1, 143.0, 132.5, 131.5, 128.8, 128.2, 126.8, 125.6, 121.8, 120.0, 95.2, 87.8, 86.2, 79.5, 63.7, 35.0, 31.3, 30.8, 22.1, 18.7, 13.7.

**MS** (Cl, NH<sub>3</sub>): m/z = 327 [M + H - H<sub>2</sub>O]<sup>+</sup>.

1-(6-(Phenylethynyl)benzo[d][1,3]dioxol-5-yl)hept-2-yn-1-ol (15)
This compound was prepared using procedure B. Starting from 6-(phenylethynyl)benzo[d][1,3]dioxole-5-carbaldehyde 6 (1.0 g, 4.0 mmol) and 1-hexyne (0.6 mL, 5.2 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 15 (1.27 g, 96%) as a colorless oil.

Rf = 0.27 (Cyclohexane/Ethyl acetate; 90/10, KMnO4, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.58 – 7.47 (m, 2H), 7.40 – 7.29 (m, 3H), 7.24 (s, 1H), 6.96 (s, 1H), 6.01 (s, 2H), 5.92 (d, $J = 2.0$ Hz, 1H), 2.46 (d, $J = 4.6$ Hz, 1H), 2.27 (td, $J = 7.0$, 2.0 Hz, 2H), 1.55 – 1.33 (m, 4H), 0.89 (t, $J = 7.2$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 148.5, 147.4, 138.6, 131.6, 128.5, 123.2, 114.9, 111.7, 107.6, 101.8, 93.4, 87.7, 86.8, 79.5, 63.2, 30.8, 22.1, 18.7, 13.7.

MS (Cl, NH$_3$): m/z = 315 [M + H - H$_2$O]$^+$. 

This compound was prepared using procedure B. Starting from 5-fluoro-2-(phenylethynyl)phenylhept-2-yne-1-ol (16)

Rf = 0.35 (Cyclohexane/Ethyl acetate; 90/10, KMnO4, UV).
Experimental part

**H NMR** (300 MHz, CDCl$_3$) $\delta$ 7.58 – 7.49 (m, 3H), 7.46 (dd, $J = 9.5$, 2.6 Hz, 1H), 7.40 – 7.32 (m, 3H), 7.01 (td, $J = 8.3$, 2.7 Hz, 1H), 5.91 (s, 1H), 2.56 (d, $J = 4.9$ Hz, 1H), 2.27 (td, $J = 7.0$, 1.9 Hz, 2H), 1.54 – 1.34 (m, 4H), 0.88 (t, $J = 7.2$ Hz, 3H).

**13C NMR** (75 MHz, CDCl$_3$) $\delta$ 162.8 (d, $J = 247.5$ Hz), 145.8 (d, $J = 7.1$ Hz), 134.4 (d, $J = 8.2$ Hz), 131.7, 128.8, 128.6, 123.0, 117.5 (d, $J = 3.3$ Hz), 115.4 (d, $J = 22.0$ Hz), 114.2 (d, $J = 23.6$ Hz), 94.6, 88.2, 85.9, 79.0, 63.1, 30.7, 22.1, 18.7, 13.7.

**F NMR** (282 MHz, (CDCl$_3$) $\delta$ -110.5 (dd, $J = 14.1$, 8.5 Hz).

**MS** (CI, NH$_3$): m/z = 289 [M + H - H$_2$O]$^+$.  

<table>
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<tr>
<th>1-(2-(phenylethynyl)phenyl)hept-2-yn-1-one (17)</th>
</tr>
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<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C$<em>{21}$H$</em>{18}$O</td>
</tr>
<tr>
<td>Exact Mass: 286.1358</td>
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</table>

This compound was prepared using procedure C. Starting from 1-(2-(phenylethynyl)phenyl)hept-2-yn-1-ol 8 (1.7 g, 5.9 mmol) and Dess-Martin periodinane (3.25 g, 7.6 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 100/0 to 98/2) afforded 17 (1.6 g, 94%) as a pale yellow oil. The analytical data were identical to the literature.\(^{191}\)

**Rt = 0.42** (Cyclohexane/Ethyl acetate; 95/5, KMnO$_4$, UV).

**H NMR** (300 MHz, CDCl$_3$), $\delta$ 8.11 (dd, $J = 7.8$, 1.3 Hz, 1H), 7.65 – 7.59 (m, 3H), 7.51 (td, $J = 7.5$, 1.4 Hz, 1H), 7.42 (td, $J = 7.6$, 1.4 Hz, 1H), 7.37 – 7.32 (m, 3H), 2.43 (t, $J = 7.1$ Hz, 2H), 1.61 – 1.56 (m, 2H), 1.47 – 1.42 (m, 2H), 0.90 (t, $J = 7.3$ Hz, 3H).

**C NMR** (75 MHz, CDCl$_3$), $\delta$ 177.8, 138.4, 134.3, 132.4, 132.0, 131.8, 128.7, 128.4, 127.9, 123.4, 122.9, 97.2, 95.2, 88.4, 80.8, 29.9, 22.2, 19.1, 13.6.

Experimental part

1-(2-(hex-1-yn-1-yl)phenyl)-hept-2-yn-1-one (18)

This compound was prepared using procedure C. Starting from 1-(2-(hex-1-yn-1-yl)phenyl)-hept-2-yn-1-ol 9 (0.68 g, 2.5 mmol) and Dess-Martin periodinane (1.39 g, 3.3 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 100/0 to 98/2) afforded 18 (0.52 g, 76%) as a pale oil.

Rf = 0.4 (Cyclohexane/Ethyl acetate; 95/5, KMN04, UV).

1H NMR (300 MHz, CDCl3) δ 8.04 (dd, J = 7.8, 1.3 Hz, 1H), 7.54 – 7.40 (m, 2H), 7.35 (td, J = 7.5, 1.5 Hz, 1H), 2.54 – 2.40 (m, 4H), 1.70 – 1.56 (m, 4H), 1.56 – 1.40 (m, 4H), 0.95 (t, J = 7.2 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H).

13C NMR (75 MHz, CDCl3) δ 178.1, 138.6, 134.7, 132.2, 131.7, 127.2, 123.8, 97.0, 96.7, 81.0, 79.3, 30.8, 30.0, 22.2, 19.8, 19.1, 13.8, 13.7.

MS (ESI, NH3): m/z = 267 [M + H]+.

1-(2-(Hex-1-yn-1-yl)phenyl)-3-phenylprop-2-yn-1-one (19)

This compound was prepared using procedure C. Starting from 1-(2-(hex-1-yn-1-yl)phenyl)-3-phenylprop-2-yn-1-ol 11 (1.25 g, 4.37 mmol) and Dess-Martin periodinane (2.4 g, 5.7 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 19 (1.05 g, 84%) as an orange oil.

Rf = 0.62 (Cyclohexane/Ethyl acetate; 90/10, KMN04, UV).
Experimental part

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.14 – 8.03 (m, 1H), 7.65 (dd, $J = 8.1$, 1.4 Hz, 2H), 7.57 – 7.34 (m, 6H), 2.43 (t, $J = 7.0$ Hz, 2H), 1.65 – 1.52 (m, 2H), 1.52 – 1.40 (m, 2H), 0.90 (t, $J = 7.2$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 178.0, 138.7, 134.7, 133.2, 132.4, 131.3, 130.8, 128.7, 127.3, 124.1, 120.6, 97.6, 93.2, 88.4, 79.2, 30.8, 22.2, 19.8, 13.7.

<table>
<thead>
<tr>
<th>3-cyclopropyl-1-(2-(phenylethynyl)phenyl)prop-2-yn-1-one (20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>

This compound was prepared using procedure C. Starting from 3-cyclopropyl-1-(2-(phenylethynyl)phenyl)prop-2-yn-1-ol 11 (1.1 g, 4.0 mmol) and Dess-Martin periodinane (2.2 g, 5.2 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 99/1 to 98/2) afforded 20 (0.82 g, 75%) as a pale yellow oil.

$R_t = 0.55$ (Cyclohexane/Ethyl acetate; 90/10, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$), $\delta$ 8.07 – 8.02 (m, 1H), 7.66 – 7.58 (m, 3H), 7.51 (td, $J = 7.5$, 1.5 Hz, 1H), 7.41 (td, $J = 7.5$, 1.5 Hz, 1H), 7.38 – 7.33 (m, 3H), 1.49 – 1.41 (m, 1H), 0.99 – 0.93 (m, 4H).

$^{13}$C NMR (75 MHz, CDCl$_3$), $\delta$ 177.6, 138.8, 134.3, 132.2, 132.0, 131.5, 128.7, 128.4, 128.0, 123.5, 122.9, 101.6, 95.3, 88.4, 10.0, 0.3.

MS (ESI, NH$_3$): m/z = 271 [M + H]$^+$. 

<table>
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<tr>
<th>1-(2-((Trimethylsilyl)ethynyl)phenyl)hept-2-yn-1-one (21)</th>
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<tbody>
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Chemical Formula: C$_{18}$H$_{22}$OSi
Exact Mass: 282.1440
This compound was prepared using procedure C. Starting from 1-(2-((trimethylsilyl)ethynyl)phenyl)hept-2-yn-1-ol 12 (2.06 g, 10.0 mmol) and Dess-Martin periodinane (5.1 g, 12.0 mmol, 1.2 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 21 (2.06 g, 74%) as a pale yellow oil.

**Rt = 0.58** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

**1H NMR** (300 MHz, CDCl₃) δ 8.10 – 7.96 (m, 1H), 7.61 – 7.51 (m, 1H), 7.48 – 7.41 (m, 1H), 7.41 – 7.35 (m, 1H), 2.45 (t, J = 7.1 Hz, 2H), 1.68 – 1.54 (m, 2H), 1.38 – 1.52 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H), 0.27 (s, 9H).

**13C NMR** (75 MHz, CDCl₃) δ 177.3, 139.2, 135.1, 132.1, 131.7, 128.2, 122.6, 103.3, 100.9, 96.8, 80.7, 29.9, 22.2, 19.1, 13.6, -0.1.

**MS** (ESI, NH₃): m/z = 283 [M + H]⁺.

This compound was prepared using procedure C. Starting from 1-(2-(p-tolylethynyl)phenyl)hept-2-yn-1-ol 13 (1.1 g, 3.64 mmol) and Dess-Martin periodinane (2.0 g, 4.73 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 22 (1.0 g, 91%) as a pale yellow solid. m.p. 35 – 37 °C.

**Rt = 0.6** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

**1H NMR** (300 MHz, CDCl₃) δ 8.14 – 8.06 (m, 1H), 7.68 – 7.58 (m, 1H), 7.56 – 7.46 (m, 3H), 7.45 – 7.37 (m, 1H), 7.20 – 7.13 (m, 2H), 2.43 (t, J = 7.2 Hz, 2H), 2.37 (s, 3H), 1.62 – 1.52 (m, 2H), 1.50 – 1.38 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H).

**13C NMR** (75 MHz, CDCl₃) δ 177.9, 138.9, 138.5, 134.3, 132.3, 132.0, 131.8, 129.2, 127.8, 123.3, 120.4, 97.2, 95.6, 87.9, 81.0, 29.9, 22.2, 21.7, 19.2, 13.6.
Experimental part

**MS** (ESI, NH₃): m/z = 301 [M + H]⁺.

![Chemical structure](image)

**1-(2-((4-(tert-Butyl)phenyl)ethynyl)-phenyl)-hept-2-yn-1-one (23)**

This compound was prepared using procedure C. Starting from 1-(2-((4-(tert-butyl)phenyl)ethynyl)-phenyl)-hept-2-yn-1-ol (0.36 g, 1.05 mmol) 14 and Dess-Martin periodinane (0.53 g, 1.25 mmol, 1.2 equiv). Purification on silica gel (Petroleum ether/ Ethyl acetate gradient from 99/1 to 98/2) afforded 23 (0.32 g, 89%) as a pale yellow oil.

**Rf = 0.55** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

**¹H NMR** (300 MHz, CDCl₃) δ 8.16 – 8.06 (m, 1H), 7.65 – 7.58 (m, 1H), 7.59 – 7.52 (m, 2H), 7.47 (td, J = 7.5, 0.8 Hz, 1H), 7.42 – 7.36 (m, 3H), 2.41 (t, J = 7.1 Hz, 2H), 1.61 – 1.50 (m, 2H), 1.46 – 1.38 (m, 2H), 1.31 (s, 9H), 0.88 (t, J = 7.3 Hz, 3H).

**¹³C NMR** (75 MHz, CDCl₃) δ 177.5, 151.9, 138.3, 134.1, 132.2, 131.6, 131.6, 127.6, 125.3, 123.1, 120.3, 96.9, 95.5, 87.8, 80.8, 34.8, 31.1, 29.8, 22.0, 19.0, 13.5.

**MS** (ESI, NH₃): m/z = 343 [M + H]⁺.

![Chemical structure](image)

**1-(6-(Phenylethynyl)benzo[d][1,3]dioxol-5-yl)hept-2-yn-1-one (24)**

This compound was prepared using procedure C. Starting from 1-(6-(phenylethynyl)benzo[d][1,3]dioxol-5-yl)hept-2-yn-1-ol 15 (1.25 g, 3.8 mmol) and Dess-
Experimental part

Martin periodinane (2.07 g, 4.9 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded 24 (0.9 g, 77%) as a pale yellow oil.

\( R_f = 0.31 \) (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

\(^1\text{H NMR}\) (300 MHz, CDCl₃) \( \delta 7.61 - 7.56 \) (m, 3H), \( 7.36 - 7.31 \) (m, 3H), 7.05 (s, 1H), 6.09 (s, 2H), 2.43 (t, \( J = 7.1 \) Hz, 2H), 1.63 – 1.53 (m, 2H), 1.46 – 1.37 (m, 2H), 0.92 (t, \( J = 7.2 \) Hz, 3H).

\(^{13}\text{C NMR}\) (75 MHz, CDCl₃) \( \delta 176.0, 151.1, 147.8, 133.9, 132.0, 128.6, 128.4, 123.6, 119.0, 113.6, 111.4, 102.5, 96.8, 94.3, 88.6, 80.8, 30.0, 22.2, 19.2, 13.6.

\( \text{MS (ESI, NH}_3\text{)}: m/z = 331 \ [M + H]^+ \).

This compound was prepared using procedure C. Starting from 1-(5-fluoro-2-(phenylethynyl)phenyl)hept-2-yn-1-ol 16 (1.1 g, 3.6 mmol) and Dess-Martin periodinane (1.98 g, 4.7 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 25 (0.95 g, 87%) as an orange oil.

\( R_f = 0.62 \) (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

\(^1\text{H NMR}\) (300 MHz, CDCl₃) \( \delta 7.79 \) (dd, \( J = 9.1, 2.7 \) Hz, 1H), \( 7.66 - 7.54 \) (m, 3H), \( 7.39 - 7.32 \) (m, 3H), 7.27 – 7.19 (m, 1H), 2.44 (t, \( J = 7.1 \) Hz, 2H), 1.66 – 1.51 (m, 2H), 1.50 – 1.36 (m, 2H), 0.90 (t, \( J = 7.3 \) Hz, 3H).

\(^{13}\text{C NMR}\) (75 MHz, CDCl₃) \( \delta 176.4, 161.8 \) (d, \( J = 249.8 \) Hz), 140.4 (d, \( J = 6.8 \) Hz), 136.2 (d, \( J = 7.5 \) Hz), 132.0, 128.8, 128.5, 123.3, 119.8 (d, \( J = 21.8 \) Hz), 119.1, 118.4 (d, \( J = 23.3 \) Hz), 98.2, 95.0, 87.4, 80.6, 29.9, 22.2, 19.2, 13.6.

\(^{19}\text{F NMR}\) (282 MHz, CDCl₃) \( \delta -111.4 \) (dd, \( J = 14.1, 8.5 \) Hz).
Experimental part

**MS** (ESI, NH₃): m/z = 305 [M + H]⁺.

### 1-(2-((4-(Trifluoromethyl)phenyl)ethynyl)phenyl)hept-2-yn-1-one (26)

![Chemical structure of 1-(2-((4-(Trifluoromethyl)phenyl)ethynyl)phenyl)hept-2-yn-1-one (26)](image)

This compound was prepared using procedure A. Starting from 1-(2-ethynylphenyl)hept-2-yn-1-one 29 (0.5 g, 2.38 mmol) and 4-iodobenzotrifluoride (0.71 g, 2.62 mmol, 1.1 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 99/1 to 98/2) afforded 26 (0.55 g, 65%) as a brown solid. m.p. 35 – 37 °C.

**Rf = 0.6** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

**¹H NMR** (300 MHz, CDCl₃) δ 8.21 – 8.11 (m, 1H), 7.75 – 7.68 (m, 2H), 7.68 – 7.58 (m, 3H), 7.58 – 7.52 (m, 1H), 7.51 – 7.44 (m, 1H), 2.46 (t, J = 7.1 Hz, 2H), 1.67 – 1.55 (m, 2H), 1.52 – 1.38 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H).

**¹³C NMR** (75 MHz, CDCl₃) δ 177.5, 138.7, 134.5, 132.5, 132.2, 132.2, 150.33 (d, J_C–F = 32.3 Hz), 128.6, 127.3, 125.9, 125.4, 125.4, 122.3, 122.2, 97.3, 93.3, 90.8, 80.7, 29.9, 22.2, 19.1, 13.6.

**¹⁹F NMR** (282 MHz, CDCl₃) δ -63.8 (s).

**MS** (ESI, NH₃): m/z = 355 [M + H]⁺.

### 1-(2-((4-Bromophenyl)-ethynyl)-phenyl)-hept-2-yn-1-one (27)

![Chemical structure of 1-(2-((4-Bromophenyl)-ethynyl)-phenyl)-hept-2-yn-1-one (27)](image)
Experimental part

This compound was prepared using procedure A. Starting from 1-(2-ethynylphenyl)-hept-2-yn-1-one 29 (0.3 g, 1.42 mmol) and 1-Bromo-4-iodobenzene (0.48 g, 1.7 mmol, 1.2 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 27 (0.25 g, 48%) as a brown oil.

Rf = 0.4 (Cyclohexane/Ethyl acetate; 95/5, KMnO4, UV).

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.14 (dd, $J = 7.7, 1.1$ Hz, 1H), 7.65 – 7.60 (m, 1H), 7.56 – 7.41 (m, 6H), 2.45 (t, $J = 7.0$ Hz, 2H), 1.65 – 1.55 (m, 2H), 1.52 – 1.38 (m, 2H), 0.92 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 177.6, 138.5, 134.3, 133.5, 132.4, 132.1, 131.8, 128.2, 123.1, 122.6, 122.5, 97.2, 93.9, 89.6, 80.8, 29.9, 22.2, 19.1, 13.6.

MS (Cl, NH$_3$): m/z = 365 [M + H]$^+$.  

<table>
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<tr>
<th>1-(2-Ethynylphenyl)hept-2-yn-1-ol (28)</th>
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<tr>
<td><img src="image" alt="Chemical Structure" /></td>
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<tr>
<td>Chemical Formula: C$<em>{13}$H$</em>{16}$O</td>
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<tr>
<td>Exact Mass: 212.1201</td>
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</table>

This compound was prepared using procedure D. Starting from 1-((trimethylsilyl)ethynyl)phenyl)-hept-2-yn-1-ol 12 (1.7 g, 6 mmol) and TBAF (6 mL, 1.0 M in THF). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 28 (1.13 g, 89%) as a pale yellow oil.

Rf = 0.2 (Cyclohexane/Ethyl acetate; 90/10, KMnO4, UV).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.72 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.51 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.40 (td, $J = 7.6, 1.4$ Hz, 1H), 7.28 (dt, $J = 7.5, 1.3$ Hz, 1H), 5.92 – 5.80 (m, 1H), 3.37 (s, 1H), 2.50 (d, $J = 4.5$ Hz, 1H), 2.27 (td, $J = 7.0, 2.0$ Hz, 2H), 1.61 – 1.37 (m, 4H), 0.91 (t, $J = 7.2$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 143.7, 133.3, 129.5, 128.2, 126.9, 120.5, 88.0, 82.6, 81.3, 79.3, 63.3, 30.8, 22.1, 18.7, 13.7.
Experimental part

**MS** (CI, NH$_3$): $m/z = 212$ [M + NH$_4$ - H$_2$O]$^+$. 

<table>
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<th>1-(2-ethynylphenyl)hept-2-yn-1-one (29)</th>
</tr>
</thead>
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<td>Exact Mass: 210.1045</td>
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This compound was prepared using procedure C. Starting from 1-(2-ethynylphenyl)hept-2-yn-1-ol 28 (1.0 g, 4.7 mmol) and Dess-Martin periodinane (2.59 g, 6.1 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded 29 (0.82 g, 83%) as a colorless oil.

**R$_f$ = 0.65** (Cyclohexane/Ethyl acetate: 90/10, KMnO$_4$, UV).

**$^1$H NMR** (300 MHz, CDCl$_3$) $\delta$ 8.15 – 8.06 (m, 1H), 7.66 – 7.56 (m, 1H), 7.54 – 7.41 (m, 2H), 3.39 (s, 1H), 2.47 (t, $J$ = 7.0 Hz, 2H), 1.68 – 1.58 (m, 2H), 1.48 (m, 2H), 0.95 (t, $J$ = 7.3 Hz, 3H).

**$^{13}$C NMR** (75 MHz, CDCl$_3$) $\delta$ 177.5, 139.2, 135.5, 132.3, 131.8, 128.6, 121.7, 97.4, 82.9, 82.1, 80.8, 29.9, 22.2, 19.1, 13.6.

**MS** (CI, NH$_3$): $m/z = 211$ [M + H]$^+$. 

<table>
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<th>3-(Phenylethynyl)furan-2-carbaldehyde (30)</th>
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<td><img src="image_url" alt="Chemical structure" /></td>
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</table>

This compound was prepared using procedure A. Starting from 3-bromofuran-2-carbaldehyde (0.59 g, 3.4 mmol) and phenylacetylene (0.41 g, 4 mmol, 1.2 equiv). Purification on silica gel
Experimental part

(Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded 30 (0.4 g, 50%) as an orange oil. The analytical data were identical to the literature.\textsuperscript{192}

\[ \text{Rf} = 0.6 \] (Cyclohexane/Ethyl acetate; 95/5, KMnO\textsubscript{4}, UV).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 9.87 (s, 1H), 7.65 (dd, \( J = 1.7, 0.8 \) Hz, 1H), 7.60 – 7.47 (m, 2H), 7.45 – 7.33 (m, 3H), 6.68 (d, \( J = 1.8 \) Hz, 1H).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \( \delta \) 176.3, 152.9, 147.7, 131.9, 129.6, 128.7, 122.0, 119.8, 115.3, 97.6, 78.4.

MS (ESI, NH\textsubscript{3}): \( m/z = 197 \) [M + H]\textsuperscript{+}.

### 3-(Phenylethynyl)thiophene-2-carbaldehyde (31)

![Chemical structure of 3-(Phenylethynyl)thiophene-2-carbaldehyde (31)]

This compound was prepared using procedure A. Starting from 3-bromothiophene-2-carbaldehyde (1.0 g, 5.23 mmol) and phenylacetylene (0.64 g, 6.28 mmol, 1.2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded 31 (0.92 g, 83%) as a brown oil. The analytical data were identical to the literature.\textsuperscript{193}

\[ \text{Rf} = 0.4 \] (Cyclohexane/Ethyl acetate; 95/5, KMnO\textsubscript{4}, UV).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 10.24 (d, \( J = 1.3 \) Hz, 1H), 7.70 (dd, \( J = 5.0, 1.3 \) Hz, 1H), 7.58 – 7.53 (m, 2H), 7.45 – 7.30 (m, 3H), 7.27 – 7.23 (m, 1H).

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \) 183.1, 143.7, 134.0, 131.9, 131.7, 131.1, 129.4, 128.7, 122.2, 96.2, 81.7.

MS (CI, NH\textsubscript{3}): \( m/z = 213 \) [M + H]\textsuperscript{+}.


Experimental part

### 3-(Phenylethynyl)benzo[b]-thiophene-2-carbaldehyde (32)

![Chemical Structure](image)

This compound was prepared using procedure A. Starting from 3-bromobenzo[b]thiophene-2-carbaldehyde (0.72 g, 3.0 mmol) and phenylacetylene (0.37 g, 3.6 mmol, 1.2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 99/1 to 98/2) afforded 32 (0.4 g, 50%) as a yellow solid. m.p. 114 – 116 °C. The analytical data were identical to the literature.\(^{194}\)

**Rt = 0.4** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

**^1H NMR** (300 MHz, CDCl₃) δ 10.48 (s, 1H), 8.16 (dd, J = 7.8, 1.5 Hz, 1H), 7.93 – 7.82 (m, 1H), 7.70 – 7.60 (m, 2H), 7.60 – 7.48 (m, 2H), 7.47 – 7.38 (m, 3H).

**^13C NMR** (75 MHz, CDCl₃) δ 184.6, 143.6, 141.3, 139.6, 132.1, 129.7, 129.0, 128.8, 127.9, 125.8, 125.2, 123.5, 122.1, 99.2, 80.7.

**MS** (ESI, NH₃): m/z = 263 [M + H]+.

### 2-(Phenylethynyl)benzofuran-3-carbaldehyde (33)

![Chemical Structure](image)

This compound was prepared using procedure A. Starting from 2-chlorobenzofuran-3-carbaldehyde (0.9 g, 5 mmol), phenylacetylene (0.61 g, 6 mmol, 1.2 equiv), PdCl₂(PPh₃)₃ (140 mg, 0.2 mmol, 4 mol %) and CuI (19 mg, 0.1 mmol, 2 mol %). Purification on silica gel

---

(Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded 33 (1.3 g, 82%) as a yellow solid. The analytical data were identical to the literature.\textsuperscript{195}

\textbf{R}_f = 0.4 \text{ (Cyclohexane/Ethyl acetate; 90/10, KMnO}_4, \text{ UV).}

\textbf{\textsuperscript{1}H NMR} (300 MHz, CDCl\textsubscript{3}) \(\delta\) 10.37 (s, 1H), 8.24 – 8.16 (m, 1H), 7.70 – 7.61 (m, 2H), 7.55 – 7.38 (m, 6H).

\textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta\) 185.7, 154.8, 148.2, 132.3, 130.5, 128.9, 127.3, 125.4, 124.0, 123.5, 122.6, 120.6, 111.4, 101.1.

\textbf{MS} (ESI, NH\textsubscript{3}): m/z = 247 [M + H\textsuperscript{+}].

\begin{center}
\begin{tabular}{|c|}
\hline
\textbf{2-(Phenylethynyl)nicotinaldehyde (34)}
\hline
\end{tabular}
\end{center}

This compound was prepared using procedure A. Starting from 2-bromonicotinaldehyde (2 g, 10.8 mmol) and phenylacetylene (1.15 g, 11.2 mmol, 1.05 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 34 (1.8 g, 80\%) as a yellow solid. The analytical data were identical to the literature.\textsuperscript{196}

\textbf{R}_f = 0.26 \text{ (Cyclohexane/Ethyl acetate; 80/20, KMnO}_4, \text{ UV).}

\textbf{\textsuperscript{1}H NMR} (300 MHz, CDCl\textsubscript{3}) \(\delta\) 10.66 (d, \(J = 0.6\) Hz, 1H), 8.81 (dd, \(J = 1.8, 4.8\) Hz, 1H), 8.20 (dd, \(J = 1.8, 7.9\) Hz, 1H), 7.66-7.59 (m, 2H), 7.43-7.37 (m, 4H).

\textbf{\textsuperscript{13}C NMR} (75 MHz, CDCl\textsubscript{3}) \(\delta\) 190.9, 154.6, 146.1, 134.9, 132.3, 131.9, 130.0, 128.7, 123.3, 121.3, 96.2, 84.7.

\textbf{MS} (Cl, NH\textsubscript{3}): m/z = 208 [M + H\textsuperscript{+}].


Experimental part

**2-((4-(tert-Butyl)phenyl)ethyl)nicotinaldehyde (35)**

![Chemical structure of 2-((4-(tert-Butyl)phenyl)ethyl)nicotinaldehyde (35)](image)

This compound was prepared using procedure A. Starting from 2-bromonicotinaldehyde (2 g, 10.8 mmol) and 4-tert-Butylbenzylacetylene (1.8 g, 11.2 mmol, 1.05 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 35 (2.5 g, 88%) as a white solid.

R_N = 0.32 (Cyclohexane/Ethyl acetate; 80/20, KMnO_4, UV).

^1^H NMR (300 MHz, CDCl_3) δ 10.66 (d, J = 0.4 Hz, 1H), 8.80 (dd, J = 1.8, 4.8 Hz, 1H), 8.19 (dd, J = 1.8, 7.9 Hz, 1H), 7.58-7.56 (m, 2H), 7.42-7.35 (m, 3H), 1.32 (s, 9H).

^13^C NMR (75 MHz, CDCl_3) δ 191.0, 154.6, 153.5, 146.4, 134.9, 132.1, 131.8, 125.7, 123.1, 118.3, 96.7, 84.3, 35.1, 31.2.

**2-Chloro-5-(phenylethynyl)isonicotinaldehyde (36)**

![Chemical structure of 2-Chloro-5-(phenylethynyl)isonicotinaldehyde (36)](image)

This compound was prepared using procedure A. Starting from 5-bromo-2-chloroisonicotinaldehyde (0.44 g, 2.0 mmol) and phenylacetylene (0.21 g, 2.1 mmol, 1.05 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded 36 (0.26 g, 54%) as a yellow solid. m.p. 69 – 71 °C.

R_N = 0.4 (Cyclohexane/Ethyl acetate; 90/10, KMnO_4, UV).

^1^H NMR (300 MHz, CDCl_3) δ 10.55 (s, 1H), 8.74 (s, 1H), 7.75 (s, 1H), 7.63 – 7.52 (m, 2H), 7.47 – 7.36 (m, 3H).
\[^{13}\text{C} \text{NMR} \ (75 \ \text{MHz, CDCl}_3) \delta 189.4, 154.6, 151.6, 142.8, 132.0, 130.0, 128.8, 121.5, 120.8, 120.4, 100.1, 81.1.\]

\[\text{MS (CI, NH}_3): m/z = 242 \ [\text{M + H}]^+.\]

**1-(3-(Phenylethynyl)furan-2-yl)hept-2-yn-1-ol (37)**

This compound was prepared using procedure B. Starting from 3-(phenylethynyl)furan-2-carbaldehyde 30 (0.43 g, 2.2 mmol) and 1-hexyne (0.37 mL, 3.3 mmol, 1.5 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 37 (0.45 g, 74%) as a yellow oil.

\[\text{R}_f = 0.28 \ (\text{Cyclohexane/Ethyl acetate; 90/10, KMnO}_4, \ \text{UV}).\]

\[^1\text{H NMR} \ (300 \ \text{MHz, CDCl}_3) \delta 7.50 \ (dd, J = 6.6, 3.0 \ \text{Hz, 2H}), \ 7.37 \ (d, J = 1.8 \ \text{Hz, 1H}), \ 7.37 – 7.29 \ (m, 3H), \ 6.48 \ (d, J = 1.8 \ \text{Hz, 1H}), \ 5.72 – 5.65 \ (m, 1H), \ 2.38 \ (d, J = 6.9 \ \text{Hz, 1H}), \ 2.25 \ (\text{td}, J = 7.0, 2.0 \ \text{Hz, 2H}), \ 1.56 – 1.44 \ (m, 2H), \ 1.44 – 1.32 \ (m, 2H), \ 0.88 \ (t, J = 7.2 \ \text{Hz, 3H}).\]

\[^{13}\text{C} \text{NMR} \ (75 \ \text{MHz, CDCl}_3) \delta 155.3, 142.3, 131.6, 128.5, 123.2, 113.4, 105.0, 93.6, 87.9, 79.9, 57.2, 30.6, 22.1, 18.7, 13.7.\]

\[\text{MS (ESI, NH}_3): m/z = 261 \ [\text{M + H - H}_2\text{O}]^+.\]

**1-(3-(Phenylethynyl)thiophen-2-yl)hept-2-yn-1-ol (38)**
Experimental part

This compound was prepared using procedure B. Starting from 3-(phenylethynyl)thiophene-2-carbaldehyde 31 (0.92 g, 4.33 mmol) and 1-Hexyne (0.65 mL, 5.6 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 38 (1.13 g, 89%) as a yellow oil.

\[ \text{Rt} = 0.28 \] (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

\[ ^1\text{H NMR} (300 \text{ MHz, CDCl}_3) \delta 7.59 – 7.46 (m, 2H), 7.35 (dd, J = 6.5, 2.7 Hz, 3H), 7.23 (d, J = 5.2 Hz, 1H), 7.08 (d, J = 5.2 Hz, 1H), 6.05 – 5.88 (m, 1H), 2.48 (d, J = 5.1 Hz, 1H), 2.28 (td, J = 6.9, 2.0 Hz, 2H), 1.47 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H). \]

\[ ^{13}\text{C NMR} (75 \text{ MHz, CDCl}_3) \delta 148.4, 131.7, 130.1, 128.6, 128.5, 124.7, 123.1, 120.2, 93.5, 87.6, 82.8, 79.2, 59.4, 30.6, 22.1, 18.6, 13.7. \]

\[ \text{MS (Cl, NH}_3\text{): m/z = 277 [M + H - H}_2\text{O}^+.} \]

1-(3-(Phenylethynyl)benzo[b]thiophen-2-yl)hept-2-yn-1-ol (39)

This compound was prepared using procedure B. Starting from 3-(phenylethynyl)benzo[b]thiophene-2-carbaldehyde 32 (0.4 g, 1.5 mmol) and 1-hexyne (0.26 mL, 2.25 mmol, 1.5 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 39 (0.46 g, 89%) as a yellow oil.

\[ \text{Rt} = 0.3 \] (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

\[ ^1\text{H NMR} (300 \text{ MHz, CDCl}_3) \delta 8.02 – 7.91 (m, 1H), 7.87 – 7.79 (m, 1H), 7.65 – 7.55 (m, 2H), 7.49 – 7.33 (m, 5H), 6.25 – 6.14 (m, 1H), 2.54 (d, J = 5.1 Hz, 1H), 2.29 (td, J = 7.0, 2.0 Hz, 2H), 1.52 – 1.36 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H). \]

\[ ^{13}\text{C NMR} (101 \text{ MHz, CDCl}_3) \delta 149.3, 139.6, 138.1, 131.8, 128.8, 128.6, 125.6, 125.0, 123.4, 123.0, 122.8, 115.9, 96.4, 88.3, 81.4, 78.8, 60.1, 30.6, 22.1, 18.7, 13.7. \]
MS (ESI, NH₃): m/z = 327 [M + H - H₂O]^+.

<table>
<thead>
<tr>
<th>1-(2-(Phenylethynyl)benzofuran-3-yl)hept-2-yn-1-ol (40)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C₂₅H₂₅O₂</td>
</tr>
<tr>
<td>Exact Mass: 328.1463</td>
</tr>
</tbody>
</table>

This compound was prepared using procedure B. Starting from 2-(phenylethynyl)benzofuran-3-carbaldehyde 33 (0.52 g, 2.1 mmol) and 1-hexyne (0.37 mL, 3.2 mmol, 1.5 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 40 (0.62 g, 90%) as a yellow solid.

Rᵣ = 0.35 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.98 – 7.88 (m, 1H), 7.64 – 7.52 (m, 2H), 7.50 – 7.43 (m, 1H), 7.43 – 7.34 (m, 4H), 7.34 – 7.25 (m, 1H), 5.92 – 5.80 (m, 1H), 2.31 – 2.20 (m, 3H), 1.59 – 1.31 (m, 4H), 0.88 (t, J = 7.2 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 155.0, 136.2, 131.9, 129.5, 128.7, 126.2, 125.7, 124.8, 123.4, 121.7, 121.3, 111.5, 98.7, 87.6, 78.6, 78.1, 57.5, 30.6, 22.1, 18.7, 13.7.

MS (ESI, NH₃): m/z = 311 [M + H - H₂O]^+.

<table>
<thead>
<tr>
<th>3-Cyclopropyl-1-(2-(phenylethynyl)pyridin-3-yl)prop-2-yn-1-ol (41)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C₉H₁₃NO</td>
</tr>
<tr>
<td>Exact Mass: 279.1154</td>
</tr>
</tbody>
</table>

This compound was prepared using procedure B. Starting from 2-(phenylethynyl)nicotinaldehyde 34 (1.8 g, 8.7 mmol) and cyclopropylacetylene (0.95 mL, 11.3
Experimental part

mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 60/40) afforded 41 (1.9 g, 80%) as a gray oil.

Rf = 0.12 (Cyclohexane/Ethyl acetate; 80/20, KMnO4, UV).

\[ ^1H \text{ NMR} (300 MHz, CDCl}_3 \delta 8.49 (d, J = 3.0 Hz, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.59-7.55 (m, 2H), 7.38-7.29 (m, 3H), 7.25-7.20 (m, 1H), 5.92 (d, J = 0.8 Hz, 1H), 3.61 (br, 1H), 1.28-1.20 (m, 1H), 0.74-0.71 (m, 2H), 0.66-0.63 (m, 2H). \]

\[ ^{13}C \text{ NMR} (75 MHz, CDCl}_3 \delta 149.2, 141.2, 139.6, 134.5, 132.1, 129.3, 128.5, 123.3, 122.1, 94.7, 90.8, 86.2, 74.3, 62.0, 8.6, 8.4, -0.4. \]

1-(2-((4-(tert-Butyl)phenyl)ethynyl)pyridin-3-yl)hept-2-yn-1-ol (42)

This compound was prepared using procedure B. Starting from 2-((4-(tert-butyl)phenyl)ethynyl)nicotinaldehyde 35 (2.13 g, 8.09 mmol) and 1-hexyne (1.21 mL, 10.5 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 70/30) afforded 42 (2.23 g, 80%) as a pale yellow oil.

Rf = 0.23 (Cyclohexane/Ethyl acetate; 90/10, KMnO4, UV).

\[ ^1H \text{ NMR} (300 MHz, CDCl}_3 \delta 8.55 (dd, J = 1.7, 4.8 Hz, 1H), 8.07 (dd, J = 1.6, 7.9 Hz, 1H), 7.58-7.54 (m, 2H), 7.41-7.38 (m, 2H), 7.30-7.26 (m, 1H), 5.98 (t, J = 2.0 Hz, 1H), 3.20 (br, 1H), 2.26 (td, J = 2.0, 7.0 Hz, 2H), 1.49-1.37 (m, 4H), 1.34 (s, 9H), 0.86 (t, J = 7.2 Hz, 3H). \]

\[ ^{13}C \text{ NMR} (75 MHz, CDCl}_3 \delta 152.8, 149.3, 141.5, 139.4, 134.5, 131.9, 125.5, 123.1, 119.0, 95.0, 88.1, 85.7, 78.9, 62.2, 35.0, 31.2, 30.6, 22.1, 18.6, 13.7. \]
This compound was prepared using procedure B. Starting from 2-chloro-5-(phenylethynyl)isonicotinaldehyde 36 (0.25 g, 1.04 mmol) and 1-hexyne (0.15 mL, 1.3 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 43 (0.24 g, 71%) as a yellow oil.

**R<sub>r</sub> = 0.2** (Cyclohexane/Ethyl acetate; 90/10, KMnO<sub>4</sub>, UV).

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.51 (s, 1H), 7.67 (s, 1H), 7.59 – 7.49 (m, 2H), 7.44 – 7.33 (m, 3H), 5.82 – 5.75 (m, 1H), 2.66 (d, J = 5.1 Hz, 1H), 2.36 – 2.18 (m, 2H), 1.53 – 1.32 (m, 4H), 0.85 (t, J = 7.2 Hz, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 153.8, 152.5, 151.3, 131.8, 129.4, 128.7, 122.3, 121.3, 117.4, 98.9, 89.0, 82.7, 62.2, 30.5, 22.1, 18.6, 13.6.

**MS** (CI, NH<sub>3</sub>): m/z = 324 [M + H]<sup>+</sup>.

<table>
<thead>
<tr>
<th>1-(3-(Phenylethynyl)furan-2-yl)hept-2-yn-1-one (44)</th>
</tr>
</thead>
</table>

This compound was prepared using procedure C. Starting from 1-(3-(phenylethynyl)furan-2-yl)hept-2-yn-1-ol 37 (0.45 g, 1.6 mmol) and Dess–Martin periodinane (0.89 g, 2.1 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient 98/2 to 95/5) afforded 44 (0.18 g, 40%) as an orange oil.

**R<sub>r</sub> = 0.4** (Cyclohexane/Ethyl acetate; 90/10, KMnO<sub>4</sub>, UV).
Experimental part

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.62 – 7.50 (m, 3H), 7.41 – 7.31 (m, 3H), 6.67 (d, $J = 1.6$ Hz, 1H), 2.37 (t, $J = 7.2$ Hz, 2H), 1.59 – 1.42 (m, 2H), 1.40 – 1.26 (m, 2H), 0.83 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 164.1, 152.7, 146.4, 131.9, 129.2, 128.6, 122.7, 116.4, 116.3, 98.0, 97.8, 80.8, 79.7, 29.8, 22.2, 19.2, 13.6.

MS (ESI, NH$_3$): m/z = 277 [M + H]$^+$. 

<table>
<thead>
<tr>
<th>1-(3-(Phenylethynyl)thiophen-2-yl)hept-2-yn-1-one (45)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C$<em>{15}$H$</em>{18}$OS</td>
</tr>
<tr>
<td>Exact Mass: 292.0922</td>
</tr>
</tbody>
</table>

This compound was prepared using procedure C. Starting from 1-(3-(phenylethynyl)thiophen-2-yl)hept-2-yn-1-ol 38 (1.12 g, 3.8 mmol) and Dess-Martin periodinane (2.1 g, 4.9 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient 99/1 to 98/2) afforded 45 (0.6 g, 55%) as a yellow solid. m.p. 33 – 35 °C.

R$_r$ = 0.33 (Cyclohexane/Ethyl acetate; 95/5, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.63 – 7.52 (m, 3H), 7.42 – 7.31 (m, 3H), 7.28 – 7.19 (m, 1H), 2.36 (t, $J = 7.1$ Hz, 2H), 1.52 – 1.45 (m, 2H), 1.41 – 1.28 (m, 2H), 0.85 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.0, 144.3, 133.3, 132.5, 131.9, 129.1, 128.6, 126.9, 123.0, 97.5, 96.3, 84.4, 80.3, 29.9, 22.2, 19.2, 13.6.

MS (CI, NH$_3$): m/z = 293 [M + H]$^+$. 

<table>
<thead>
<tr>
<th>1-(3-(Phenylethynyl)benzo[b]thiophen-2-yl)hept-2-yn-1-one (46)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image2" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C$<em>{16}$H$</em>{19}$OS</td>
</tr>
<tr>
<td>Exact Mass: 342.1078</td>
</tr>
</tbody>
</table>
This compound was prepared using procedure C. Starting from 1-(3-(phenylethynyl)benzo[b]thiophen-2-yl)hept-2-yn-1-ol 39 (0.46 g, 1.34 mmol) and Dess-Martin periodinane (0.74 g, 1.7 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient 98/2 to 95/5) afforded 46 (0.34 g, 74%) as a yellow solid. m.p. 90 – 92 °C.

R\text{f} = 0.62 \text{ (Cyclohexane/Ethyl acetate; 90/10, KMnO}_4\text{, UV).}

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.19 – 8.09 (m, 1H), 7.88 – 7.62 (m, 1H), 7.72 – 7.62 (m, 2H), 7.58 – 7.45 (m, 2H), 7.45 – 7.34 (m, 3H), 2.41 (t, $J = 7.2$ Hz, 2H), 1.62 – 1.48 (m, 2H), 1.45 – 1.29 (m, 2H), 0.85 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.5, 144.3, 140.7, 145.0, 129.3, 128.7, 128.6, 125.6, 123.3, 122.9, 99.7, 98.8, 83.1, 80.6, 77.5, 77.2, 76.8, 29.9, 22.2, 19.4, 13.6.

MS (ESI, NH$_3$): m/z = 343 [M + H]$^+$.  

<table>
<thead>
<tr>
<th>1-(2-(Phenylethynyl)benzofuran-3-yl)hept-2-yn-1-one (47)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image.png" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C$<em>{23}$H$</em>{18}$O$_2$</td>
</tr>
<tr>
<td>Exact Mass: 326.1307</td>
</tr>
</tbody>
</table>

This compound was prepared using procedure C. Starting from 1-(2-(phenylethynyl)benzofuran-3-yl)hept-2-yn-1-ol 40 (0.62 g, 1.9 mmol) and Dess-Martin periodinane (1.04 g, 2.4 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient 98/2 to 95/5) afforded 47 (0.45 g, 72%) as a yellow solid.

R\text{f} = 0.5 \text{ (Cyclohexane/Ethyl acetate; 90/10, KMnO}_4\text{, UV).}

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.35 – 8.22 (m, 1H), 7.71 – 7.60 (m, 2H), 7.55 – 7.32 (m, 6H), 2.39 (t, $J = 7.2$ Hz, 2H), 1.61 – 1.46 (m, 2H), 1.44 – 1.28 (m, 2H), 0.83 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.7, 154.3, 144.3, 132.2, 130.2, 128.8, 127.0, 125.0, 124.9, 124.0, 123.1, 121.4, 111.2, 101.2, 96.4, 81.1, 79.6, 30.0, 22.2, 19.2, 13.6.
Experimental part

MS (ESI, NH₃): m/z = 327 [M + H]^+.

### 3-Cyclopropyl-1-(2-(phenylethynyl)pyridin-3-yl)prop-2-yn-1-one (48)

This compound was prepared using procedure C. Starting from 3-cyclopropyl-1-(2-(phenylethynyl)pyridin-3-yl)prop-2-yn-1-ol 41 (1.9 g, 7 mmol) and Dess-Martin periodinane (3.83 g, 9 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient 80/20 to 70/30) afforded 48 (1.6 g, 84%) as a brown oil.

\[ R_f = 0.57 \] (Cyclohexane/Ethyl acetate; 70/30, KMnO₄, UV).

\(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 8.72 (dd, \( J = 1.7, 4.7 \) Hz, 1H), 8.26 (dd, \( J = 1.8, 8.0 \) Hz, 1H), 7.70-7.64 (m, 2H), 7.38-7.32 (m, 4H), 1.48-1.29 (m, 1H), 0.97-0.92 (m, 4H).

\(^13\)C NMR (75 MHz, CDCl₃) \( \delta \) 175.4, 151.7, 140.8, 137.5, 134.0, 131.5, 128.5, 127.4, 121.3, 102.4, 94.2, 87.0, 9.2, -0.73.

### 1-(2-((4-(tert-Butyl)phenyl)ethynyl)pyridin-3-yl)hept-2-yn-1-one (49)

This compound was prepared using procedure C. Starting from 1-(2-((4-(tert-butyl)phenyl)ethynyl)pyridin-3-yl)hept-2-yn-1-ol 42 (2.3 g, 6.7 mmol) and Dess-Martin periodinane (3.67 g, 8.7 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient 95/5 to 80/20) afforded 49 (2.14 g, 94%) as a brown oil.

\[ R_f = 0.35 \] (Cyclohexane/Ethyl acetate; 85/15, KMnO₄, UV).
Experimental part

**1H NMR** (300 MHz, CDCl$_3$) $\delta$ 8.73 (dd, $J = 1.7$, 4.8 Hz, 1H), 8.31 (dd, $J = 1.8$, 8.0 Hz, 1H), 7.63–7.59 (m, 2H), 7.40–7.32 (m, 3H), 2.42 (t, $J = 7.1$ Hz, 2H), 1.58–1.53 (m, 2H), 1.40–1.38 (m, 2H), 1.31 (s, 9H), 0.87 (t, $J = 7.3$ Hz, 3H).

**13C NMR** (75 MHz, CDCl$_3$) $\delta$ 177.8, 138.4, 134.3, 132.4, 132.0, 131.8, 128.7, 128.4, 127.9, 123.4, 122.9, 97.2, 95.2, 88.4, 80.8, 29.8, 22.2, 19.1, 13.6.

<table>
<thead>
<tr>
<th>1-(2-chloro-5-(phenylethynyl)pyridin-4-yl)hept-2-yn-1-one (50)</th>
</tr>
</thead>
</table>

This compound was prepared using procedure C. Starting from 1-(2-chloro-5-(phenylethynyl)pyridin-4-yl)hept-2-yn-1-ol 43 (0.23 g, 0.71 mmol) and Dess-Martin periodinane (0.39 g, 0.92 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient 98/2) afforded 50 (0.16 g, 70%) as a yellow solid. m.p. 34 – 36 °C.

R$_f$ = 0.5 (Cyclohexane/Ethyl acetate; 90/10, KMnO$_4$, UV).

**1H NMR** (300 MHz, CDCl$_3$) $\delta$ 8.66 (d, $J = 0.6$ Hz, 1H), 7.85 (d, $J = 0.6$ Hz, 1H), 7.63 – 7.55 (m, 2H), 7.42 – 7.33 (m, 3H), 2.46 (t, $J = 7.1$ Hz, 2H), 1.63 – 1.54 (m, 2H), 1.50 – 1.35 (m, 2H), 0.91 (t, $J = 7.3$ Hz, 3H).

**13C NMR** (75 MHz, CDCl$_3$) $\delta$ 175.2, 154.7, 150.8, 146.4, 132.1, 129.5, 128.6, 124.3, 122.5, 117.2, 100.5, 98.9, 84.1, 80.2, 29.7, 22.2, 19.3, 13.6.

**MS** (Cl, NH$_3$): m/z = 322 [M + H]$^+$.  

2.2. Preparation of internal alkynes

**1.4-Di-tert-butoxybut-2-yne (55)**
**Experimental part**

1,4-Diol-2-butyne 52 (1.72 g, 20 mmol), 4Å molecular sieves (4 g) and MTBE (20 mL) were introduced in a 50 mL round bottom flask fitted with septum and cooled to 25 °C. To this solution sulfuric acid (3.7 mL, 40 mmo, 2 equiv) was added dropwise using a syringe. The reaction was carried out at 25 °C for 10 h. The resulting mixture was slowly quenched into a saturated aqueous sodium bicarbonate solution (20 mL). The organic layer was separated and washed with water and brine, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) to afford compound 55 (1.7 g, 43%) as a colorless oil. The analytical data were identical to the literature.⁹⁷

\[ R_f = 0.45 \] (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV)

\[ ^1H \text{ NMR} \) (300 MHz, CDCl₃) \( \delta \) 4.06 (s, 4H), 1.18 (s, 18H).

\[ ^13C \text{ NMR} \) (75 MHz, CDCl₃) \( \delta \) 82.5, 74.2, 50.8, 27.5.

**MS** (CI, NH₃): \( m/z = 216 \) [M + NH₄]⁺.

---

**1,4-Bis(benzyloxy)but-2-yne (56)**

In an oven-dried argon-filled round bottom flask, sodium hydride (0.88 g, 22 mmol, 2.2 equiv) was dissolved in dry THF (20 mL). A THF solution (10 mL) of 2-butyne-1,4-diol 52 (0.86 g, 1.0 equiv) was added dropwise at 0 °C. The mixture was stirred at room temperature for 1 h. The solution was cooled to 0 °C and benzyl bromide (2.6 mL, 2.2 equiv) was added. The resulting mixture was allowed to warm to room temperature for 48 h. When the reaction was complete (TLC monitoring), water (20 mL) was added and the residue was extracted with diethyl ether (2 × 40 mL). The organic layer was separated and washed with water and brine, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue
was purified by flash chromatography (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) to afford compound 56 (2.0 g, 75%) as a colorless oil. The analytical data were identical to the literature.\(^98\)

\[ R_f = 0.52 \] (Cyclohexane/Ethyl acetate; 90/10, KMnO\(_4\), UV)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.49 – 7.24 (m, 10H), 4.62 (s, 4H), 4.26 (s, 4H).

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 137.6, 128.2, 128.0, 82.7, 71.8, 57.6.

<table>
<thead>
<tr>
<th>2,2,3,3,10,10,11,11-Octamethyl-4,9-dioxa-3,10-disiladodec-6-yne (57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO-(\equiv)OH + Me(_2)Si-(\equiv)Me (\rightarrow) Me(_2)BuSiO(-\equiv)O(\equiv)SiBuMe(_2)</td>
</tr>
<tr>
<td>DMAP 10 mol % Imidazole 2.4 equiv DCM, rt, 1.5 h 80%</td>
</tr>
<tr>
<td>52</td>
</tr>
</tbody>
</table>

Chemical Formula: C\(_{19}\)H\(_{34}\)O\(_2\)Si\(_2\)

Exact Mass: 314.2097

2-Butyn-1,4-diol 52 (2.0 g, 23.2 mmol), imidazole (3.8 g, 55.8 mmol), and \(N,N\)-dimethylaminopyridine (0.28 g, 2.32 mmol) were introduced in an oven-dried 250 mL round-bottom flask with a stir bar containing dichloromethane (200 mL). Recrystallized chloro-tert-butyl(dimethyl)silane (8.4 g, 55.8 mmol) was added. The resulting solution was stirred at room temperature for 3 h. Then the reaction mixture was poured into 40 mL 10% aqueous potassium carbonate. The resulting aqueous fraction was extracted with diethyl ether (2 \times 40 mL). The combined organic fractions were washed with water and brine, dried over anhydrous MgSO\(_4\), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) to afford compound 57 (5.85 g, 80%) as a colorless oil. The analytical data were identical to the literature.\(^99\)

\[ R_f = 0.5 \] (Cyclohexane/Ethyl acetate; 95/5, KMnO\(_4\), UV).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 4.34 (s, 4H), 0.90 (s, 18H), 0.11 (s, 12H).

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 83.5, 52.0, 26.0, 18.5, -5.0.

2.3. RuCl\(_3\cdot n\)H\(_2\)O-catalyzed [2+2+2] cycloadditions for the formation of fluoreone and related derivatives

General procedure E:
Experimental part

A sealed tube was equipped with RuCl$_3$·$n$H$_2$O (5 mol%) and diyne (1 equiv), followed by the addition of alkyne (2 equiv) under argon atmosphere. The tube was sealed and the reaction mixture was stirred for the required time at 50-80 °C. When the reaction was complete (TLC monitoring), the crude reaction mixture was directly purified by flash chromatography over silica gel to afforded cycloadducts.

### 1-Butyl-2,3-bis(methoxymethyl)-4-phenyl-9H-fluoren-9-one (65)

This compound was obtained following the general procedure E. Starting from diyne 17 (100 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne 51 (80 mg, 0.7 mmol, 2 equiv) and RuCl$_3$·$n$H$_2$O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 50 °C for 2 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded 65 (101 mg, 72%) as a yellow solid. m.p. 88 – 90 °C.

$R_f$ = 0.34 (Cyclohexane/Ethyl acetate; 95/5, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.60 – 7.57 (m, 1H), 7.54 – 7.46 (m, 3H), 7.36 – 7.28 (m, 2H), 7.13 (td, $J$ = 7.5, 0.9 Hz, 1H), 7.04 (td, $J$ = 7.5, 1.2 Hz, 1H), 5.94 (d, $J$ = 7.5 Hz, 1H), 4.57 (s, 2H), 4.19 (s, 2H), 3.51 (s, 3H), 3.29 – 3.20 (m, 2H), 3.18 (s, 3H), 1.67 – 1.49 (m, 4H), 1.02 (t, $J$ = 6.9 Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 194.6, 144.8, 143.6, 142.9, 142.4, 138.3, 137.6, 137.0, 135.2, 134.1, 130.8, 129.6, 128.9, 128.5, 128.1, 123.6, 123.2, 68.5, 67.4, 58.9, 58.6, 33.6, 27.3, 23.5, 14.1.
Experimental part

HRMS (ESI\(^+\)): calcd. for C\(_{27}\)H\(_{28}\)O\(_3\)Na [M+Na]\(^+\): 423.1931, found 423.1928.

<table>
<thead>
<tr>
<th>1,4-Dibutyl-2,3-bis(methoxymethyl)-9H-fluoren-9-one (66)</th>
</tr>
</thead>
</table>

This compound was obtained following the general procedure E. Starting from diyne 18 (93 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne 51 (80 mg, 0.7 mmol, 2.0 equiv) and RuCl\(_3\)-nH\(_2\)O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 80 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 66 (50 mg, 38%) as a yellow solid. m.p. 76 – 78 °C.

R\(_f\) = 0.33 (Cyclohexane/Ethyl acetate; 95/5, KMnO\(_4\), UV).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) 6 7.68 – 7.62 (m, 1H), 7.62 – 7.56 (m, 1H), 7.47 (td, \(J = 7.5, 1.2\) Hz, 1H), 7.27 (td, \(J = 7.5, 1.2\) Hz, 1H), 4.52 (s, 2H), 4.48 (s, 2H), 3.51 (s, 3H), 3.49 (s, 3H), 3.22 – 3.12 (m, 2H), 3.01 – 2.91 (m, 2H), 1.68 – 1.56 (m, 4H), 1.55 – 1.46 (m, 4H), 1.03 (t, \(J = 6.9\) Hz, 3H), 0.98 (t, \(J = 6.9\) Hz, 3H).

\(^13\)C NMR (75 MHz, CDCl\(_3\)) 6 194.9, 144.0, 143.1, 142.9, 142.8, 137.8, 137.5, 135.4, 134.6, 131.3, 128.4, 124.0, 123.5, 68.1, 67.5, 59.0, 58.8, 33.6, 32.3, 29.2, 27.2, 23.4, 14.1.

MS (Cl, NH\(_3\)): m/z = 349 [M + H - MeOH] \(^+\).

<table>
<thead>
<tr>
<th>4-Butyl-2,3-bis(methoxymethyl)-1-phenyl-9H-fluoren-9-one (67)</th>
</tr>
</thead>
</table>

This compound was obtained following the general procedure E. Starting from diyne 19 (100 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne 51 (80 mg, 0.7 mmol, 2.0 equiv) and RuCl\(_3\)-nH\(_2\)O
Experimental part

(3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 50 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 99/1 to 98/2) afforded 67 (60 mg, 43%) as a yellow oil.

Rr = 0.38 (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

\[^1\text{H}\text{ NMR}\] (300 MHz, CDCl₃) δ 7.67 (dt, \(J = 7.7, 0.9\) Hz, 1H), 7.59 – 7.48 (m, 2H), 7.49 – 7.42 (m, 3H), 7.32 – 7.24 (m, 3H), 4.64 (s, 2H), 4.18 (s, 2H), 3.55 (s, 3H), 3.22 (s, 3H), 3.13 – 3.02 (m, 2H), 1.80 – 1.57 (m, 4H), 1.09 (t, \(J = 7.1\) Hz, 3H).

\[^{13}\text{C}\text{ NMR}\] (75 MHz, CDCl₃) δ 192.9, 143.9, 142.9, 142.8, 140.6, 139.4, 137.6, 136.9, 135.2, 134.6, 131.3, 129.2, 128.6, 127.8, 127.6, 124.1, 123.6, 68.2, 68.1, 59.1, 58.4, 32.2, 29.3, 23.5, 14.1.

\[^{1}\text{MS}\] (CI, NH₃): \(m/z = 401\) [M + H]⁺.

This compound was obtained following the general procedure E. Starting from diyne 20 (100 mg, 0.37 mmol), 1,4-dimethoxy-2-butyn 51 (85 mg, 0.74 mmol, 2.0 equiv) and RuCl₃·nH₂O (3.8 mg, 0.0185 mmol). The reaction mixture was stirred at 80 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 68 (90 mg, 63%) as a yellow solid. m.p. 166 – 168 °C.

Rr = 0.31 (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

\[^{1}\text{H}\text{ NMR}\] (300 MHz, CDCl₃) δ 7.61 – 7.55 (m, 1H), 7.53 – 7.46 (m, 3H), 7.35 – 7.29 (m, 2H), 7.13 (t, \(J = 7.2\) Hz, 1H), 7.04 (td, \(J = 7.5, 1.2\) Hz, 1H), 5.92 (d, \(J = 7.5\) Hz, 1H), 4.81 (s, 2H), 4.20 (s, 2H, \(CH\)), 3.51 (s, 3H), 3.17 (s, 3H), 2.11 – 1.99 (m, 1H), 1.26 – 1.17 (m, 2H), 0.71 – 0.68 (m, 2H).
**Experimental part**

\[^{13}\text{C NMR}\] (75 MHz, CDCl\(_3\)) \(\delta\) 193.4, 143.8, 143.4, 142.9, 142.6, 139.5, 138.1, 137.8, 135.1, 134.0, 133.2, 129.5, 128.8, 128.5, 128.1, 123.6, 123.1, 68.4, 68.2, 59.0, 58.7, 10.9, 8.4.

\[\text{HRMS (ESI\(^{+}\))}: \text{calcd. for C}_{26}\text{H}_{24}\text{O}_3\text{Na [M+Na]}^{+}: 407.1618, \text{found 407.1623.}\]

<table>
<thead>
<tr>
<th>1-Butyl-2,3-bis(methoxymethyl)-4-(trimethylsilyl)-9H-fluoren-9-one (69)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Chemical structure" /></td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure E. Starting from diyne 21 (99.0 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne 51 (80 mg, 0.7 mmol, 2.0 equiv) and RuCl\(_3\)-\(n\)H\(_2\)O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 50 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 69 (81 mg, 58%) as a yellow oil.

\(R_r = 0.46\) (Cyclohexane/Ethyl acetate; 90/10, KMnO\(_4\), UV).

\[^{1}\text{H NMR}\] (300 MHz, CDCl\(_3\)) \(\delta\) 7.62 (t, \(J = 7.5\) Hz, 2H), 7.42 (td, \(J = 7.5, 1.2\) Hz, 1H), 7.30 – 7.20 (m, 1H), 4.59 (s, 2H), 4.47 (s, 2H), 3.44 (s, 3H), 3.34 (s, 3H), 3.26 – 3.15 (m, 2H), 1.58 – 1.44 (m, 4H), 0.98 (t, \(J = 6.6\) Hz, 3H), 0.46 (s, 9H).

\[^{13}\text{C NMR}\] (75 MHz, CDCl\(_3\)) \(\delta\) 195.0, 152.9, 151.9, 145.5, 144.6, 135.4, 135.3, 133.2, 130.7, 128.5, 125.9, 123.5, 71.9, 67.3, 58.5, 57.7, 33.5, 27.0, 23.4, 14.1, 2.8.

\[\text{HRMS (ESI\(^{+}\))}: \text{calcd. for C}_{24}\text{H}_{32}\text{O}_3\text{SiNa [M+Na]}^{+}: 419.2013, \text{found 419.2008.}\]

<table>
<thead>
<tr>
<th>1-Butyl-2,3-bis(methoxymethyl)-4-(p-tolyl)-9H-fluoren-9-one (70)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image2" alt="Chemical structure" /></td>
</tr>
</tbody>
</table>

Chemical Formula: C\(_{28}\)H\(_{30}\)O\(_3\) 
Exact Mass: 414.2195
Experimental part

This compound was obtained following the general procedure E. Starting from diyne 22 (102 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne 51 (80 mg, 0.7 mmol, 2.0 equiv) and RuCl₃·nH₂O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 50 °C for 2 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 70 (101 mg, 71%) as a yellow solid. m.p. 86 – 88 °C.

Rᵣ = 0.4 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.56 (d, J = 7.5 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.24 – 7.17 (m, 2H), 7.17 – 7.02 (m, 2H), 6.02 (d, J = 7.5 Hz, 1H), 4.57 (s, 2H), 4.19 (s, 2H), 3.51 (s, 3H), 3.28 – 3.18 (m, 2H), 3.20 (s, 3H), 2.49 (s, 3H), 1.66 – 1.51 (m, 4H), 1.02 (t, J = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 194.7, 144.6, 143.8, 143.0, 142.6, 137.8, 137.6, 137.1, 135.1, 134.1, 130.7, 129.6, 129.4, 128.4, 123.6, 123.3, 68.5, 67.4, 58.9, 58.5, 33.6, 27.3, 23.5, 21.5, 14.1.


1-Butyl-4-(4-(tert-butyl)-phenyl)-2,3-bis(methoxymethyl)-9H-fluoren-9-one (71)

This compound was obtained following the general procedure E. Starting from diyne 23 (120 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne 51 (80 mg, 0.7 mmol, 2.0 equiv) and RuCl₃·nH₂O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 60 °C for 14 h, then at 80 °C for 4 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 71 (90 mg, 56%) as a yellow oil.

Rᵣ = 0.52 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.60 – 7.48 (m, 3H), 7.25 – 7.20 (m, 2H), 7.12 (td, J = 7.5, 0.9 Hz, 1H), 7.03 (td, J = 7.5, 1.2 Hz, 1H), 5.91 (d, J = 7.5 Hz, 1H), 4.57 (s, 2H), 4.20 (s, 2H), 3.51...
(s, 3H), 3.29 – 3.21 (m, 2H), 3.19 (s, 3H), 1.64 – 1.52 (m, 4H), 1.43 (s, 9H), 1.02 (t, J = 6.9 Hz, 3H).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.79 (d, $J$ = 8.0 Hz, 2H), 7.59 (dd, $J$ = 7.3, 0.6 Hz, 1H), 7.49 (d, $J$ = 7.9 Hz, 2H), 7.17 (td, $J$ = 7.5, 1.0 Hz, 1H), 7.08 (td, $J$ = 7.6, 1.3 Hz, 1H), 5.91 (d, $J$ = 7.5 Hz, 1H), 4.55 (s, 2H), 4.11 (s, 2H), 3.51 (s, 3H), 3.30 – 3.20 (m, 2H), 3.17 (s, 3H), 1.64 – 1.50 (m, 4H), 1.02 (t, $J$ = 7.0 Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 194.3, 145.4, 143.2, 142.7, 142.3, 142.1, 137.9, 135.5, 135.2, 134.3, 130.9, 130.3, 128.9, 125.8, 125.8, 124.0, 122.9, 68.4, 67.3, 59.0, 58.7, 33.7, 27.4, 23.5, 14.1.

$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -63.4 (s).

**Experimental part**

This compound was obtained following the general procedure E. Starting from diyne 26 (100.0 mg, 0.28 mmol), 1,4-dimethoxy-2-butyne 51 (80 mg, 0.56 mmol, 2.0 equiv) and RuCl$_3$·nH$_2$O (2.9 mg, 0.014 mmol). The reaction mixture was stirred at 50 °C for 14 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded 72 (85 mg, 65%) as a brown solid. m.p. 113 – 115 °C.

$R_f$ = 0.53 (Cyclohexane/Ethyl acetate; 95/5, KMnO$_4$, UV).
Experimental part

HRMS (ESI⁺): calcd. for C_{28}H_{27}F_{3}O_{3}Na [M+Na]⁺: 491.1805, found 491.1803.

<table>
<thead>
<tr>
<th>4-(4-Bromophenyl)-1-butyl-2,3-bis(methoxymethyl)-9H-fluoren-9-one (73)</th>
</tr>
</thead>
</table>

This compound was obtained following the general procedure E. Starting from diyne 27 (127.0 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne 51 (80 mg, 0.7 mmol, 2.0 equiv) and RuCl₃·nH₂O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 50 °C for 14 h. Purification on silica gel (Petroleum ether/ Ethyl acetate gradient from 98/2 to 95/5) afforded 73 (94 mg, 56%) as a yellow oil.

Rᵣ = 0.43 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.71 – 7.61 (m, 2H), 7.61 – 7.54 (m, 1H), 7.25 – 7.20 (m, 2H), 7.20 – 7.07 (m, 2H), 6.04 (d, J = 7.5 Hz, 1H), 4.54 (s, 2H), 4.13 (s, 2H), 3.50 (s, 3H), 3.28 – 3.18 (m, 2H), 3.20 (s, 3H), 1.64 – 1.51 (m, 4H), 1.01 (t, J = 6.9 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 194.4, 145.2, 143.3, 142.8, 142.3, 137.8, 137.2, 135.6, 135.1, 134.3, 132.1, 131.5, 130.9, 128.8, 123.9, 123.1, 122.4, 68.5, 67.4, 59.0, 58.7, 33.7, 27.3, 23.5, 14.1.

HRMS (ESI⁺): calcd. for C_{27}H_{27}BrO_{3}Na [M+Na]⁺: 501.1036, found 501.1036.

<table>
<thead>
<tr>
<th>8-Butyl-6,7-bis(methoxymethyl)-5-phenyl-9H-fluoreno[2,3-d][1,3]dioxol-9-one (74)</th>
</tr>
</thead>
</table>

234
This compound was obtained following the general procedure E. Starting from diyne 24 (115.5 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne 51 (80 mg, 0.7 mmol, 2.0 equiv) and RuCl₃·nH₂O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 50 °C for 6 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 74 (105 mg, 68%) as a yellow oil.

\[ R_f = 0.25 \] (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

\[^1H\, NMR\] (300 MHz, CDCl₃) \( \delta \) 7.52 – 7.46 (m, 3H), 7.33 – 7.27 (m, 2H), 6.99 (s, 1H), 5.88 (s, 2H), 5.32 (s, 1H), 4.53 (s, 2H), 4.14 (s, 2H), 3.49 (s, 3H), 3.22 – 3.15 (m, 2H), 3.16 (s, 3H), 1.61 – 1.49 (m, 4H), 1.00 (t, \( J = 6.9 \) Hz, 3H).

\[^{13}C\, NMR\] (75 MHz, CDCl₃) \( \delta \) 193.0, 152.4, 147.9, 144.2, 142.0, 140.6, 138.0, 137.0, 136.0, 131.2, 130.1, 129.6, 128.9, 128.2, 104.6, 104.5, 101.9, 68.5, 67.4, 58.9, 58.6, 33.7, 27.2, 23.5, 14.1.


<table>
<thead>
<tr>
<th>1-Butyl-7-fluoro-2,3-bis(methoxymethyl)-4-phenyl-9H-fluoren-9-one (75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Formula: C₂₇H₂₇FO₃</td>
</tr>
<tr>
<td>Exact Mass: 418.1944</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure E. Starting from diyne 25 (106 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne 51 (80 mg, 0.7 mmol, 2.0 equiv) and RuCl₃·nH₂O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 50 °C for 6 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 75 (98 mg, 65%) as a yellow oil.

\[ R_f = 0.36 \] (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).
Experimental part

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.54 – 7.47 (m, 3H), 7.35 – 7.27 (m, 2H), 7.22 (dd, $J$ = 7.2, 2.4 Hz, 1H), 6.72 (td, $J$ = 8.7, 2.4 Hz, 1H), 5.86 (dd, $J$ = 8.1, 4.5 Hz, 1H), 4.56 (s, 2H), 4.17 (s, 2H), 3.50 (s, 3H), 3.26 – 3.18 (m, 2H), 3.18 (s, 3H), 1.66 – 1.51 (m, 4H), 1.01 (t, $J$ = 6.9 Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 193.1, 163.2 (d, $J$ = 247.5 Hz), 145.2, 142.8, 142.4, 139.4 (d, $J$ = 2.8 Hz), 138.1, 137.5, 137.4, 136.7, 131.0 (d, $J$ = 1.6 Hz), 129.5, 129.0, 128.3, 124.6 (d, $J$ = 7.7 Hz), 120.2 (d, $J$ = 22.5 Hz), 111.1 (d, $J$ = 23.6 Hz), 68.5, 67.4, 59.0, 58.6, 33.6, 27.4, 23.5, 14.1.

$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -113.6 (dd, $J$ = 11.3, 8.5 Hz).

HRMS (ESI$^+$): calcd. for C$_{27}$H$_{27}$FO$_3$Na [M+Na]$^+$: 441.1836, found 441.1837.

<table>
<thead>
<tr>
<th>2,3-Bis(tert-butoxymethyl)-1-butyl-4-phenyl-9H-fluoren-9-one (76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Chemical structure image]</td>
</tr>
<tr>
<td>Chemical Formula: C$<em>{33}$H$</em>{42}$O$_3$</td>
</tr>
<tr>
<td>Exact Mass: 484.2977</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure E. Starting from diyne 17 (100 mg, 0.35 mmol), 1,4-di-tert-butoxybut-2-yn 55 (139 mg, 0.7 mmol, 2.0 equiv) and RuCl$_3$·nH$_2$O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 60 °C for 14 h, then at 80 °C for 4 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 99/1 to 98/2) afforded 76 (140 mg, 83%) as a yellow solid. m.p. 158 – 160 °C.

R$_t$ = 0.46 (Cyclohexane/Ethyl acetate; 90/10, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$), $\delta$ 7.58 – 7.52 (m, 1H), 7.56 – 7.44 (m, 3H), 7.39 – 7.29 (m, 2H), 7.11 (td, $J$ = 7.5, 0.9 Hz, 1H), 7.02 (td, $J$ = 7.5, 1.2 Hz, 1H), 5.89 (d, $J$ = 7.5 Hz, 1H), 4.55 (s, 2H), 4.19 (s, 2H), 3.28 – 3.15 (m, 2H), 1.72 – 1.51 (m, 4H), 1.36 (s, 9H), 1.03 (t, $J$ = 6.9 Hz, 3H), 1.01 (s, 9H).
**Experimental part**

$^{13}$C NMR (75 MHz, CDCl$_3$), $\delta$ 194.8, 145.1, 143.9, 143.3, 142.8, 138.4, 138.3, 137.3, 135.2, 134.0, 130.7, 129.9, 128.7, 128.3, 128.0, 123.5, 123.1, 73.7, 73.6, 57.9, 56.8, 33.7, 27.9, 27.6, 27.5, 23.7, 14.1.

**HRMS (ESI$^+$)**: calculated for C$_{39}$H$_{36}$O$_3$Na$^+$ [M+Na$^+$]: 575.2557, found 575.2551.

<table>
<thead>
<tr>
<th>2,3-Bis((benzyloxy)-methyl)-1-butyl-4-phenyl-9H-fluoren-9-one (77)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image_url" alt="Chemical Diagram" /></td>
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<tr>
<td>Chemical Formula: C$<em>{39}$H$</em>{36}$O$_3$</td>
</tr>
<tr>
<td>Exact Mass: 552.2864</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure E. Starting from diyne 17 (100 mg, 0.35 mmol), 1,4-bis(benzyloxy)but-2-yne 56 (186 mg, 0.7 mmol, 2.0 equiv) and RuCl$_3$·nH$_2$O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 50 °C for 14 h. The excess of alkyne was removed by bulb to bulb distillation (condition: 3.0x10$^{-3}$ mbar, 175°C for 20 minutes). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 77 (156 mg, 81%) as a yellow solid. m.p. 145 – 147 °C.

$R_f = 0.25$ (Cyclohexane/Ethyl acetate; 95/5, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$), $\delta$ 7.58 – 7.53 (m, 1H), 7.53 – 7.46 (m, 3H), 7.40 – 7.27 (m, 10H), 7.22 – 7.17 (m, 2H), 7.13 (td, $J = 7.5$, 0.9 Hz, 1H), 7.04 (td, $J = 7.5$, 1.2 Hz, 1H), 5.93 (d, $J = 7.5$ Hz, 1H), 4.53 (s, 2H), 4.50 (s, 2H), 4.16 (s, 2H), 4.15 (s, 2H), 3.23 – 3.12 (m, 2H), 1.57 – 1.41 (m, 4H), 0.97 (t, $J = 6.9$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$), $\delta$ 194.7, 144.9, 143.7, 143.0, 142.6, 138.2, 138.0, 137.7, 137.1, 135.2, 134.1, 130.8, 129.7, 128.9, 128.7, 128.5, 128.6, 128.3, 128.1, 127.9, 123.7, 123.2, 73.6, 73.3, 66.2, 64.7, 33.7, 27.4, 23.5, 14.1

**HRMS (ESI$^+$)**: calculated for C$_{33}$H$_{40}$O$_3$Na$^+$ [M+Na$^+$]: 507.2870, found 507.2867.

<table>
<thead>
<tr>
<th>1-Butyl-2,3-diethyl-4-phenyl-9H-fluoren-9-one (78)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image_url" alt="Chemical Diagram" /></td>
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<tr>
<td>Chemical Formula: C$<em>{33}$H$</em>{40}$O$_3$</td>
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<td>Exact Mass: 507.2864</td>
</tr>
</tbody>
</table>
Experimental part

This compound was obtained following the general procedure E. Starting from diyne 17 (100 mg, 0.35 mmol), 3-hexyne 53 (86.3 mg, 1.05 mmol, 3.0 equiv) and RuCl₃·nH₂O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 80 °C for 16 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 100/0 to 99/1) afforded 78 (pure, 14 mg, 11%) as a sticky oil.

Rₐ = 0.8 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.57 – 7.41 (m, 4H), 7.38 – 7.27 (m, 2H), 7.12 – 7.03 (m, 1H), 7.03 – 6.92 (m, 1H), 5.73 (d, J = 7.5 Hz, 1H), 3.23 – 3.05 (m, 2H), 2.73 (q, J = 7.5 Hz, 2H), 2.48 (q, J = 7.5 Hz, 2H), 1.66 – 1.49 (m, 4H), 1.23 (t, J = 7.7 Hz, 3H), 1.10 – 0.89 (m, 6H).

¹³C NMR (75 MHz, CDCl₃) δ 195.1, 147.8, 144.2, 143.2, 142.8, 140.8, 139.6, 136.0, 136.0, 135.3, 133.8, 129.5, 129.0, 128.9, 127.9, 127.8, 123.4, 122.6, 33.6, 27.6, 23.7, 23.6, 21.5, 15.8, 15.5, 14.1.

7-Butyl-5,6-bis(methoxymethyl)-4-phenyl-8H-indeno[2,1-b]furan-8-one (83)

This compound was obtained following the general procedure E. Starting from diyne 44 (97 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne 51 (80 mg, 0.7 mmol, 2.0 equiv) and RuCl₃·nH₂O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 60 °C for 14 h, then at 80 °C for 4 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 83 (75 mg, 55 %) as a yellow oil.
Experimental part

R_t = 0.32 (Cyclohexane/Ethyl acetate; 90/10, KMnO_4, UV).

^1^H NMR (300 MHz, CDCl_3)  δ 7.52 – 7.38 (m, 3H), 7.35 – 7.27 (m, 3H), 5.40 (d, J = 1.7 Hz, 1H), 4.49 (s, 2H), 4.16 (s, 2H), 3.48 (s, 3H), 3.23 (s, 3H), 3.13 – 3.02 (m, 2H), 1.60 – 1.46 (m, 4H), 0.99 (t, J = 7.0 Hz, 3H).

^1^H NMR (300 MHz, CDCl_3) δ 7.49 – 7.43 (m, 3H), 7.34 (d, J = 4.5 Hz, 1H), 7.33 – 7.27 (m, 2H), 5.62 (d, J = 4.8 Hz, 1H), 4.51 (s, 2H), 4.16 (s, 2H), 3.49 (s, 3H), 3.19 (s, 3H), 3.17 – 3.07 (m, 2H), 1.62 – 1.47 (m, 4H), 1.00 (t, J = 7.2 Hz, 3H).

^1^C NMR (75 MHz, CDCl_3) δ 186.6, 154.6, 151.3, 144.6, 140.9, 138.2, 137.7, 135.1, 134.8, 131.6, 129.7, 128.4, 128.0, 108.0, 68.8, 67.4, 58.9, 58.5, 33.7, 26.7, 23.4, 14.1.

HRMS (ESI^+): calculated for C_{25}H_{28}O_3SNa [M+Na]^+; 413.1723, found 413.1723.

This compound was obtained following the general procedure E. Starting from diyne 45 (102 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne 51 (80 mg, 0.7 mmol, 2.0 equiv) and RuCl_3·nH_2O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 50 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 84 (101 mg, 71%) as a yellow oil.

R_t = 0.4 (Cyclohexane/Ethyl acetate; 90/10, KMnO_4, UV).

^1^H NMR (300 MHz, CDCl_3) δ 7.49 – 7.43 (m, 3H), 7.34 (d, J = 4.5 Hz, 1H), 7.33 – 7.27 (m, 2H), 5.62 (d, J = 4.8 Hz, 1H), 4.51 (s, 2H), 4.16 (s, 2H), 3.49 (s, 3H), 3.19 (s, 3H), 3.17 – 3.07 (m, 2H), 1.62 – 1.47 (m, 4H), 1.00 (t, J = 7.2 Hz, 3H).

^1^C NMR (75 MHz, CDCl_3) δ 186.6, 154.6, 151.3, 144.6, 141.2, 139.3, 138.5, 138.1, 137.3, 134.8, 133.7, 129.8, 128.5, 128.0, 122.3, 68.8, 67.4, 58.9, 58.5, 33.7, 26.9, 23.5, 14.1.

This compound was obtained following the general procedure E. Starting from diyne 45 (102 mg, 0.35 mmol), 1,4-bis(benzyloxy)-but-2-yn 56 (186 mg, 0.7 mmol, 2.0 equiv) and RuCl$_3$·nH$_2$O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 80 °C for 14 h. The excess of alkyne was removed by bulb to bulb distillation (condition: 3.0x10$^{-3}$ mbar, 175 °C for 20 minutes). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 85 (121 mg, 62%) as a yellow solid. m.p. 124 – 126 °C.

**Rt = 0.34** (Cyclohexane/Ethyl acetate; 95/5, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$), $\delta$ 7.48 – 7.42 (m, 3H), 7.38 – 7.27 (m, 11H), 7.22 – 7.17 (m, 2H), 5.62 (d, $J$ = 4.8 Hz, 1H), 4.49 (s, 2H), 4.48 (s, 2H), 4.17 (s, 2H), 4.15 (s, 2H), 3.13 – 3.03 (m, 2H), 1.52 – 1.38 (m, 4H), 0.95 (t, $J$ = 6.9 Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$), $\delta$ 186.6, 157.2, 144.6, 141.5, 139.3, 138.5, 138.0, 137.4, 137.3, 134.9, 133.7, 129.8, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 122.3, 73.5, 73.2, 66.4, 64.7, 33.7, 26.9, 23.4, 14.0.

**HRMS** (ESI$^+$): calculated for C$_{37}$H$_{34}$O$_3$SNa$^+$ [M+Na$^+$]: 581.2121, found 581.2115.

7-Butyl-8,9-bis(methoxymethyl)-10-phenyl-6H-benzo[b]indeno[1,2-d]thiophen-6-one (86)

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</table>
This compound was obtained following the general procedure E. Starting from diyne 46 (120 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne 51 (80 mg, 0.7 mmol, 2.0 equiv) and RuCl₃·nH₂O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 60 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 86 (124 mg, 78 %) as a red solid. m.p. 135 – 137 °C.

Rₜ = 0.32 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.68 (d, J = 8.2 Hz, 1H), 7.51 – 7.40 (m, 5H), 7.20 – 7.10 (m, 1H), 6.83 – 6.72 (m, 1H), 5.19 (d, J = 8.6 Hz, 1H), 4.52 (s, 2H), 4.10 (s, 2H), 3.51 (s, 3H), 3.24 – 3.11 (m, 2H), 3.19 (s, 3H), 1.69 – 1.52 (m, 4H), 1.03 (t, J = 7.0 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 188.4, 151.6, 147.4, 144.6, 142.1, 141.3, 140.2, 139.9, 137.4, 135.0, 133.2, 132.6, 131.2, 128.7, 128.4, 126.6, 126.3, 125.1, 124.0, 68.9, 67.4, 59.0, 58.6, 33.6, 27.0, 23.5, 14.0.


1-Butyl-2,3-bis(methoxymethyl)-4-phenyl-10H-indeno[1,2-b]benzofuran-10-one (87)

This compound was obtained following the general procedure E. Starting from diyne 47 (114.1 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne 51 (80 mg, 0.7 mmol, 2.0 equiv) and RuCl₃·nH₂O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 60 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 87 (42 mg, 30 %) as a yellow oil.

Rₜ = 0.32 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).
Experimental part

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.71–7.63 (m, 1H), 7.55–7.46 (m, 3H), 7.46–7.37 (m, 2H), 7.26–7.11 (m, 3H), 4.54 (s, 2H), 4.18 (s, 2H), 3.51 (s, 3H), 3.26 (s, 3H), 3.17 (t, $J = 7.8$ Hz, 2H), 1.68–1.51 (m, 4H), 1.02 (t, $J = 6.9$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 186.3, 177.5, 160.7, 144.3, 140.3, 136.7, 134.2, 133.0, 129.8, 128.2, 128.1, 125.1, 124.8, 122.2, 120.7, 119.6, 112.7, 68.5, 67.4, 59.0, 58.5, 33.7, 27.0, 23.5, 14.1.

6-Butyl-9-(4-(tert-butyl)phenyl)-7,8-bis(methoxymethyl)-5H-indeno[1,2-b]pyridin-5-one (89)

This compound was obtained following the general procedure E. Starting from diyne 49 (100 mg, 0.29 mmol), 1,4-dimethoxy-2-butyne 51 (200 mg, 1.75 mmol, 6.0 equiv) and RuCl$_3$·$n$H$_2$O (3.0 mg, 0.0146 mmol). The reaction mixture was stirred at 80 °C for 18 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 89 (8 mg, 6%) as a brown oil.

$R_f = 0.65$(Cyclohexane/Ethyl acetate; 95/5, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.23 (dd, $J = 5.0$, 1.7 Hz, 1H), 7.76 (dd, $J = 7.4$, 1.7 Hz, 1H), 7.45 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 8.3$ Hz, 2H), 6.99 (dd, $J = 7.5$, 5.1 Hz, 1H), 4.59 (s, 2H), 4.18 (s, 2H), 3.51 (s, 3H), 3.27–3.18 (m, 2H), 3.20 (s, 3H), 1.62–1.54 (m, 2H), 1.41 (s, 9H), 1.37–1.32 (m, 2H), 1.01 (t, $J = 6.9$ Hz, 3H).

6-Butyl-3-chloro-7,8-bis(methoxymethyl)-9-phenyl-5H-indeno[1,2-c]pyridin-5-one (90)
This compound was obtained following the general procedure E. Starting from diyne 50 (112 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne 51 (80 mg, 0.7 mmol, 2.0 equiv) and RuCl₃·nH₂O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 80 °C for 2 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 90 (91 mg, 60%) as a yellow solid. m.p. 94 – 96 °C.

\[ R_f = 0.31 \] (Cyclohexane/Ethyl acetate: 90/10, KMnO₄, UV).

\(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.55 – 7.48 (m, 3H), 7.40 (d, \( J = 0.9 \) Hz, 1H), 7.32 – 7.27 (m, 2H), 6.90 (d, \( J = 1.2 \) Hz, 1H), 4.57 (s, 2H), 4.22 (s, 2H), 3.51 (s, 3H), 3.24 – 3.15 (m, 2H), 3.20 (s, 3H), 1.60 – 1.52 (m, 4H), 1.01 (t, \( J = 6.9 \) Hz, 3H).

\(^13\)C NMR (75 MHz, CDCl₃) \( \delta \) 191.9, 151.7, 146.4, 144.2, 143.7, 141.5, 138.8, 137.8, 137.6, 136.0, 130.3, 129.4, 129.1, 128.9, 128.8, 118.1, 67.3, 59.1, 58.7, 33.5, 27.6, 23.5, 14.0.

HRMS (ESI\(^+\)): calcd. for C₂₆H₂₆ClNO₃Na \([\text{M+Na}]^+\): 458.1493, found 458.1494.

Thess compounds were obtained following the general procedure E. Starting from diyne 17 (200 mg, 0.7 mmol), cyclopropyl acetylene 58 (93 mg, 1.4 mmol, 2.0 equiv) and RuCl₃·nH₂O (7.2 mg, 0.035 mmol). The reaction mixture was stirred at 80 °C for 14 h. Purification on silica
Experimental part

gel (Petroleum ether/Ethyl acetate 99/1) afforded the title regioisomers 91 (208 mg, 84%) in the ratio of 67/33 as an orange oil.

R_t = 0.6 (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

Major product: ¹H NMR (300 MHz, CDCl₃) δ 7.60 – 7.45 (m, 4H), 7.39 – 7.33 (m, 2H), 7.15 – 7.08 (m, 2H), 6.56 (s, 1H), 6.04 – 5.98 (m, 1H), 3.05 (t, J = 7.8 Hz, 2H), 1.68 – 1.55 (m, 3H), 1.51 – 1.40 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H), 0.86 – 0.74 (m, 2H), 0.75 – 0.64 (m, 2H).

¹³C NMR (75 MHz, CDCl₃) δ 194.5, 149.6, 144.2, 144.1, 142.6, 138.9, 136.0, 133.8, 129.7, 129.1, 128.3, 127.9, 125.3, 123.5, 123.1, 33.1, 31.5, 22.9, 14.1, 12.5, 10.2.

Minor product: ¹H NMR (300 MHz, CDCl₃) δ 7.60 – 7.45 (m, 4H), 7.43 – 7.39 (m, 2H), 7.04 (td, J = 7.5, 1.4 Hz, 2H), 6.88 (s, 1H), 6.64 – 6.60 (m, 1H), 3.35 (t, J = 7.8 Hz, 2H), 2.05 – 1.97 (m, 1H), 1.68 – 1.50 (m, 4H), 1.02 (t, J = 7.8 Hz, 3H), 0.86 – 0.74 (m, 2H), 0.75 – 0.64 (m, 2H).

¹³C NMR (75 MHz, CDCl₃) δ 195.2, 143.9, 143.4, 140.2, 139.4, 135.8, 135.2, 134.0, 133.3, 131.1, 129.1 128.8, 128.6, 128.2, 128.0, 123.7, 122.7, 32.6, 27.0, 23.5, 14.0, 12.5, 7.8.

HRMS (ESI⁺): calculated for C₂₆H₂₄OH⁺ [M+H⁺]: 353.1900, found 353.1900.

1-Butyl-3,4-diphenyl-9H-fluoren-9-one and 1-butyl-2,4-diphenyl-9H-fluoren-9-one (92)

Thess compounds were obtained following the general procedure E. Starting from diyne 17 (200 mg, 0.7 mmol), phenyl acetylene 59 (93 mg, 1.4 mmol, 2.0 equiv) and RuCl₃·nH₂O (7.2 mg, 0.035 mmol). The reaction mixture was stirred at 80 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate 99/1) afforded the title regioisomers 92 (191 mg, 70%) in the ratio of 73/27 as an orange solid.

R_t = 0.45 (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).
Experimental part

Major product: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.66-7.58 (m, 1H), 7.34-7.30 (m, 3H), 7.20-7.05 (m, 10H), 6.22–6.13 (m, 1H), 3.15 (t, $J$ = 7.8 Hz, 2H), 1.75-1.65 (m, 2H), 1.55-1.46 (m, 2H), 0.99 (t, $J$ = 7.2 Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 194.7, 148.0, 144.1, 143.8, 143.1, 140.4, 138.3, 135.3, 134.6, 134.1, 132.8, 130.4, 130.0, 129.6, 128.6, 128.5, 127.8, 127.7, 127.1, 123.6, 123.3, 33.1, 31.2, 23.0, 14.1.

Minor product: $^1$H NMR (300 MHz, CDCl$_3$), $\delta$ 7.66-7.58 (m, 1H), 7.50-7.33 (m, 10H), 7.22-7.05 (m, 3H), 6.77-6.72 (m, 1H), 3.08-3.03 (m, 1H), 1.55-1.46 (m, 2H), 1.37-1.30 (m, 2H), 0.82 (t, $J$ = 7.2 Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$), $\delta$ 194.9, 144.2, 143.7, 142.2, 141.2, 140.4, 139.7, 137.9, 135.7, 135.1, 134.1, 131.4, 129.4, 129.1, 129.0 128.8, 128.3, 128.1, 127.4, 123.8, 123.0, 33.3, 27.7, 23.1,13.8.

HRMS (ESI$^+$): calculated for C$_{29}$H$_{24}$ONa$^+$ [M+Na$^+$]: 411.1719, found 411.1722.

This compound was obtained following the general procedure E. Starting from diyne 17 (200 mg, 0.7 mmol), 5-chloro-1-pentyne 60 (143 mg, 1.4 mmol, 2.0 equiv) and RuCl$_3$-nH$_2$O (7.2 mg, 0.035 mmol). The reaction mixture was stirred at 80 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate 99/1) afforded the title regioisomers 93 (165 mg, 61%) in the ratio of 55/45 as an orange oil.

**Rr = 0.5** (Cyclohexane/Ethyl acetate; 95/5, KMnO$_4$, UV).
Experimental part

Major product: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.57-7.50 (m, 4H), 7.30-7.27 (m, 2H), 7.19 -7.11 (m, 1H), 7.05 (dd, $J = 7.5$, 1.4 Hz, 1H), 7.01 (s, 1H), 5.95-5.92 (m, 1H), 3.40 (t, $J = 6.6$ Hz, 2H), 3.08 (t, $J = 7.7$ Hz, 2H), 2.57-2.52 (m, 2H), 1.91-1.86 (m, 2H), 1.68-1.64 (m, 2H), 1.52-1.46 (m, 2H), 0.99 (t, $J = 7.7$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 194.7, 146.3, 144.1, 144.0, 143.1, 138.2, 135.4, 135.2, 134.0, 131.6, 129.4, 129.3, 128.4, 128.2, 123.6, 123.0, 44.4, 33.6, 33.1, 31.2, 30.6, 22.9, 14.1. Minor product $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.59-7.57 (m, 1H), 7.49-7.49 (m, 2H), 7.45-7.40 (m, 3H), 7.16 -7.11 (m, 3H), 6.67-6.63 (m, 1H), 3.62 (t, $J = 6.3$ Hz, 2H), 3.20-3.12 (m, 2H), 2.88-2.78 (m, 2H), 2.12-2.04 (m, 2H), 1.59-1.53 (m, 4H), 1.09 (t, $J = 7.7$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 195.0, 143.8, 142.6, 140.9, 140.3, 139.9, 137.2, 136.0, 135.0, 134.7, 134.1, 131.5, 129.1, 128.8, 128.1, 123.8, 122.8, 44.6, 34.0, 33.3, 29.1, 26.9, 23.5, 14.1.

HRMS (ESI$^+$): calculated for C$_{26}$H$_{25}$ClONa$^+$ [M+Na$^+$]: 411.1486, found 411.1490.

2.4. Post-functionalization of [2+2+2] cycloadducts

![Diagram of chemical reaction](image)

A solution of 65 (400 mg, 1.0 mmol) in trifluoroacetic acid (3 mL) was refluxed for 36 h. Evaporation of the excess of trifluoroacetic acid under reduced pressure gave a residue which was purified by column chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) to afford compound 94 (300 mg, 85%) as a yellow solid. m.p. 109 – 111 °C. $R_f = 0.28$ (Cyclohexane/Ethyl acetate; 90/10, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$), $\delta$ 7.60 – 7.55 (m, 1H), 7.53 – 7.47 (m, 3H), 7.37 – 7.32 (m, 2H), 7.18 – 7.05 (m, 2H), 6.38 (d, $J = 7.2$ Hz, 1H), 5.17 (s, 1H), 4.86 (s, 1H), 2.97 (t, $J = 7.5$ Hz, 2H), 1.68 – 1.54 (m, 2H), 1.52 – 1.40 (m, 2H), 0.97 (t, $J = 7.2$ Hz, 3H).
**Experimental part**

\[^{13}\text{C NMR}\ (75\text{ MHz, CDCl}_3), \delta 194.3, 145.4, 143.6, 142.7, 139.9, 137.8, 137.5, 135.4, 134.1, 131.2, 129.8, 129.3, 128.5, 123.8, 122.8, 73.9, 73.3, 32.2, 29.0, 23.2, 14.1.\]

**HRMS (ESI\(^+\)):** calculated for C\(_{25}\)H\(_{22}\)O\(_2\)Na\(^+\) [M+Na\(^+\)]: 377.1512, found 377.1515.

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</thead>
<tbody>
<tr>
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</table>
| Chemical Formula: C\(_{25}\)H\(_{24}\)O\(_3\)  
Exact Mass: 372.1725 |

To a solution of \(76\) (100 mg, 0.21 mmol) in CH\(_2\)Cl\(_2\) (1 mL) was added trifluoroacetic acid (1 mL, large excess amount). The reacton mixture was stirred at room temperature for 36 h. When the reaction was complete (TLC monitoring), CH\(_2\)Cl\(_2\) and the excess of trifluoroacetic acid were evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) to afford compound \(95\) (60 mg, 75\%) as a yellow solid. m.p. 166 – 168 °C.

**R\(_f\) = 0.28** (Cyclohexane/Ethyl acetate; 90/10, KMnO\(_4\), UV).

\[^{1}\text{H NMR}\ (300\text{ MHz, CDCl}_3), \delta 7.66 – 7.60 \text{ (m, } 1\text{H}), 7.58 – 7.51 \text{ (m, } 3\text{H}), 7.34 – 7.27 \text{ (m, } 2\text{H}), 7.22 \text{ (td, } J = 7.5, 0.9 \text{ Hz, } 1\text{H}), 7.11 \text{ (td, } J = 7.5, 1.2 \text{ Hz, } 1\text{H}), 5.96 \text{ (d, } J = 7.5 \text{ Hz, } 1\text{H}), 5.57 \text{ (s, } 2\text{H}), 5.22 \text{ (s, } 2\text{H}), 3.33 – 3.22 \text{ (m, } 2\text{H}), 1.63 – 1.52 \text{ (m, } 4\text{H}), 1.01 \text{ (t, } J = 6.9 \text{ Hz, } 3\text{H}).\]

\[^{13}\text{C NMR}\ (75\text{ MHz, CDCl}_3), \delta 193.7, 145.4, 144.9, 142.7, 138.2, 138.0, 136.5, 134.9, 134.7, 133.1, 132.1, 129.6, 129.6, 129.2, 124.2, 123.6, 63.7, 62.7, 33.8, 27.4, 23.4, 13.9.\]

**HRMS (ESI\(^+\)):** calculated for C\(_{25}\)H\(_{24}\)O\(_3\)Na\(^+\) [M+Na\(^+\)]: 395.1618, found 395.1619.

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<th>2,3-Bis(bromomethyl)-1-butyl-4-phenyl-9H-fluoren-9-one (96)</th>
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| Chemical Formula: C\(_{25}\)H\(_{22}\)Br\(_2\)O  
Exact Mass: 496.0037 |

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Experimental part

To a solution of 76 (480 mg, 1.0 mmol) in CHCl₃ (10 mL) were added nBu₄NBr (0.16 g, 0.5 mmol), aq. HBr (48% in water, 3 mL) and conc. H₂SO₄ (0.3 mL). The resulting mixture was heated at 60 °C for 24 h. At the end of the reaction (TLC monitoring), the reaction mixture was poured into water (50 mL). The product was extracted with CH₂Cl₂ (3×30 mL) and the combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Petroleum ether/Dichloromethane = 2/1) to afford compound 96 (444 mg, 90%) as a yellow solid. m.p. 132 – 133 °C.

Rᵣ = 0.52 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.62 – 7.50 (m, 4H), 7.48 – 7.35 (m, 2H), 7.17 (td, J = 7.5, 0.9 Hz, 1H), 7.07 (td, J = 7.6, 1.3 Hz, 1H), 5.88 (d, J = 7.5 Hz, 1H), 4.79 (s, 2H), 4.42 (s, 2H), 3.37 – 3.13 (m, 2H), 1.75 – 1.50 (m, 4H), 1.04 (t, J = 7.0 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 194.0, 144.5, 143.8, 143.1, 142.1, 137.0, 136.9, 136.8, 135.0, 134.4, 131.2, 129.4, 129.3, 129.1, 128.9, 123.9, 123.4, 33.3, 27.5, 27.3, 26.3, 23.5, 14.0.

HRMS (ESI⁺): calcd. for C₂₅H₂₂Br₂O₂H [M+H]⁺: 497.0110, found 497.0109.

<table>
<thead>
<tr>
<th>1-Butyl-4-iodo-2,3-bis(methoxymethyl)-9H-fluoren-9-one (97)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Reaction Diagram" /></td>
</tr>
</tbody>
</table>

To a solution of 69 (0.56 g, 1.41 mmol) in CH₂Cl₂ (10 mL) was added a solution of iodine monochloride (240 mg, 1.5 mmol) in DCM (2 mL) at -78 °C and the mixture was allowed to warm to room temperature and stirred for additional 30 minutes. The reaction was quenched with aqueous saturated Na₂S₂O₃ and extracted with CH₂Cl₂ (3×30 mL). The organic layer was washed with brine and dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) to afford compound 97 (0.53 g, 84%) as a yellow solid. m.p. 93 – 95 °C.

Rᵣ = 0.3 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).
**Experimental part**

1H NMR (300 MHz, CDCl₃) δ 8.98 – 8.87 (m, 1H), 7.67 (dd, J = 7.3, 0.6 Hz, 1H), 7.56 (td, J = 7.7, 1.3 Hz, 1H), 7.35 (td, J = 7.4, 0.8 Hz, 1H), 4.74 (s, 2H), 4.55 (s, 2H), 3.54 (s, 3H), 3.48 (s, 3H), 3.18 (t, J = 7.5 Hz, 2H), 1.55 – 1.44 (m, 4H), 0.98 (t, J = 6.8 Hz, 3H).

13C NMR (101 MHz, CDCl₃) δ 193.3, 147.8, 146.5, 145.3, 144.2, 138.9, 135.1, 133.8, 133.1, 129.6, 124.1, 122.9, 95.8, 75.2, 67.8, 59.0, 58.9, 33.5, 27.0, 23.4, 14.0.


<table>
<thead>
<tr>
<th>1-Butyl-2,3-bis(methoxymethyl)-4-(phenylethynyl)-9H-fluoren-9-one (98)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical structure of 1-Butyl-2,3-bis(methoxymethyl)-4-(phenylethynyl)-9H-fluoren-9-one (98)" /></td>
</tr>
</tbody>
</table>

PdCl₂(PPh₃)₂ (5 mol%, 19.6 mg) and CuI (5 mol%, 2.7 mg) were added to a NEt₃/THF (1:1, 2 mL) solution containing iodo-substituted fluorenone 97 (250 mg, 0.56 mmol), phenylacetylene (86 mg, 0.84 mmol, 1.5 equiv). The mixture was stirred at 40 °C for 4 h under argon. When the reaction was complete (TLC monitoring), a saturated aqueous solution of ammonium chloride was added and the mixture was stirred for 5 minutes. The organic layer was extracted with ethyl acetate (3×20 mL), washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) to afford compound 98 (232 mg, 98%) as a yellow solid. m.p. 124 – 126 °C.

Rᵣ = 0.28 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

1H NMR (300 MHz, CDCl₃) δ 8.43 (d, J = 7.6 Hz, 1H), 7.72 – 7.57 (m, 3H), 7.55 – 7.39 (m, 4H), 7.36 – 7.29 (m, 1H), 4.86 (s, 2H), 4.57 (s, 2H), 3.52 (s, 3H), 3.48 (s, 3H), 3.21 (t, J = 7.5 Hz, 2H), 1.68 – 1.40 (m, 4H), 0.99 (t, J = 6.9 Hz, 3H).

13C NMR (75 MHz, CDCl₃) δ 193.9, 145.9, 145.3, 143.3, 138.1, 134.9, 134.7, 131.6, 131.0, 129.4, 129.1, 128.8, 123.9, 123.2, 123.1, 116.9, 97.8, 86.2, 69.5, 67.1, 59.0, 58.8, 33.6, 27.4, 23.5, 14.1.
Experimental part

HRMS (ESI\(^+\)): calcd. for C\(_{29}\)H\(_{28}\)O\(_3\)Na [M+Na]\(^+\): 447.1931, found 447.1930.

| 1-Butyl-2,3-bis(methoxymethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9H-fluoren-9-one (99) |
|---|---|
| ![Chemical Structure](image) |

To a dry DMF solution (1 mL) of 97 (135 mg, 0.3 mmol) were added bis(pinacolato)diboron (114 mg, 0.45 mmol), PdCl\(_2\)(dppf)-CH\(_2\)Cl\(_2\) (11 mg, 0.015 mmol), and KOAc (60 mg, 0.6 mmol). The mixture was stirred at 80 °C for 18 h. After cooling, the DMF was removed under vacuum, and CH\(_2\)Cl\(_2\) and water were added. The resulting mixture was extracted with dichloromethane (2×30 mL), and the organic layer was washed with water and brine, dried over anhydrous MgSO\(_4\). The organic solvent was concentrated in vacuo to yield a dark-black oil. The excess bis(pinacolato)diboron was removed under reduced pressure with heating. The residue was purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded 99 (88 mg, 65%) as a yellow oil.

R\(_f\) = 0.23 (Cyclohexane/Ethyl acetate; 90/10, K\(\text{MnO}_4\), UV).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.07 (d, \(J = 7.6\) Hz, 1H), 7.60 (d, \(J = 7.2\) Hz, 1H), 7.42 (td, \(J = 7.6, 1.3\) Hz, 1H), 7.30 – 7.19 (m, 1H), 4.70 (s, 2H), 4.42 (s, 2H), 3.39 (s, 3H), 3.27 (s, 3H), 3.24 – 3.13 (m, 2H), 1.47 (s, 16H), 1.01 – 0.90 (m, 3H).

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 194.9, 150.5, 148.7, 145.2, 144.9, 135.2, 135.0, 134.0, 129.8, 128.8, 123.7, 122.7, 84.1, 71.2, 66.7, 58.3, 57.5, 33.6, 27.0, 25.9, 23.3, 14.1.

| 1-Butyl-2,3-bis(methoxymethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-9H-fluoren-9-one (100) |
|---|---|
To a dry DMF solution (1 mL) of 73 (150 mg, 0.313 mmol) were added bis(pinacolato)diboron (120 mg, 0.47 mmol), PdCl$_2$(dppf)$\cdot$CH$_2$Cl$_2$ (11.4 mg, 0.0156 mmol), and KOAc (61 mg, 0.626 mmol). The mixture was stirred at 80 °C for 18 h. After the solution was cooled, the DMF was removed under vacuum, and CH$_2$Cl$_2$ and water were added. The resulting mixture was extracted with dichloromethane (2×30 mL), and the organic layer was washed with water and brine, dried over anhydrous MgSO$_4$. The solvent was concentrated in vacuo to yield a dark-black oil. The excess bis(pinacolato)diboron was removed under reduced pressure with heating. The residue was purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded 100 (140 mg, 85%) as a yellow oil.

R$_f$ = 0.2 (Cyclohexane/Ethyl acetate; 90/10, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.93 (d, $J$ = 7.7 Hz, 2H), 7.56 (d, $J$ = 7.0 Hz, 1H), 7.34 (d, $J$ = 7.7 Hz, 2H), 7.09 (dt, $J$ = 23.8, 7.2 Hz, 2H), 6.00 (d, $J$ = 7.4 Hz, 1H), 4.55 (s, 2H), 4.14 (s, 2H), 3.49 (s, 3H), 3.31 – 3.18 (m, 2H), 3.17 (s, 3H), 1.66 – 1.45 (m, 4H), 1.42 (s, 12H), 1.01 (t, $J$ = 6.6 Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 194.6, 144.9, 143.5, 142.7, 142.2, 141.3, 137.7, 136.9, 135.2, 135.1, 134.3, 130.8, 129.0, 128.5, 123.6, 123.4, 84.2, 68.5, 67.4, 58.9, 58.6, 33.6, 27.3, 25.1, 23.5, 14.1.

MS (ESI, NH$_3$): m/z = 549 [M + Na]$^+$. 

3. Formation of 2-aminopyridine and related derivatives

3.1. Synthesis of symmetrical diynes

General procedure F:
Experimental part

To a suspension of NaH (60% in mineral oil, 1.1-2.4 equiv) in THF was added dropwise a solution of nucleophile (1.0 equiv) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. A solution of 1-bromo-2-butene or propargyl bromide (1.2 or 2.4 equiv) in THF was added to the mixture. The reaction was allowed to warm up to room temperature and stirred until completion. The mixture was finally quenched with saturated ammonium chloride and extracted with diethyl ether (×3). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography or distillation under vacuum to afford the desired product.

General procedure G:

\[
\text{TsNH}_{2} + \begin{array}{c}
\text{Br} \\
(3 \text{ equiv})
\end{array} \xrightarrow{\text{K}_{2}\text{CO}_{3}, 5 \text{ equiv}} \begin{array}{c}
\text{TsN} \\
(\text{R} = \text{Me, H})
\end{array} \xrightarrow{\text{CH}_{2}\text{CN}, 80 \degree \text{C}, 14 \text{ h}} \begin{array}{c}
\text{TsNH} \\
(\text{R} = \text{Me, H})
\end{array}
\]

To a round bottom flask p-toluenesulfonamide (1 equiv), 1-bromo-2-butene or propargyl bromide (3.0 equiv), potassium carbonate (5 equiv) and acetonitrile (5 M) were employed. The resulting mixture was stirred at 80 °C for 14 h. When the reaction was complete (TLC monitoring), the reaction mixture was filtered, and the organic layer was concentrated under reduced pressure. The residue was purified by column chromatography to afford the desired product.

General procedure H:

\[
\begin{array}{c}
\text{R} \\
(\text{X = Br or I})
\end{array} + \begin{array}{c}
\text{NXS}
\end{array} \xrightarrow{\text{AgNO}_{3}, 10 \text{ mol \%}} \begin{array}{c}
\text{R} \\
\text{X}
\end{array}
\]

Silver nitrate (10 mol%) and N-bromosuccinimide (NBS) or N-iodosuccinimide (NIS) (1.2-2 equiv) were added to a solution of terminal alkyne (1 equiv) in dry acetone or DMF, and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with Et₂O and washed with water. The aqueous phase was extracted with Et₂O (×3), the combined organic fractions were washed with water, saturated Na₂S₂O₃ aqueous solution and
brine. The solvent was dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desired compound.

### Dimethyl 2,2-di(but-2-yn-1-yl)malonate (101)

![Chemical Structure](image)

**Chemical Formula:** C₁₆H₁₆O₄  
**Exact Mass:** 236.1049

This compound was obtained following the general procedure F. Starting from dimethyl malonate (4.01 g, 30 mmol), 1-bromo-2-butyne (5.84 mL, 66 mmol, 2.2 equiv) and NaH (2.64 g, 66 mmol). The reaction mixture was stirred at room temperature for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded 101 (6.15 g, 87 %) as a white solid. The analytical data were identical to the literature.¹⁵⁴

**Rf = 0.51** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

**¹H NMR** (300 MHz, CDCl₃) δ 3.73 (s, 6H), 2.88 (q, J = 2.7 Hz, 4H), 2.05 (t, J = 2.7 Hz, 6H).

**¹³C NMR** (75 MHz, CDCl₃) δ 169.8, 79.1, 73.2, 57.1, 53.0, 23.1, 3.6.

### 5,5-Di(but-2-yn-1-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (102)

![Chemical Structure](image)

**Chemical Formula:** C₁₄H₁₄N₂O₅  
**Exact Mass:** 260.1161

This compound was obtained following the general procedure F. Starting from 1,3-dimethylbarbituric acid (0.94 g, 6 mmol), 1-bromo-2-butyne (1.26 mL, 14.4 mmol, 2.4 equiv) and NaH (0.58 g, 14.4 mmol, 2.4 equiv). The reaction mixture was stirred at room temperature for 12 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 85/15) afforded 102 (0.96 g, 62 %) as a white solid. m.p. 118-120 °C.

**Rf = 0.62** (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

**¹H NMR** (300 MHz, CDCl₃) δ 3.40 – 3.24 (m, 6H), 2.78 – 2.51 (m, 4H), 1.75 – 1.50 (m, 6H).
Experimental part

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.3, 151.4, 80.0, 72.4, 56.6, 28.8, 28.3, 3.4.

MS (CI, NH$_3$): $m/z = 261$ [M + H]$^+$.

### 2,2-Di(but-2-yn-1-yl)-1H-indene-1,3(2H)-dione (103)

![Chemical structure of 103]

This compound was obtained following the general procedure F. Starting from indene dione (0.84 g, 6 mmol), 1-bromo-2-butyne (1.26 mL, 14.4 mmol, 2.4 equiv) and NaH (0.58 g, 14.4 mmol, 2.4 equiv). The reaction mixture was stirred at room temperature for 3 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded 103 (1.15 g, 77%) as a yellow solid. m.p. 97-99 °C. The analytical data were identical to the literature.$^{145e}$

$R_f = 0.28$ (Cyclohexane/Ethyl acetate; 90/10, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.06 – 7.93 (m, 2H), 7.92 – 7.76 (m, 2H), 2.63 – 2.46 (m, 4H), 1.39 (s, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 201.9, 142.8, 135.6, 123.2, 79.5, 73.1, 56.6, 23.5, 3.2.

### 2,2-Di(but-2-yn-1-yl)propane-1,3-diol (104)

![Chemical structure of 104]

To a stirred mixture of LiAlH$_4$ (2.89 g, 76.2 mmol, 6 equiv) in dry THF (50 mL) at 0 °C was added dropwise a solution of dimethyl 2,2-di(but-2-ynyl)malonate 101 (3.0 g, 12.7 mmol, 1 equiv) in THF (20 mL). The resulting mixture was stirred at room temperature for 1 h. The reaction was quenched carefully with water (2.9 mL), followed by stirring at 0 °C for 10 min. Then a solution of NaOH (15%, 2.9 mL) was added and stirred for additional 10 min, followed by addition of water (8.7 mL) and stirred for additional 1 h. The resulting solution was dried over MgSO$_4$, filtered through Celite, and concentrated to give the diol 104 (2.05 g, 95%) as a white solid. m.p. 85-87 °C. The analytical data were identical to the literature.$^{34}$

254
Experimental part

\[ \text{Rf} = 0.1 \] (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

\[ ^1H \text{ NMR} \] (300 MHz, CDCl₃) \( \delta \) 3.68 (s, 4H), 2.46 (br, 2H), 2.24 (q, \( J \) = 2.4 Hz, 4H), 1.78 (s, 6H).

\[ ^{13}C \text{ NMR} \] (75 MHz, CDCl₃) \( \delta \) 78.5, 75.2, 67.1, 42.5, 22.5, 3.6.

### 2,2-Di(but-2-yn-1-yl)propane-1,3-diyl diacetate (105)

![2,2-Di(but-2-yn-1-yl)propane-1,3-diyl diacetate (105)]

To a solution of diol 104 (0.72 g, 4 mmol) in DCM (20 mL) at 0 °C was added dropwise acetic anhydride (1.63 g, 16 mmol, 4 equiv) and diisopropylethylamine (2.27 g, 17.6 mmol, 4.4 equiv). The reaction mixture was stirred at room temperature for 24 h and then quenched with water. The aqueous layer was extracted with Et₂O (2 × 50 mL), and the combined organic layers were washed with brine, dried with MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded 105 (0.98 g, 92%) as a colorless oil. The analytical data were identical to the literature.\(^{145b}\)

\[ \text{Rf} = 0.48 \] (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

\[ ^1H \text{ NMR} \] (300 MHz, CDCl₃) \( \delta \) 4.07 (s, 4H), 2.30 (q, \( J \) = 2.6 Hz, 4H), 2.05 (s, 6H), 1.76 (t, \( J \) = 2.6 Hz, 6H).

\[ ^{13}C \text{ NMR} \] (75 MHz, CDCl₃) \( \delta \) 170.9, 78.8, 73.8, 65.6, 40.4, 22.6, 21.0, 3.7.

### (((2,2-Di(but-2-yn-1-yl)propane-1,3-diyl)bis(oxy))bis(methylene))dibenzene (106)

![(((2,2-Di(but-2-yn-1-yl)propane-1,3-diyl)bis(oxy))bis(methylene))dibenzene (106)]

To a suspension of NaH (60% in mineral oil, 2.5 equiv, 2.14 g) in THF (20 mL) was added dropwise diol 104 (0.9 g, 5 mmol) in THF (5 mL). The reaction mixture was stirred at 0 °C for 30 minutes before a solution of benzyl bromide (2.14 g, 12.5 mmol, 2.5 equiv) was added
Experimental part

dropwise. The reaction mixture was stirred at room temperature for 12 h and then quenched with water. The aqueous layer was extracted with Et₂O (2×50 mL), and the combined organic layers were washed with brine, dried with MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded 106 (1.8 g, 99%) as a colorless oil. The analytical data were identical to the literature.¹⁴⁵b

Rᵣ = 0.45 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.41 – 7.22 (m, 10H), 4.53 (s, 4H), 3.47 (s, 4H), 2.41 – 2.23 (m, 4H), 1.75 (s, 6H).

¹³C NMR (75 MHz, CDCl₃) δ 139.0, 128.3, 127.5, 127.4, 75.6, 73.4, 71.7, 42.6, 22.5, 3.7.

<table>
<thead>
<tr>
<th>1-(But-2-yn-1-yloxy)but-2-yne (107)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
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<tr>
<td>Chemical Formula: C₃H₁₀O</td>
</tr>
<tr>
<td>Exact Mass: 122.0732</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure F. Starting from 2-butyne-1-ol (1.05 g, 15 mmol), 1-bromo-2-buten (1.6 mL, 18 mmol, 1.2 equiv) and NaH (1.32 g, 33 mmol, 2.2 equiv). The reaction mixture was stirred at room temperature for 4 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 99/1 to 80/20) afforded 107 (1.75 g, 96%) as a colorless oil. The analytical data were identical to the literature.¹⁵⁴

Rᵣ = 0.5 (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 4.18 (q, J = 2.3 Hz, 4H), 1.85 (t, J = 2.3 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃) δ 83.0, 74.7, 57.1, 3.7.

<table>
<thead>
<tr>
<th>N,N-di(but-2-yn-1-yl)-4-methylbenzenesulfonamide (108)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
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<tr>
<td>Chemical Formula: C₁₆H₁₇NO₂S</td>
</tr>
<tr>
<td>Exact Mass: 275.0980</td>
</tr>
</tbody>
</table>
This compound was obtained following the general procedure G. Starting from \( p \)-toluenesulfonamide (2 g, 11.7 mmol), 1-bromo-2-butyne (4.66 g, 35.1 mmol, 3 equiv) and \( \text{K}_2\text{CO}_3 \) (8 g, 58.5 mmol, 5 equiv). The reaction mixture was stirred at 80 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate; 90/10) afforded 108 (2.8 g, 70 %) as a white solid. The analytical data were identical to the literature.\(^{145d}\)

\[ \text{Rr} = 0.76 \text{ (Cyclohexane/Ethyl acetate; 70/30, KMnO}_4, \text{ UV).} \]

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \( \delta \) 7.71 (d, \( J = 8.4 \text{ Hz}, 2\text{H} \)), 7.32 – 7.20 (m, 2H), 4.07 (q, \( J = 2.2 \text{ Hz}, 4\text{H} \)), 2.41 (s, 3H), 1.64 (t, \( J = 2.2 \text{ Hz}, 6\text{H} \)).

\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \( \delta \) 150.4, 143.3, 129.2, 128.0, 81.7, 71.8, 36.8, 21.6, 3.5.

---

**Dimethyl 2,2-di(prop-2-yn-1-yl)malonate (109)**

This compound was obtained following the general procedure F. Starting from dimethyl malonate (4.01 g, 30 mmol), propargyl bromide (7.12 mL, 67.5 mmol, 2.2 equiv) and \( \text{NaH} \) (2.64 g, 66 mmol). The reaction mixture was stirred at room temperature for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded 109 (5.7 g, 91 %) as a white solid. The analytical data were identical to the literature.\(^{41}\)

\[ \text{Rr} = 0.3 \text{ (Cyclohexane/Ethyl acetate; 85/15, KMnO}_4, \text{ UV).} \]

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \( \delta \) 3.75 (s, 6H), 2.98 (d, \( J = 2.7 \text{ Hz}, 4\text{H} \)), 2.03 (t, \( J = 2.6 \text{ Hz}, 2\text{H} \)).

\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \( \delta \) 169.0, 78.3, 71.8, 56.4, 53.2, 22.6.

---

**Dimethyl 2,2-bis(3-(trimethylsilyl)prop-2-yn-1-yl)malonate (110)**
Experimental part

To a solution of dimethyl 2,2-di(prop-2-yn-1-yl)malonate 109 (1.04 g, 5 mmol) in THF (40 mL) was slowly added lithium hexamethyldisilazide (11 mmol, 11 mL, 1 M in THF) at -78 °C, and the solution was stirred at the same temperature for 1 h. To the resulting mixture was added at chlorotrimethylsilane (1.08 mL, 12.5 mmol, 2.5 equiv) at -78 °C, and the reaction mixture was allowed to warm to room temperature and stirred for additional 1 h. The reaction was quenched with water (10 mL). The aqueous layer was extracted with Et₂O (2×30 mL), and the combined organic layer was washed with brine, dried with MgSO₄, filtered and concentrated under reduced pressure. The residues was purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 110 (0.8 g, 45%) as a colorless sticky oil. The analytical data were identical to the literature.¹⁴⁵a

Rᵣ = 0.65 (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 3.74 (s, 6H), 2.97 (s, 4H), 0.12 (s, 18H).

¹³C NMR (75 MHz, CDCl₃) δ 169.2, 101.1, 88.5, 57.4, 53.0, 24.2, 0.1.

To a solution of diol 120 (0.6 g, 4.0 mmol) in dry acetone (20 mL) was added phosphorus pentoxide (1.14 g, 8.0 mmol, 2 equiv) by one portion and the reaction mixture was stirred at room temperature for 20 mins. Then the resulting mixture was poured into a mixture of NaOH (2 g) and ice (30 g), and extracted with diethyl ether (3×30 mL). The combined organic fractions were washed with saturated aqueous NaHCO₃ and brine, dried with MgSO₄, filtered and concentrated under reduced pressure. The residues was purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded 121 (0.61 g, 80%) as a slight yellow oil. The analytical data were identical to the literature.¹⁴⁵i

Rᵣ = 0.65 (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 3.77 (s, 4H), 2.43 (d, J = 2.7 Hz, 4H), 2.05 (t, J = 2.7 Hz, 2H), 1.42 (s, 6H).
**Experimental part**

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 98.4, 79.9, 71.5, 66.0, 35.2, 23.9, 22.8.

---

### 4-Methyl-N,N-di(prop-2-yn-1-yl)benzenesulfonamide (122)

<table>
<thead>
<tr>
<th>Chemical Formula: C$<em>{13}$H$</em>{12}$NO$_2$S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exact Mass: 247.0667</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure G. Starting from $p$-toluenesulfonamide (6.84 g, 40 mmol), propargyl bromide (11.4 mL, 120 mmol, 3 equiv) and K$_2$CO$_3$ (27.2 g, 200 mmol, 5 equiv). The reaction mixture was stirred at 80 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate; 85/15) afforded 122 (9.2 g, 91 %) as a white solid. The analytical data were identical to the literature.$^{145j}$

$R_r = 0.3$ (Cyclohexane/Ethyl acetate; 85/15, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.71 (d, $J = 7.8$ Hz, 2H), 7.30 (d, $J = 7.8$ Hz, 2H), 4.16 (d, $J = 2.7$ Hz, 4H), 2.42 (s, 3H), 2.14 (t, $J = 2.7$ Hz, 2H).

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 144.2, 136.9, 129.2, 128.2, 76.2, 74.4, 36.2, 21.6.

---

### tert-Butyl di(prop-2-yn-1-yl)carbamate (123)

<table>
<thead>
<tr>
<th>Chemical Formula: C$<em>{11}$H$</em>{13}$NO$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exact Mass: 193.1103</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure F. Starting from Boc-protected propargylamine (3.45 g, 22.3 mmol), propargyl bromide (3.5 mL, 33.4 mmol, 1.5 equiv) and NaH (1.34 g, 33.4 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate; 90/10) afforded 123 (3.13 g, 73%) as pale yellow oil. The analytical data were identical to the literature.$^{145k}$

$R_r = 0.57$ (Cyclohexane/Ethyl acetate; 90/10, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.16 (br, 4H), 2.22 (t, $J = 2.5$ Hz, 2H), 1.47 (s, 9H).

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 154.4, 81.3, 79.0, 72.0, 35.3, 28.4.
Experimental part

Dimethyl 2,2-bis(3-bromoprop-2-yn-1-yl)malonate (124)

![Chemical Structure](image)

This compound was obtained following the general procedure H. Starting from dimethyl 2,2-di(prop-2-yn-1-yl)malonate 109 (1.04 g, 5 mmol), NBS (1.78 g, 10 mmol, 2 equiv) and silver nitrate (85 mg, 0.5 mmol). The reaction mixture was stirred at room temperature for 3 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded 124 (5.7 g, 98 %) as a slight yellow solid. m.p. 60-62 °C. The analytical data were identical to the literature.\(^{1451}\)

R\(_f\) = 0.38 (Cyclohexane/Ethyl acetate; 90/10, KMnO\(_4\), UV).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.76 (s, 6H), 2.99 (s, 4H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 169.0, 74.4, 56.5, 53.4, 42.3, 24.2.

MS (Cl, NH\(_3\)): m/z = 384 [M + NH\(_4\)]\(^+\).

3.2. Synthesis of unsymmetrical diynes

General procedure I:

\[
\text{ROH} + \text{Br} = \text{KOH 1.3-2 equiv} \quad \text{H}_2\text{O/DM}SO, \text{rt, 4 h} \quad \text{RO} 
\]

To a solution of alcohol (1.0 equiv) in DMSO (1 M) was slowly added an aqueous solution of potassium hydroxide (1 M, 1.3 equiv) at 0 °C. After 10 mins, a solution of propargyl bromide (1.0 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 4 h. The reaction was quenched with water, and the aqueous layer was extracted with Et\(_2\)O (\(\times\) 3). The combined organic layers were washed with water and brine, dried over MgSO\(_4\), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desired compound.

Dimethyl 2-(but-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate (125)
This compound was obtained following the general procedure F. Starting from dimethyl 2-(but-2-yn-1-yl)malonate \textsubscript{144} (3.3 g, 18 mmol), propargyl bromide (2.4 mL, 21.6 mmol, 1.2 equiv) and NaH (1.08 g, 27 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 4 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded \textsubscript{125} (3.2 g, 80%) as a pale yellow solid. The analytical data were identical to the literature.\textsuperscript{1451}

\[ R_t = 0.35 \] (Cyclohexane/Ethyl acetate; 90/10, KMnO\(_4\), UV).

\[ ^1H\text{ NMR} \] (300 MHz, CDCl\(_3\)) \( \delta \) 3.75 (s, 6H), 2.97 (d, \( J = 2.6 \) Hz, 2H), 2.93 (q, \( J = 2.5 \) Hz, 2H), 2.02 (t, \( J = 2.7 \) Hz, 1H), 1.75 (t, \( J = 2.6 \) Hz, 3H).

\[ ^{13}C\text{ NMR} \] (75 MHz, CDCl\(_3\)) \( \delta \) 169.5, 79.4, 78.8, 73.0, 71.6, 57.0, 53.1, 23.2, 22.9, 3.6.

<table>
<thead>
<tr>
<th>1-(Prop-2-yn-1-yloxy)but-2-yne (127)</th>
</tr>
</thead>
</table>

This compound was obtained following the general procedure I. Starting from 2-butyne-1-ol (2.8 g, 40 mmol), propargyl bromide (4.3 mL, 40 mmol, 1 equiv) and KOH (2.92 g, 52 mmol, 1.3 equiv). The reaction mixture was stirred at room temperature for 4 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded \textsubscript{127} (3.4 g, 79%) as a pale yellow oil. The analytical data were identical to the literature.\textsuperscript{197}

\[ R_t = 0.5 \] (Cyclohexane/Ethyl acetate; 95/5, KMnO\(_4\), UV).

\[ ^1H\text{ NMR} \] (300 MHz, CDCl\(_3\)) \( \delta \) 4.23 (d, \( J = 2.4 \) Hz, 2H), 4.20 (q, \( J = 2.3 \) Hz, 2H), 2.46 – 2.38 (m, 1H), 1.85 (t, \( J = 2.4 \) Hz, 3H).

\textsuperscript{197} For diyne \textsubscript{127}, see: Trost, B. M.; Rudd, M. T. \textit{J. Am. Chem. Soc.} \textbf{2005}, \textit{127}, 4763.
**Experimental part**

\[ ^{13}C\text{ NMR}\] \((75\text{ MHz, CDCl}_3)\ \delta 83.3, 79.3, 74.8, 74.3, 57.3, 56.4, 3.7.\]

**Dimethyl 2-(3-bromoprop-2-yn-1-yl)-2-(but-2-yn-1-yl)malonate (129)**

This compound was obtained following the general procedure H. Starting from dimethyl 2-(but-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate 125 \((0.89\text{ g, 4 mmol}), \text{ NBS (1 g, 5.5 mmol, 1.4 equiv})\) and silver nitrate \((0.1\text{ g, 0.6 mmol})\). The reaction mixture was stirred at room temperature for 3 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded 129 \((1.17\text{ g, 98 %})\) as a white solid. m.p. 65-67°C. The analytical data were identical to the literature.\(^{1451}\)

\[ R_f = 0.44\] (Cyclohexane/Ethyl acetate; 90/10, KMnO\(_4\), UV).

\[ ^1H\text{ NMR}\] \((300\text{ MHz, CDCl}_3)\ \delta 3.74\text{ (s, 6H), 2.98\ (s, 2H), 2.89\ (q, \ J = 2.5\ Hz, 2H), 1.74\ (t, \ J = 2.6\ Hz, 3H).}\]

\[ ^{13}C\text{ NMR}\] \((75\text{ MHz, CDCl}_3)\ \delta 169.4, 79.5, 74.8, 72.9, 56.9, 53.2, 41.7, 24.1, 23.3, 3.6.\]

**1-((3-Bromoprop-2-yn-1-yl)oxy)but-2-yne (130)**

This compound was obtained following the general procedure H. Starting from 1-(prop-2-yn-1-yloxy)but-2-yne 127 \((1.08\text{ g, 10 mmol}), \text{ NBS (1.96 g, 11 mmol, 1.1 equiv})\) and silver nitrate \((0.17\text{ g, 1 mmol})\). The reaction mixture was stirred at room temperature for 3 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 130 \((1.8\text{ g, 97 %})\) as a pale yellow oil. The analytical data were identical to the literature.\(^{1451}\)

\[ R_f = 0.4\] (Cyclohexane/Ethyl acetate; 95/5, KMnO\(_4\), UV).

\[ ^1H\text{ NMR}\] \((300\text{ MHz, CDCl}_3)\ \delta 4.26\text{ (s, 2H), 4.20\ (q, \ J = 2.3\ Hz, 2H), 1.86\ (t, \ J = 2.3\ Hz, 3H).}\]
13C NMR (75 MHz, CDCl3) δ 83.5, 75.9, 74.3, 57.5, 57.4, 46.4, 3.7.

<table>
<thead>
<tr>
<th>1-Bromo-3-(prop-2-yn-1-yloxy)prop-1-yne (131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Formula: C8H9BrO</td>
</tr>
<tr>
<td>Exact Mass: 171.9524</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure I. Starting from 3-bromoprop-2-yn-1-ol 145 (1.6 g, 12 mmol), propargyl bromide (1.55 mL, 14.4 mmol, 1.2 equiv) and KOH (0.87 g, 15.6 mmol, 1.3 equiv). The reaction mixture was stirred at room temperature for 4 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded 131 (1 g, 50%) as a pale yellow oil. The analytical data were identical to the literature.145

Rf = 0.66 (Cyclohexane/Ethyl acetate; 80/20, KMnO4, UV).

1H NMR (300 MHz, CDCl3) δ 4.29 (s, 2H), 4.25 (d, J = 2.4 Hz, 2H), 2.46 (t, J = 2.4 Hz, 1H).

13C NMR (75 MHz, CDCl3) δ 78.8, 75.5, 75.3, 57.6, 56.8, 46.9.

<table>
<thead>
<tr>
<th>N-(3-bromoprop-2-yn-1-yl)-N-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Formula: C13H15BrNO2S</td>
</tr>
<tr>
<td>Exact Mass: 338.9929</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure H. Starting from N-(but-2-yn-1-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide 128 (0.51 g, 2 mmol), NBS (0.43 g, 2.4 mmol, 1.2 equiv) and silver nitrate (0.034 g, 0.2 mmol). The reaction mixture was stirred at room temperature for 3 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 90/10 to 80/20) afforded 132 (0.65 g, 96 %) as a white solid. m.p. 86 – 88°C.

Rf = 0.5 (Cyclohexane/Ethyl acetate; 80/20, KMnO4, UV).

1H NMR (300 MHz, CDCl3) δ 7.73 – 7.68 (m, 2H), 7.39 – 7.30 (m, 2H), 4.16 (s, 2H), 4.10 – 4.00 (m, 2H), 2.41 (s, 3H), 1.72 – 1.59 (m, 3H).
Experimental part

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 143.9, 135.3, 129.6, 128.1, 82.3, 73.0, 71.5, 45.2, 37.4, 37.2, 21.7, 3.5.

MS (CI, NH$_3$): m/z = 339 [M + H]$^+$.  

<table>
<thead>
<tr>
<th>Dimethyl 2-(but-2-yn-1-yl)-2-(3-iodoprop-2-yn-1-yl)malonate (133)</th>
</tr>
</thead>
</table>

This compound was obtained following the general procedure H. Starting from dimethyl 2-(but-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate 125 (0.67 g, 3 mmol), NIS (0.87 g, 3.6 mmol, 1.2 equiv) and silver nitrate (0.05 g, 0.3 mmol). The reaction mixture was stirred at room temperature for 3 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 90/10 to 80/20) afforded 133 (1.02 g, 99 %) as a yellow solid. m.p. 68-70 °C. The analytical data were identical to the literature.\textsuperscript{145l}

$R_f = 0.34$ (Cyclohexane/Ethyl acetate; 90/10, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.75 (s, 6H), 3.13 (s, 2H), 2.90 (q, $J = 2.5$ Hz, 2H), 1.75 (t, $J = 2.5$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.4, 88.9, 79.5, 77.4, 72.9, 57.2, 53.2, 25.1, 23.3, 3.6.

<table>
<thead>
<tr>
<th>3-(3-(But-2-yn-1-yloxy)prop-1-yn-1-yl)oxazolidin-2-one (134)</th>
</tr>
</thead>
</table>

To a 250 mL flask were added CuCl$_2$ (0.26 g, 2 mmol, 0.2 equiv), 2-Oxazolidone (4.35 g, 50.0 mmol, 5 equiv) and sodium carbonate (2.12 g, 20 mmol, 2.0 equiv). The reaction flask was purged with oxygen for 15 min. A solution of pyridine (1.58 g, 20.0 mmol, 2.0 equiv) in dry toluene (40 mL) was added. A balloon filled with oxygen was connected to the reaction flask via a needle. The flask was placed in an oil-bath and heated at 70 °C. After 15 min, a solution of 1-(prop-2-yn-1-yloxy)but-2-yn 127 (1.08 g, 10.0 mmol, 1 equiv) in dry toluene (40...
mL) was added over 4 h using syringe pump. After this addition, the mixture was allowed to stir at 70 °C for additional 16 h and was then cooled to room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/Ethyl acetate gradient from 60/40 to 50/50) to afford 134 (1.15 g, 60%) as a slight yellow solid. m.p. 63 – 65 °C.

Rf = 0.11 (Cyclohexane/Ethyl acetate; 70/30, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 4.49 – 4.38 (m, 2H), 4.36 (s, 2H), 4.16 (q, J = 2.3 Hz, 2H), 3.95 – 3.85 (m, 2H), 1.84 (t, J = 2.3 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 156.2, 83.2, 76.5, 74.4, 67.6, 63.2, 57.2, 56.8, 46.8, 3.7.

MS (Cl, NH₃): m/z = 194 [M + H]⁺.

<table>
<thead>
<tr>
<th>Dimethyl 2-(pent-4-en-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate (135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Formula: C₈H₁₄O₄</td>
</tr>
<tr>
<td>Exact Mass: 234.0892</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure F. Starting from dimethyl 2-(pent-4-en-2-yn-1-yl)malonate 147 (0.35 g, 1.8 mmol), propargyl bromide (0.32 g, 2.1 mmol, 1.2 equiv) and NaH (0.84 g, 2.1 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 2 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 135 (0.36 g, 85%) as a colorless oil.

Rf = 0.27 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 5.78 – 5.65 (m, 1H), 5.60 – 5.50 (m, 1H), 5.45 – 5.37 (m, 1H), 3.75 (s, 6H), 3.12 – 3.07 (m, 2H), 2.99 – 2.94 (m, 2H), 2.03 (t, J = 2.7 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 169.3, 127.1, 117.0, 84.3, 82.6, 78.6, 71.8, 56.9, 53.2, 23.7, 22.9.

MS (Cl, NH₃): m/z = 235 [M + H]⁺.

| Dimethyl 2-(but-2-yn-1-yl)-2-(3-(pyridin-2-yl)prop-2-yn-1-yl)malonate (137) |

---
This compound was obtained following the general procedure A. Starting from dimethyl 2-(but-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate 125 (1.1 g, 5 mmol), 2-bromo pyridine (0.57 mL, 6 mmol, 1.2 equiv), PdCl_2(PPh_3)_2 (70 mg, 2 mol %) and CuI (9.5 mg, 1 mol %). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 70/30) afforded 137 (0.9 g, 60%) as a pale yellow oil. The analytical data were identical to the literature.\(^{198}\)

**R_f = 0.2** (Cyclohexane/Ethyl acetate; 90/10, KMnO_4, UV).

**^1H NMR** (300 MHz, CDCl_3) \(\delta\) 8.53 (ddd, \(J = 4.9, 1.8, 1.0\) Hz, 1H), 7.60 (td, \(J = 7.7, 1.8\) Hz, 1H), 7.34 (dt, \(J = 7.8, 1.1\) Hz, 1H), 7.19 (ddd, \(J = 7.6, 4.9, 1.2\) Hz, 1H), 3.77 (s, 6H), 3.23 (s, 2H), 3.04 – 2.94 (m, 2H), 1.75 (t, \(J = 2.4\) Hz, 3H).

**^13C NMR** (75 MHz, CDCl_3) \(\delta\) 169.6, 150.0, 136.1, 127.4, 122.8, 84.8, 83.3, 79.6, 73.0, 57.1, 53.2, 23.7, 23.5, 3.6.

This compound was obtained following the general procedure F. Starting from 3-butyn-1-ol (0.84 g, 12 mmol, 1.2 equiv), 1-brom-2-butynne (1.33 g, 10 mmol, 1.0 equiv) and NaH (0.48 g, 12 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 1 h. Purification on silica gel (pure dichloromethane) afforded 138 (0.92 g, 75%) as a pale yellow oil.

**R_f = 0.52** (Cyclohexane/Ethyl acetate; 95/5, KMnO_4, UV).

**^1H NMR** (300 MHz, CDCl_3) \(\delta\) 4.17 – 4.09 (m, 2H), 3.63 (t, \(J = 7.0\) Hz, 2H), 2.49 (td, \(J = 7.0, 2.7\) Hz, 2H), 1.99 (t, \(J = 2.7\) Hz, 1H), 1.85 (t, \(J = 2.4\) Hz, 3H).

Experimental part

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 82.8, 81.2, 74.9, 69.5, 67.8, 58.9, 19.8, 3.7.

MS (Cl, NH$_3$): m/z = 140 [M + NH$_4$]$^+$. 

<table>
<thead>
<tr>
<th>5-(Prop-2-yn-1-yloxy)pent-2-yne (140)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C$_9$H$_8$O</td>
</tr>
<tr>
<td>Exact Mass: 122.0732</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure I. Starting from pent-3-yn-1-ol (1.68 g, 20 mmol), propargyl bromide (2.2 mL, 20 mmol, 1 equiv) and KOH (2.26 g, 40 mmol, 2 equiv). The reaction mixture was stirred at room temperature for 4 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 140 (2.05 g, 84%) as a pale yellow oil. The analytical data were identical to the literature.$^{199}$

Rf = 0.67 (Cyclohexane/Ethyl acetate; 90/10, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.18 (d, $J$ = 2.4 Hz, 2H), 3.61 (t, $J$ = 7.0 Hz, 2H), 2.50 – 2.38 (m, 3H), 1.78 (t, $J$ = 2.6 Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 79.7, 77.0, 75.7, 74.6, 68.7, 58.3, 20.1, 3.6.

<table>
<thead>
<tr>
<th>5-((3-Bromoprop-2-yn-1-yl)oxy)pent-2-yne (141)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C$_9$H$_7$BrO</td>
</tr>
<tr>
<td>Exact Mass: 199.9837</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure H. Starting from 5-(prop-2-yn-1-yloxy)pent-2-yne 140 (0.61 g, 5 mmol), NBS (1.06 g, 6 mmol, 1.2 equiv) and silver nitrate (0.085 g, 0.5 mmol). The reaction mixture was stirred at room temperature for 3 h. Purification

---

Experimental part

on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded 141 (0.75 g, 75 %) as a pale yellow oil.

R<sub>f</sub> = 0.44 (Cyclohexane/Ethyl acetate; 95/5, KMnO<sub>4</sub>, UV).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.19 (s, 2H), 3.57 (t, J = 6.9 Hz, 2H), 2.41 (ddt, J = 6.9, 4.4, 2.5 Hz, 2H), 1.76 (t, J = 2.6 Hz, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 77.0, 76.2, 75.6, 68.8, 59.2, 46.2, 20.0, 3.6.

<table>
<thead>
<tr>
<th>5-(But-2-yn-1-yloxy)pent-1-yne (142)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C&lt;sub&gt;9&lt;/sub&gt;H&lt;sub&gt;17&lt;/sub&gt;O</td>
</tr>
<tr>
<td>Exact Mass: 136.0888</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure F. Starting from 4-pentyn-1-ol (0.84 g, 10 mmol), 1-bromo-2-butyne (1.6 g, 12 mmol, 1.2 equiv) and NaH (0.48 g, 12 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 5 h. Purification on silica gel (Pentane/diethyl ether; 95/5) afforded 142 (1.07 g, 79%) as a colorless oil.

R<sub>f</sub> = 0.51 (Cyclohexane/Ethyl acetate; 85/15, KMnO<sub>4</sub>, UV).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.10 – 4.02 (m, 2H), 3.55 (t, J = 6.2 Hz, 2H), 2.27 (td, J = 7.1, 2.7 Hz, 2H), 1.95 – 1.89 (m, 1H), 1.83 (t, J = 2.4 Hz, 3H), 1.82 – 1.74 (m, 2H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 84.0, 82.4, 75.3, 68.5, 68.4, 58.8, 28.6, 15.4, 3.7.

<table>
<thead>
<tr>
<th>(8R,9S,13S,14S,17R)-17-(But-2-yn-1-yloxy)-17-ethynyl-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene (143)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image2.png" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C&lt;sub&gt;29&lt;/sub&gt;H&lt;sub&gt;20&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Exact Mass: 362.2246</td>
</tr>
</tbody>
</table>
Experimental part

This compound was obtained following the general procedure F. Starting from Mestranol (0.31 g, 1 mmol), 1-bromo-2-butyne (0.16 g, 1.2 mmol, 1.2 equiv) and NaH (48 mg, 1.2 mmol, 1.2 equiv). The reaction mixture was stirred at 60 °C for 20 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded 143 (0.13 g, 36%) as a white solid. m.p. 138-140 °C.

\[ R_t = 0.4 \] (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

\[ ^1H\text{NMR} \ (300 \text{ MHz, CDCl}_3) \delta \ 7.20 \ (d, \ J = 8.6 \text{ Hz, 1H}), \ 6.71 \ (dd, \ J = 8.6, 2.8 \text{ Hz, 1H}), \ 6.63 \ (d, \ J = 2.7 \text{ Hz, 1H}), \ 4.33 - 4.20 \ (m, 2H), \ 3.78 \ (s, 3H), \ 2.90 - 2.76 \ (m, 2H), \ 2.65 \ (s, 1H), \ 2.39 - 1.92 \ (m, 5H), \ 1.91 - 1.66 \ (m, 7H), \ 1.53 - 1.27 \ (m, 4H), \ 0.92 \ (s, 3H). \]

\[ ^{13}C\text{NMR} \ (75 \text{ MHz, CDCl}_3) \delta \ 157.6, \ 158.1, \ 138.1, \ 132.7, \ 126.5, \ 113.9, \ 111.6, \ 85.9, \ 84.35, \ 81.76, \ 76.6, \ 76.1, \ 55.4, \ 54.5, \ 49.7, \ 47.8, \ 43.6, \ 39.4, \ 37.4, \ 34.3, \ 30.0, \ 27.4, \ 26.7, \ 22.9, \ 13.0, \ 3.9. \]

\[ \text{MS (Cl, NH}_3\text{): m/z = 380 [M + NH}_4\text{]^+}. \]

<table>
<thead>
<tr>
<th>Dimethyl 2-(but-2-yn-1-yl)malonate (144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Chemical Diagram]</td>
</tr>
<tr>
<td>Chemical Formula: C₇H₁₂O₄</td>
</tr>
<tr>
<td>Exact Mass: 184.0736</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure F. Starting from dimethyl malonate (11.6 g, 87.5 mmol, 2.3 equiv), 1-bromo-2-butyne (3.3 mL, 37.5 mmol, 1 equiv) and NaH (1.65 g, 41.3 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 5 h. The residue was purified by distillation under vacuum (80 °C, 1.5 torr) to afford 144 (4.3 g, 62%) as a colorless oil. The analytical data were identical to the literature.²⁰⁰

\[ R_t = 0.29 \] (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

\[ ^1H\text{NMR} \ (300 \text{ MHz, CDCl}_3) \delta \ 3.76 \ (s, 6H), \ 3.55 \ (t, \ J = 7.7 \text{ Hz, 1H}), \ 2.76 - 2.70 \ (m, 2H), \ 1.74 \ (t, \ J = 2.5 \text{ Hz, 3H}). \]

\[ ^{13}C\text{NMR} \ (75 \text{ MHz, CDCl}_3) \delta \ 168.7, \ 78.1, \ 74.7, \ 52.8, \ 51.6, \ 19.0, \ 3.6. \]

Experimental part

### 3-Bromoprop-2-yn-1-ol (145)

![Chemical Structure](image)

This compound was obtained following the general procedure **H**. Starting from propargyl alcohol (2.8 g, 50 mmol), NBS (10 g, 55 mmol, 1.1 equiv) and silver nitrate (0.43 g, 5 mmol). The reaction mixture was stirred at room temperature for 3 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 90/10 to 80/20) afforded **145** (4.35 g, 65 %) as a colorless oil. The analytical data were identical to the literature.201

**Rf = 0.38** (Cyclohexane/Ethyl acetate; 80/20, KMnO4, UV).

1H NMR (300 MHz, CDCl3) δ 4.28 (s, 2H), 3.40 (br, 1H).

13C NMR (75 MHz, CDCl3) δ 78.4, 52.1, 46.1.

### Dimethyl 2-(prop-2-yn-1-yl)malonate (146)

![Chemical Structure](image)

In a round bottom flask, dimethyl malonate (4.76 g, 36 mmol, 1.2 equiv), propargyl bromide (3.34 mL, 30 mmol, 1 equiv), potassium carbonate (9.95 g, 72 mmol, 2.4 equiv) and acetone (60 mL) were placed. The resulting mixture was stirred at 50 °C for 24 h. After the reaction was complete, the reaction mixture was filtered, and the organic layers were concentrated under reduced pressure. The residue was purified by distillation under vacuum (70 °C, 1.5 torr) to afford **146** (3.1 g, 60%) as a colorless oil. The analytical data were identical to the literature.202

**Rf = 0.25** (Cyclohexane/Ethyl acetate; 90/10, KMnO4, UV).

---


Experimental part

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.77 (s, 6H), 3.61 (t, $J = 7.7$ Hz, 1H), 2.79 (dd, $J = 7.7$, 2.7 Hz, 2H), 2.02 (t, $J = 2.7$ Hz, 1H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 168.6, 80.1, 70.8, 53.2, 51.2, 18.8.

<table>
<thead>
<tr>
<th>Dimethyl 2-(pent-4-en-2-yn-1-yl)malonate (147)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Chemical Formula: $C_{14}H_{12}O_4$</td>
</tr>
<tr>
<td>Exact Mass: 196.0736</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure A. Starting from dimethyl 2-(prop-2-yn-1-yl)malonate (1.02 g, 6 mmol), vinyl bromide (7.2 mL, 7.2 mmol, 1.2 equiv), PdCl$_2$(PPh$_3$)$_2$ (84 mg, 2 mol %) and CuI (11 mg, 1 mol %). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 147 (0.5 g, 43%) as a colorless oil.

$R_r = 0.2$ (Cyclohexane/Ethyl acetate; 90/10, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.79 – 5.65 (m, 1H), 5.62 – 5.50 (m, 1H), 5.48 – 5.38 (m, 1H), 3.77 (s, 6H), 3.61 (t, $J = 7.7$ Hz, 1H), 2.95 – 2.84 (m, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 168.5, 126.8, 117.1, 86.0, 81.3, 52.9, 51.2, 19.5.

MS (CI, NH$_3$): m/z = 214 [M + NH$_4$]$^+$.  

3.3. Synthesis of benzoyl or benzyl bridged $\alpha,\omega$-diynes

<table>
<thead>
<tr>
<th>1-(2-(Hex-1-yn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-ol (148)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Chemical Formula: $C_{14}H_{22}OSi$</td>
</tr>
<tr>
<td>Exact Mass: 284.1596</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure B. Starting from 2-(hex-1-yn-1-yl)benzaldehyde 2 (1.0 g, 5.4 mmol), trimethylsilylacetylene (1.14 mL, 8 mmol, 1.5 equiv) and $n$-BuLi (3.5 mL, 1.85 M in hexane, 6.5 mmol, 1.2 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded 148 (1.2 g, 78%) as a pale yellow oil.
Experimental part

$R_t = 0.33$ (Cyclohexane/Ethyl acetate; 95/5, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.70 – 7.63 (m, 1H), 7.44 – 7.38 (m, 1H), 7.36 – 7.21 (m, 2H), 5.84 (d, $J = 5.7$ Hz, 1H), 2.69 (dd, $J = 5.7$, 0.4 Hz, 1H), 2.46 (t, $J = 7.0$ Hz, 2H), 1.68 – 1.56 (m, 2H), 1.54 – 1.43 (m, 2H), 0.96 (t, $J = 7.2$ Hz, 3H), 0.20 (s, 9H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 141.9, 132.6, 128.3, 128.2, 126.8, 122.6, 104.5, 96.5, 91.5, 78.0, 63.9, 30.9, 22.2, 19.4, 13.8, 0.0.

MS (Cl, NH$_3$): $m/z = 267$ [M + H – H$_2$O]$^+$.  

| 1-(2-(Hex-1-yn-1-yl)phenyl)prop-2-yn-1-ol (149). |

This compound was obtained following the general procedure D. Starting from 1-(2-(Hex-1-yn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-ol 148 (1.2 g, 4.2 mmol) and TBAF (4.2 mL, 1.0 M in THF). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 85/15) afforded 149 (0.72 g, 81%) as a pale yellow oil.

$R_t = 0.4$ (Cyclohexane/Ethyl acetate; 90/10, KMnO$_4$, UV).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.67 (dd, $J = 7.5, 1.6$ Hz, 1H), 7.43 (dd, $J = 7.1, 1.9$ Hz, 1H), 7.45 – 7.30 (m, 2H), 5.85 (d, $J = 2.3$ Hz, 1H), 2.64 (s, 1H), 2.64 (s, 1H), 2.48 (t, $J = 7.0$ Hz, 2H), 1.70 – 1.57 (m, 2H), 1.57 – 1.41 (m, 2H), 0.96 (t, $J = 7.2$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 141.6, 132.7, 128.4, 128.3, 126.6, 122.4, 96.7, 83.1, 77.9, 74.6, 63.3, 30.9, 22.2, 19.4, 13.7.

MS (Cl, NH$_3$): $m/z = 212$ [M + NH$_4$ – H$_2$O]$^+$.  

| 2-(Cyclopropylethynyl)benzaldehyde (150) |

272
Experimental part

This compound was obtained following the general procedure A. Starting from 2-bromobenzoaldehyde (4.0 g, 21.7 mmol), cyclopropylacetylene (1.7 g, 26 mmol, 1.2 equiv), PdCl$_2$(PPh$_3$)$_2$ (0.75 mg, 1.09 mmol, 5 mol %) and CuI (0.1 g, 0.55 mmol, 2.5 mol %). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded **150** (2.1 g, 57%) as an orange oil.

**$^1$H NMR** (300 MHz, CDCl$_3$) $\delta$ 10.48 (d, $J = 0.6$ Hz, 1H), 7.89 – 7.82 (m, 1H), 7.53 – 7.43 (m, 2H), 7.39 – 7.30 (m, 1H), 1.57 – 1.45 (m, 1H), 0.98 – 0.85 (m, 4H).

**$^{13}$C NMR** (75 MHz, CDCl$_3$) $\delta$ 192.2, 136.2, 133.8, 133.4, 128.0, 127.9, 127.1, 101.4, 71.6, 9.0, 0.5.

---

**1-(2-(Cyclopropylethynyl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-ol (151).**

This compound was obtained following the general procedure B. Starting from 2-(cyclopropylethynyl)benzaldehyde **150** (2.0 g, 11.8 mmol), trimethylsilylacetylene (3.25 mL, 23.5 mmol, 2 equiv) and $n$-BuLi (8.8 mL, 2.0 M in hexane, 17.6 mmol, 1.5 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **151** (2.5 g, 80%) as a pale yellow oil.

**$^1$H NMR** (300 MHz, CDCl$_3$) $\delta$ 7.70 – 7.55 (m, 1H), 7.43 – 7.35 (m, 1H), 7.35 – 7.18 (m, 2H), 5.79 (d, $J = 5.5$ Hz, 1H), 2.70 (d, $J = 5.7$ Hz, 1H), 1.54 – 1.40 (m, 1H), 0.94 – 0.76 (m, 4H), 0.20 (s, 9H).

**$^{13}$C NMR** (75 MHz, CDCl$_3$) $\delta$ 142.1, 132.6, 128.3, 128.2, 126.8, 122.4, 104.5, 99.6, 91.4, 73.1, 63.9, 9.0, 8.9, 0.5, -0.01.
Experimental part

**MS** (Cl, NH₃): m/z = 267 [M + H – H₂O]⁺.

<table>
<thead>
<tr>
<th>1-(2-(Cyclopropylethynyl)phenyl)prop-2-yn-1-ol (152)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
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<tr>
<td>Chemical Formula: C₁₄H₁₂O</td>
</tr>
<tr>
<td>Exact Mass: 196.0888</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure D. Starting from 1-(2-(cyclopropylethynyl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-ol 151 (2.5 g, 9.3 mmol) and TBAF (9.3 mL, 1.0 M in THF). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 152 (1.5 g, 82%) as a pale yellow solid. m.p. 45 – 48 °C.

**¹H NMR** (300 MHz, CDCl₃) δ 7.71 – 7.56 (m, 1H), 7.44 – 7.36 (m, 1H), 7.36 – 7.20 (m, 2H), 5.80 (s, 1H), 2.72 (s, 1H, OH), 2.63 (d, J = 2.3 Hz, 1H), 1.56 – 1.42 (m, 1H), 0.98 – 0.80 (m, 4H).

**¹³C NMR** (75 MHz, CDCl₃) δ 141.8, 132.7, 128.4, 128.2, 126.6, 122.2, 99.8, 83.1, 74.6, 73.0, 63.3, 9.0, 0.5.

**MS** (Cl, NH₃): m/z = 196 [M + NH₄ - H₂O]⁺.

<table>
<thead>
<tr>
<th>1-(2-(Cyclopropylethynyl)phenyl)prop-2-yn-1-one (153)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
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<tr>
<td>Chemical Formula: C₁₄H₁₀O</td>
</tr>
<tr>
<td>Exact Mass: 194.0732</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure C. Starting from 1-(2-(cyclopropylethynyl)phenyl)prop-2-yn-1-ol 152 (0.92 g, 4.7 mmol) and Dess-Martin periodinane (2.4 g, 5.6 mmol, 1.2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 153 (0.75 g, 82%) as yellow solid. m.p. 181 – 183 °C.
**Experimental part**

**1H NMR** (300 MHz, CDCl$_3$) $\delta$ 8.20 – 8.05 (m, 1H), 7.52 – 7.42 (m, 2H), 7.41 – 7.30 (m, 1H), 3.41 (d, $J$ = 0.3 Hz, 1H), 1.58 – 1.42 (m, $J$ = 6.6 Hz, 1H), 0.91 (d, $J$ = 6.6 Hz, 4H).

**13C NMR** (75 MHz, CDCl$_3$) $\delta$ 175.7, 136.3, 133.6, 131.9, 131.2, 126.2, 123.2, 99.9, 80.3, 79.6, 73.6, 8.0, -0.1.

**MS** (Cl, NH$_3$): m/z = 195 [M + H]$^+$.  

**3.4. Synthesis of cyanamides**

**General procedure J:**

\[
\begin{align*}
\text{R}_1^\text{N}^\text{R}_2^\text{H} & \quad \text{BrCN} \quad \text{Et}_2\text{O/THF (1:1, 5 M)} \quad 0^\circ\text{C to rt} \quad \text{R}_1^\text{N}^\text{R}_2^\text{CN} \\
\text{(2 equiv)} & \quad \text{(2 equiv)} & \quad \text{Et}_2\text{O/THF (1:1)} & \quad 0^\circ\text{C to rt} & \quad \text{Et}_2\text{O/THF (1:1)} & \quad 0^\circ\text{C to rt} & \quad \text{R}_1^\text{N}^\text{R}_2^\text{CN}
\end{align*}
\]

$N$-substituted amine (2 equiv) was added to a solution of cyanogen bromide (1 equiv) in Et$_2$O/THF (1:1, 5 M) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. Hexane (5 mL) was added, and the mixture was stirred for an additional 10 min. It was then filtered through a pad of Celite, and the filtrate was washed with water ($\times$ 3) and brine ($\times$ 3). The solution was dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desired product.

**General procedure K:**

\[
\begin{align*}
\text{R}_1^\text{N}^\text{R}_2^\text{H} & \quad \text{BrCN} \quad \text{NaHCO}_3 \text{ 2 equiv} \quad \text{H}_2\text{O/DCM (1:1)} \quad 0^\circ\text{C to rt, 2 h} \quad \text{R}_1^\text{N}^\text{R}_2^\text{CN} \\
\text{(1.05 equiv)} & \quad \text{(1.05 equiv)} & \quad \text{H}_2\text{O/DCM (1:1)} & \quad 0^\circ\text{C to rt, 2 h} & \quad \text{R}_1^\text{N}^\text{R}_2^\text{CN}
\end{align*}
\]

A solution of sodium hydrogen carbonate (2 equiv) in H$_2$O (2 M) was slowly added to a solution of $N$-substituted amine (1 equiv) in DCM (1 M) at 0 °C. Then, a solution of cyanogen bromide (1.05 equiv) in DCM (1 M) was added to the reaction mixture at 0 °C. The mixture was stirred at the same temperature for 30 min, and then allowed to warm to room temperature for an additional 2 h. The organic layers were separated and washed with saturated sodium hydrogen carbonate solution ($\times$ 3) and brine ($\times$ 3), dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desired product.
Experimental part

**Piperidine-1-carbonitrile (157)**

![Chemical structure](image)

This compound was obtained following the general procedure J. Starting from piperidine (1.83 mL, 20.0 mmol, 2 equiv) and cyanogen bromide (1.06 g, 10 mmol, 1 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate from 90/10 to 85/15) afforded 157 (0.9 g, 82%) as a colorless oil. The analytical data were identical to the literature.\(^{203}\)

\[ R_t = 0.35 \] (Cyclohexane/Ethyl acetate; 90/10, KMnO\(_4\), UV).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 3.23 – 3.01 \) (m, 4H), 1.72 – 1.49 (m, 6H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 118.7, 50.3, 24.7, 23.1\).

**N-Benzyl-N-methylcyanamide (158)**

![Chemical structure](image)

This compound was obtained following the general procedure J. Starting from \(N\)-methybenzylamine (1.45 g, 12 mmol, 2 equiv) and cyanogen bromide (0.64 g, 6 mmol, 1 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 70/30) afforded compound 158 (0.75 g, 86 %) as a colorless oil. The analytical data were identical to the literature.\(^{204}\)

\[ R_t = 0.52 \] (Cyclohexane/Ethyl acetate; 80/20, KMnO\(_4\), UV).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.30 – 7.47 \) (m, 5H), 4.15 (s, 2 H.), 2.77 (s, 3 H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 134.5, 129.1, 128.8, 128.5, 119.0, 57.3, 37.9\).


\(^{204}\) Bakunov, S. A.; Rukavishnikov, A. V.; Tkachev, A. V. Synthesis, 2000, 1148.
Experimental part

### N,N-Dibenzylcyanamide (159)

![Chemical Structure](image)

This compound was obtained following the general procedure K. Starting from dibenzylamine (2.96 g, 15 mmol, 1 equiv), cyanogen bromide (1.69 g, 16 mmol, 1.05 equiv) and sodium hydrogen carbonate (2.5 g, 30 mmol, 2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded compound 159 (3.2 g, 96 %) as a white solid. The analytical data were identical to the literature.\textsuperscript{147b}

R\textsubscript{f} = 0.31 (Cyclohexane/Ethyl acetate; 85/15, KMnO\textsubscript{4}, UV).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 7.48 – 7.27 (m, 10H), 4.12 (s, 4 H,).

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 134.5, 129.0, 128.8, 128.7, 118.4, 54.4.

### N,N-Dipropylcyanamide (161)

![Chemical Structure](image)

This compound was obtained following the general procedure J. Starting from dipropylamine (3 mL, 20 mmol, 2 equiv) and cyanogen bromide (1.06 g, 10 mmol, 1 equiv). The reaction provided the compound 161 (1.13 g, 90 %) as a colorless oil, pure enough to be used without purification. The analytical data were identical to the literature.\textsuperscript{135a}

R\textsubscript{f} = 0.6 (Cyclohexane/Ethyl acetate; 80/20, KMnO\textsubscript{4}, UV).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 2.91 (t, \(J\) = 7.2 Hz, 4H), 1.69 – 1.53 (m, 4H), 0.93 (t, \(J\) = 7.4 Hz, 6H).

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 117.9, 53.3, 21.1, 11.1.

### N-Methyl-N-phenylcyanamide (162)
This compound was obtained following the general procedure J. Starting from *N*-methylaniline (2.16 mL, 20.0 mmol, 2 equiv) and cyanogen bromide (1.06 g, 10 mmol, 1 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 80/20 to 50/50) afforded compound 162 (1.2 g, 91 %) as a white solid. The analytical data were identical to the literature.135

R<sub>t</sub> = 0.45 (Cyclohexane/Ethyl acetate; 90/10, KMnO<sub>4</sub>, UV).

1<sup>H</sup> NMR (300 MHz, CDCl<sub>3</sub>) δ 7.47 – 7.32 (m, 2H), 7.16 – 7.01 (m, 3H), 3.34 (s, 3H).

13<sup>C</sup> NMR (75 MHz, CDCl<sub>3</sub>) δ 140.5, 129.7, 123.5, 115.0, 114.2, 36.9.

This compound was obtained following the general procedure J. Starting from *N*-butylamine (2.93 g, 40.0 mmol, 2 equiv) and cyanogen bromide (2.12 g, 20 mmol, 1 equiv). The reaction provided the compound 163 (1.9 g, 96 %) as a colorless oil, pure enough to be used without purification. The analytical data were identical to the literature.205

R<sub>t</sub> = 0.2 (Cyclohexane/Ethyl acetate; 80/20, KMnO<sub>4</sub>, UV).

1<sup>H</sup> NMR (300 MHz, CDCl<sub>3</sub>) δ 3.36 (br, 1H), 3.07 (t, J = 7.0 Hz, 2H), 1.67 – 1.50 (m, 2H), 1.47 – 1.25 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H).

13<sup>C</sup> NMR (75 MHz, CDCl<sub>3</sub>) δ 116.4, 46.1, 31.8, 19.6, 13.7.

**N-butyl-N-methylcyanamide (164)**

This compound was obtained following the general procedure K. Starting from N-methylbutylamine (1.74 g, 20 mmol, 1 equiv), cyanogen bromide (2.22 g, 21 mmol, 1.05 equiv) and sodium hydrogen carbonate (3.3 g, 40 mmol, 2 equiv). The reaction provided the compound 164 (2.23 g, 99 %) as a pale yellow oil, pure enough to be used without purification.

\[ R_f = 0.3 \] (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

**¹H NMR** (300 MHz, CDCl₃) \( \delta \) 2.96 (t, \( J = 7.2 \) Hz, 2H), 2.84 (s, 3H), 1.67 – 1.57 (m, 2H), 1.45 – 1.33 (m, 2H), 0.94 (t, \( J = 7.3 \) Hz, 3H).

**¹³C NMR** (75 MHz, CDCl₃) \( \delta \) 118.8, 52.8, 38.9, 29.4, 19.8, 13.7.

**N-butyl-N-cyanoacetamide (165)**

To a suspension of NaH (0.77 g, 19.2 mmol, 1.2 equiv) in THF (30 mL) was added N-butylecyanamide (1.6 g, 16 mmol) in Et₂O (10 mL) at 0 °C. The mixture was warmed to room temperature, and acetyl chloride (1.36 mL, 19.2 mmol, 1.2 equiv) was added. The reaction mixture was stirred at room temperature for 1 h, and quenched with H₂O (1 mL). The crude reaction mixture was extracted with Et₂O (3 × 15 mL), washed with water and brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (Petroleum ether/Ethyl acetate gradient from 90/10 to 80/20) to afford compound 165 (1.8 g, 80 %) as a colorless oil. The analytical data were identical to the literature.¹³⁵a

\[ R_f = 0.45 \] (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).
Experimental part

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.60 – 3.50 (m, 2H), 2.39 (s, 3H), 1.77 – 1.53 (m, 2H), 1.45 – 1.29 (m, 2H), 0.95 (t, $J$ = 7.3 Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.4, 111.1, 46.1, 29.7, 22.3, 19.6, 13.6.

<table>
<thead>
<tr>
<th>N,N-diallylcyanamide (166)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C$<em>9$H$</em>{16}$N$_2$</td>
</tr>
<tr>
<td>Exact Mass: 122.0844</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure K. Starting from diallylamine (1.46 g, 15 mmol, 1 equiv), cyanogen bromide (1.69 g, 16 mmol, 1.05 equiv) and sodium hydrogen carbonate (2.5 g, 30 mmol, 2 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 80/20 to 70/30) afforded compound 166 (1.7 g, 93 %) as a pale yellow oil. The analytical data were identical to the literature.$^203$

$R_f$ = 0.36 (Cyclohexane/Ethyl acetate; 80/20, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.90 – 5.75 (m, 2H), 5.41 – 5.32 (m, 2H), 5.32 – 5.24 (m, 2H), 3.65 – 3.54 (m, 4H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 131.1, 120.6, 117.7, 53.5.

<table>
<thead>
<tr>
<th>4-Methylpiperazine-1-carbonitrile (167)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C$<em>9$H$</em>{17}$N$_3$</td>
</tr>
<tr>
<td>Exact Mass: 125.0953</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure K. Starting from $N$-methyl piperazine (2 g, 20 mmol, 1 equiv), cyanogen bromide (2.22 g, 21 mmol, 1.05 equiv) and sodium hydrogen carbonate (3.3 g, 4 mmol, 2 equiv). The reaction provided the compound 167 (1.45 g, 58 %) as a pale yellow oil, pure enough to be used without purification.

$R_f$ = 0.24 (EA, KMnO$_4$, UV).
Experimental part

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.29 – 3.19 (m, 4H), 2.50 – 2.39 (m, 4H), 2.30 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 117.9, 53.7, 49.2, 46.4.

3.5. Ruthenium-catalyzed [2+2+2] cycloaddition of $\alpha,\omega$-diynes with cyanamides

General procedure L:

A sealed tube was equipped with RuCl$_3$·$n$H$_2$O (5 mol %) and $\alpha,\omega$-diyne (1 mmol, 1 equiv), followed by the addition of cyanamide (2.0 mmol, 2.0 equiv) under argon atmosphere. The tube was sealed and the reaction mixture was stirred vigorously at 80 °C or 110 °C. When the reaction was complete (TLC monitoring), the crude reaction mixture was directly purified by flash chromatography over silica gel to afford cycloadduct. In some cases, the excess of cyanamide was removed by bulb to bulb distillation.

General procedure M:

A sealed tube was equipped with Cp*Ru(CH$_3$CN)$_3$PF$_6$ (1-5 mol %) and diyne (1 equiv), followed by the addition of cyanamide (2 equiv) under argon atmosphere. The reaction mixture was stirred vigorously at room temperature or 50 °C. When the reaction was complete (TLC monitoring), the crude mixture was directly purified by flash chromatography over silica gel to afford cycloadduct. In some cases, the excess of cyanamide was removed by bulb to bulb distillation.

General procedure N:
Experimental part

**[diyne]**

A sealed tube was equipped with \( \text{Cp}^*\text{Ru}([\text{CH}_3\text{CN}]_3)\text{PF}_6 \) (1-5 mol %) and cyanamide (1.2 or 2.0 equiv), a solution of diyne (1 equiv) in DCM (1 or 2 M) was added under argon atmosphere. The reaction mixture was stirred vigorously at room temperature or 50 °C. When the reaction was complete (TLC monitoring), the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel to afford cycloadduct. In some cases, the excess of cyanamide was removed by bulb to bulb distillation.

<table>
<thead>
<tr>
<th>Dimethyl 3-(dimethylamino)-1,4-dimethyl-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (168)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure L. Starting from diyne **101** (236 mg, 1.0 mmol), \( \text{N,N-dimethylcyanamide} \) **154** (140 mg, 2.0 mmol, 2.0 equiv) and \( \text{RuCl}_3\cdot n\text{H}_2\text{O} \) (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 110 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 70/30) afforded **168** (225 mg, 74%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10^{-3} mbar, 70 °C for 10 minutes). The analytical data were identical to the literature.\(^{135a}\)

**Rf = 0.34** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

\(^1\text{H NMR} \) (300 MHz, CDCl₃) \( \delta \) 3.74 (s, 6H), 3.48 (s, 2H), 3.47 (s, 2H), 2.75 (s, 6H), 2.31 (s, 3H), 2.14 (s, 3H).

\(^{13}\text{C NMR} \) (75 MHz, CDCl₃) \( \delta \) 172.2, 161.6, 150.3, 147.9, 127.2, 117.1, 59.9, 53.2, 42.5, 40.1, 38.7, 21.8, 14.9.

**MS** (Cl, NH₃): \( m/z = 307 \) [M + H]⁺.
a) This compound was obtained following the general procedure L. Starting from diyne 101 (236 mg, 1.0 mmol), 4-cyanomorpholine 155 (224 mg, 2.0 mmol, 2.0 equiv) and RuCl₃·nH₂O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 80 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 169 (330 mg, 95%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes). The analytical data were identical to the literature.¹³⁵a

b) This compound was obtained following the general procedure M. Starting from diyne 101 (118 mg, 0.5 mmol), 4-cyanomorpholine 155 (112 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 2 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 169 (158 mg, 91%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes).

Rᵣ = 0.24 (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 3.86 – 3.78 (m, 4H), 3.76 (s, 6H), 3.50 (s, 2H), 3.48 (s, 2H), 3.12 – 2.99 (m, 4H), 2.33 (s, 3H), 2.14 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 172.1, 160.2, 150.5, 148.5, 128.3, 117.9, 67.4, 59.9, 53.2, 50.8, 40.0, 38.7, 21.7, 14.4.

MS (CI, NH₃): m/z = 349 [M + H]+.
Experimental part

![Chemical structure](image)

**Chemical Formula:** C_{16}H_{24}N_{2}O_{4}

**Exact Mass:** 332.1736

a) This compound was obtained following the general procedure L. Starting from diyne 101 (236 mg, 1.0 mmol), pyrrolidine-1-carbonitrile 156 (192 mg, 2.0 mmol, 2.0 equiv) and RuCl₃·nH₂O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 80 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 70/30) afforded 170 (285 mg, 86%) as a pale yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 80 °C for 10 minutes).

b) This compound was obtained following the general procedure M. Starting from diyne 101 (118 mg, 0.5 mmol), pyrrolidine-1-carbonitrile 156 (96 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 15 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 70/30) afforded 170 (134 mg, 81%) as a pale yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 80 °C for 10 minutes).

The analytical data were identical to the literature.¹³⁵ᵃ

**Rf = 0.35** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

**¹H NMR** (300 MHz, CDCl₃) δ 3.75 (s, 6H), 3.44 (m, 8H), 2.29 (s, 3H), 2.15 (s, 3H), 1.87 (m, 4H).

**¹³C NMR** (75 MHz, CDCl₃) δ 172.3, 158.9, 150.3, 147.4, 124.6, 113.5, 60.0, 53.1, 50.3, 40.1, 38.6, 25.6, 21.7, 15.8.

**MS** (Cl, NH₃): m/z = 333 [M + H]^⁺.

| Dimethyl 1,4-dimethyl-3-(piperidin-1-yl)-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (171) |  |
Experimental part

This compound was obtained following the general procedure L. Starting from diyne 101 (236 mg, 1.0 mmol), piperidine-1-carbonitrile 157 (220 mg, 2.0 mmol, 2.0 equiv) and RuCl$_3$·nH$_2$O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 110 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 171 (251 mg, 73%) as a colorless oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10$^{-3}$ mbar, 80 °C for 10 minutes). The analytical data were identical to the literature.$^{143}$

Rr = 0.33 (Petroleum ether/Ethyl acetate; 90/10, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) δ 3.75 (s, 6H), 3.49 (s, 2H), 3.47 (s, 2H), 3.06 – 2.91 (m, 4H), 2.32 (s, 3H), 2.13 (s, 3H), 1.73 – 1.61 (m, 4H), 1.61 – 1.50 (m, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 172.2, 161.7, 150.1, 148.1, 127.5, 118.1, 59.8, 53.2, 51.6, 40.01, 38.7, 26.5, 24.8, 21.7, 14.4.

MS (CI, NH$_3$): m/z = 347 [M + H]$^+$.  

**Dimethyl 3-(benzyl(methyl)amino)-1,4-dimethyl-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (172)**

This compound was obtained following the general procedure L. Starting from diyne 101 (236 mg, 1.0 mmol), N-benzyl-N-methylcyanamide 158 (292 mg, 2.0 mmol, 2.0 equiv) and RuCl$_3$·nH$_2$O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 80 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 85/15) afforded 172 (306 mg, 81%) as a colorless oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10$^{-3}$ mbar, 120 °C for 10 minutes).
Experimental part

R<sub>f</sub> = 0.26 (Petroleum ether/Ethyl acetate; 90/10, KMnO<sub>4</sub>, UV).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.45 – 7.38 (m, 2H), 7.32 (t, J = 7.3 Hz, 2H), 7.28 – 7.16 (m, 1H), 4.26 (s, 2H), 3.77 (s, 6H), 3.55 – 3.45 (m, 4H), 2.67 (s, 3H), 2.35 (s, 3H), 2.20 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 172.2, 161.4, 150.4, 148.1, 140.0, 128.4, 128.2, 127.7, 126.8, 117.8, 59.9, 58.4, 53.2, 40.1, 39.8, 38.8, 21.7, 14.8.

MS (Cl, NH<sub>3</sub>): m/z = 383 [M + H]<sup>+</sup>.

<table>
<thead>
<tr>
<th>Dimethyl 3-(dibenzylamino)-1,4-dimethyl-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (173)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C&lt;sub&gt;29&lt;/sub&gt;H&lt;sub&gt;30&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
</tr>
<tr>
<td>Exact Mass: 458.2206</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure L. Starting from diyne 101 (236 mg, 1.0 mmol), dibenzylcyanamide 159 (444 mg, 2.0 mmol, 2.0 equiv) and RuCl<sub>3</sub>·nH<sub>2</sub>O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 110 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 173 (344 mg, 75%) as a sticky yellow oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10<sup>-3</sup> mbar, 180 °C for 20 minutes).

R<sub>f</sub> = 0.17 (Petroleum ether/Ethyl acetate; 80/20, KMnO<sub>4</sub>, UV).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.39 – 7.13 (m, 10H), 4.25 (s, 4H), 3.76 (s, 6H), 3.49 (s, 4H), 2.29 (s, 3H), 2.24 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 172.2, 159.9, 150.4, 148.2, 139.9, 128.6, 128.3, 128.2, 126.7, 118.9, 59.7, 55.4, 53.2, 40.1, 38.8, 21.6, 14.5.

MS (Cl, NH<sub>3</sub>): m/z = 459 [M + H]<sup>+</sup>.

<table>
<thead>
<tr>
<th>1,1',3',4-Tetramethyl-3-morpholino-5,7-dihydro-2'H-spiro[cyclopenta[c]pyridine-6,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione (181)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical structure" /></td>
</tr>
</tbody>
</table>

286
This compound was obtained following the general procedure L. Starting from diyne 102 (260 mg, 1.0 mmol), 4-cyanomorpholine 155 (224 mg, 2.0 mmol, 2.0 equiv) and RuCl₃·nH₂O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 110 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 50/50) afforded 181 (275 mg, 74%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes). m.p. 175 – 178 °C.

Rᵣ = 0.12 (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 3.90 – 3.76 (m, 4H), 3.49 (s, 2H), 3.45 (s, 2H), 3.34 (s, 6H), 3.17 – 2.94 (m, 4H), 2.30 (s, 3H), 2.15 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 172.2, 160.7, 151.4, 150.6, 148.3, 127.3, 117.8, 67.4, 55.8, 50.8, 44.0, 42.6, 29.3, 21.8, 14.5.

MS (Cl, NH₃): m/z = 373 [M + H]^⁺.

1,4-Dimethyl-3-morpholino-5,7-dihydrospiro[cyclopenta[c]pyridine-6,2'-indene]-1',3'-dione (182)

This compound was obtained following the general procedure L. Starting from diyne 103 (250 mg, 1.0 mmol), 4-cyanomorpholine 155 (224 mg, 2.0 mmol, 2.0 equiv) and RuCl₃·nH₂O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 80 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 182 (268 mg, 74%) as a yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes). m.p. 206 – 209 °C.
Experimental part

R<sub>t</sub> = 0.21 (Petroleum ether/Ethyl acetate; 80/20, KMnO<sub>4</sub>, UV).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.08 – 7.98 (m, 2H), 7.93 – 7.85 (m, 2H), 3.89 – 3.73 (m, 4H), 3.23 (s, 2H), 3.22 (s, 2H), 3.14 – 3.01 (m, 4H), 2.31 (s, 3H), 2.13 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 202.9, 160.6, 151.3, 148.4, 141.7, 136.2, 128.9, 123.9, 118.0, 67.4, 58.5, 50.8, 39.6, 21.8, 14.5.

MS (CI, NH<sub>3</sub>): m/z = 363 [M + H]<sup>+</sup>.

This compound was obtained following the general procedure L. Starting from diyne 104 (180 mg, 1.0 mmol), 4-cyanomorpholine 155 (224 mg, 2.0 mmol, 2.0 equiv) and RuCl<sub>3</sub>:nH<sub>2</sub>O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 80 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate 80/20) afforded 183 (30 mg, 10%) as a pale yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10<sup>-3</sup> mbar, 90 °C for 10 minutes). The analytical data were identical to the literature.<sup>143</sup>

R<sub>t</sub> = 0.2 (Petroleum ether/Ethyl acetate; 2/1, KMnO<sub>4</sub>, UV).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.86– 3.81 (m, 4H), 3.81 – 3.67 (m, 4H), 3.13 – 2.99 (m, 4H), 2.72 – 2.60 (m, 4H), 2.31 (s, 3H), 2.12 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 159.8, 152.4, 149.1, 130.0, 118.6, 69.5, 67.4, 50.8, 48.7, 37.9, 36.6, 21.7, 14.4.

MS (CI, NH<sub>3</sub>): m/z = 293 [M + H]<sup>+</sup>.

(1,4-Dimethyl-3-morpholino-6,7-dihydro-5H-cyclopenta[c]pyridine-6,6-diyl)dimethanol (183)

(1,4-Dimethyl-3-morpholino-6,7-dihydro-5H-cyclopenta[c]pyridine-6,6-diyl)bis(methylene) diacetate (184)
This compound was obtained following the general procedure L. Starting from diyne 105 (264 mg, 1.0 mmol), 4-cyanomorpholine 155 (224 mg, 2.0 mmol, 2.0 equiv) and RuCl₃·ₙH₂O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 80 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 184 (255 mg, 68%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes). m.p. 102 – 104 °C.

**Rf = 0.3** (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

**¹H NMR** (300 MHz, CDCl₃) δ 4.08 (s, 4H), 3.89 – 3.73 (m, 4H), 3.16 – 2.92 (m, 4H), 2.78 – 2.70 (m, 4H), 2.31 (s, 3H), 2.12 (s, 3H), 2.07 (s, 6H).

**¹³C NMR** (75 MHz, CDCl₃) δ 171.1, 160.1, 151.4, 149.1, 129.2, 118.4, 67.4, 66.9, 50.8, 46.2, 38.1, 36.8, 21.7, 21.0, 14.4.

**MS** (Cl, NH₃): m/z = 377 [M + H]+.

<table>
<thead>
<tr>
<th>4-(6,6-Bis((benzyloxy)methyl)-1,4-dimethyl-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)morpholine (185)</th>
</tr>
</thead>
</table>

This compound was obtained following the general procedure L. Starting from diyne 106 (360 mg, 1.0 mmol), 4-cyanomorpholine 155 (224 mg, 2.0 mmol, 2.0 equiv) and RuCl₃·ₙH₂O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 80 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate 80/20) afforded 185 (390 mg, 83%) as a pale yellow oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes).
Experimental part

**R**<sub>f</sub> = 0.38 (Petroleum ether/Ethyl acetate; 90/10, KMnO<sub>4</sub>, UV).

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.40 – 7.18 (m, 10H), 4.53 (s, 4H), 3.96 – 3.72 (m, 4H), 3.50 (s, 4H), 3.16 – 2.94 (m, 4H), 2.79 – 2.70 (m, 4H), 2.31 (s, 3H), 2.11 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 159.7, 152.9, 148.9, 138.8, 130.7, 128.5, 127.6, 118.5, 73.7, 73.4, 67.5, 50.9, 48.1, 38.5, 37.1, 21.7, 14.4.

**MS** (CI, NH<sub>3</sub>): m/z = 473 [M + H]<sup>+</sup>.

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### 4,7-Dimethyl-6-morpholino-1,3-dihydrofuro[3,4-<i>c</i>]pyridine (186)

![Chemical structure of 4,7-Dimethyl-6-morpholino-1,3-dihydrofuro[3,4-<i>c</i>]pyridine](image)

Chemical Formula: C<sub>13</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub>  
Exact Mass: 234.1368

a) This compound was obtained following the general procedure L. Starting from diyne 107 (122 mg, 1.0 mmol), 4-cyanomorpholine 155 (224 mg, 2.0 mmol, 2.0 equiv) and RuCl<sub>3</sub>·nH<sub>2</sub>O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 80 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 186 (150 mg, 64%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10<sup>-3</sup> mbar, 90 °C for 10 minutes).

b) This compound was obtained following the general procedure M. Starting from diyne 107 (61 mg, 0.5 mmol), 4-cyanomorpholine 155 (112 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH<sub>3</sub>CN)<sub>3</sub>PF<sub>6</sub> (5.0 mg, 0.01 mmol). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 186 (94 mg, 80%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10<sup>-3</sup> mbar, 90 °C for 10 minutes).

The analytical data were identical to the literature.<sup>143</sup>

**R**<sub>f</sub> = 0.13 (Petroleum ether/Ethyl acetate; 90/10, KMnO<sub>4</sub>, UV).

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 5.05 (s, 2H), 5.00 (s, 2H), 3.86 – 3.81 (m, 4H), 3.12 – 3.07 (m, 4H), 2.32 (s, 3H), 2.12 (s, 3H).
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 160.5, 150.1, 146.2, 127.6, 115.1, 73.2, 72.7, 67.3, 50.7, 21.9, 14.6.

MS (Cl, NH$_3$): m/z = 235 [M + H]$^+$. 

**4-(4,7-Dimethyl-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)morpholine (187)**

![Chemical structure](image_url)

Chemical Formula: C$_{28}$H$_{38}$N$_4$O$_3$S

Exact Mass: 387.1617

a) This compound was obtained following the general procedure L. Starting from diyne 108 (275 mg, 1.0 mmol), 4-cyanomorpholine 155 (224 mg, 2.0 mmol, 2.0 equiv) and RuCl$_3$·$n$H$_2$O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 110 $^\circ$C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 187 (280 mg, 72%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x$10^{-3}$ mbar, 90 $^\circ$C for 10 minutes).

b) This compound was obtained following the general procedure N. Starting from diyne 108 (137.5 mg, 0.5 mmol), 4-cyanomorpholine 155 (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH$_3$CN)$_3$PF$_6$ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 187 (180 mg, 93%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x$10^{-3}$ mbar, 90 $^\circ$C for 10 minutes).

The analytical data were identical to the literature.$^{143}$

R$_t$ = 0.15 (Petroleum ether/Ethyl acetate; 80/20, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.78 (d, $J$ = 8.3 Hz, 2H), 7.33 (d, $J$ = 8.0 Hz, 2H), 4.52 – 4.40 (m, 4H), 3.85 – 3.75 (m, 4H), 3.10 – 3.00 (m, 4H), 2.41 (s, 3H), 2.27 (s, 3H), 2.08 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 160.8, 147.7, 146.8, 144.0, 134.1, 130.1, 127.8, 124.8, 116.4, 67.3, 53.5, 52.6, 50.69, 21.7, 14.5.

MS (Cl, NH$_3$): m/z = 388 [M + H]$^+$. 

291
Experimental part

**Dimethyl 3-morpholino-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (188)**

This compound was obtained following the general procedure N. Starting from diyne 109 (104 mg, 0.5 mmol), 4-cyanomorpholine 155 (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH3CN)3PF6 (2.5 mg, 0.005 mmol). The reaction mixture was stirred at room temperature for 2 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 60/40) afforded 188 (152 mg, 95%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes). The analytical data were identical to the literature.¹²⁸

Rf = 0.1 (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.02 (s, 1H), 6.52 (s, 1H), 3.88 – 3.77 (m, 4H), 3.74 (s, 6H), 3.50 (s, 4H), 3.47 – 3.37 (m, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 171.8, 159.4, 151.7, 143.1, 126.3, 102.8, 66.9, 60.7, 53.2, 46.3, 40.6, 37.6.

MS (CI, NH₃): m/z = 321 [M + H]⁺.

**Dimethyl 1-methyl-3-morpholino-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (193)**

a) This compound was obtained following the general procedure L. Starting from diyne 125 (222 mg, 1.0 mmol), 4-cyanomorpholine 155 (224 mg, 2.0 mmol, 2.0 equiv) and RuCl₃·nH₂O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 100 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 193 (71 mg, 43%, ratio
= 87:13) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10^{-3} mbar, 90 °C for 10 minutes).

b) This compound was obtained following the general procedure M. Starting from diyne 125 (111 mg, 0.5 mmol), 4-cyanomorpholine 155 (112 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH3CN)3PF6 (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 10 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 193 (148 mg, 89%, ratio = 98:2) as a slight yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10^{-3} mbar, 90 °C for 10 minutes). m.p. 110 – 112 °C.

Rt = 0.17 (Cyclohexane/Ethyl acetate; 85/15, KMnO4, UV).

^1H NMR (400 MHz, CDCl3) δ 6.33 (s, 1H, H8), 3.83 – 3.78 (m, 4H, H13), 3.75 (s, 6H, H1), 3.49 (s, 2H, H4), 3.47 – 3.41 (m, 6H, H5,12), 2.32 (s, 3H, H11)

^13C NMR (101 MHz, CDCl3) δ 172.0 (C2), 159.3 (C7), 151.7 (C9), 151.5 (C10), 124.3 (C6), 100.1 (C5), 67.0 (C13), 60.0 (C3), 53.2 (C1), 46.4 (C12), 40.8 (C4), 38.0 (C3), 22.2 (C11).

NOESY (400 MHz, CDCl3) H8 (6.33 ppm) correlates to H12 (3.47 – 3.41 ppm), H5 (3.47 – 3.41 ppm) correlates to H11 (2.32 ppm).

HRMS (ESI^+): calcd. for C_{17}H_{23}N_{2}O_{5} [M+H]^+: 335.1601, found 335.1603.

Dimethyl 3-morpholino-1-phenyl-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (194)

![Chemical Structure of Dimethyl 3-morpholino-1-phenyl-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (194)](image)

Chemical Formula: C_{22}H_{24}N_{2}O_{5}
Exact Mass: 396.1685

a) This compound was obtained following the general procedure L. Starting from diyne 126 (142 mg, 0.5 mmol), 4-cyanomorpholine 155 (112 mg, 1.0 mmol, 2.0 equiv) and RuCl3·nH2O (5.2 mg, 0.025 mmol). The reaction mixture was stirred at 100 °C for 18 h. Purification on silica
Experimental part

gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 194 (32 mg, 16%, ratio = 90:10) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes).

b) This compound was obtained following the general procedure M. Starting from diyne 126 (142 mg, 0.5 mmol), 4-cyanomorpholine 155 (112 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at 50 °C for 15 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 70/30) afforded 194 (190 mg, 96%, ratio > 99:1) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes). m.p. 166 – 168 °C.

Rr = 0.2 (Petroleum ether/Ethyl acetate; 85/15, KMnO₄, UV).

¹H NMR (400 MHz, CDCl₃) δ 7.81 – 7.78 (m, 2H, H₁₂), 7.47 – 7.41 (m, 2H, H₁₃), 7.39 – 7.35 (m, 1H, H₁₄), 6.52 (s, 1H, H₈), 3.86 – 3.80 (m, 4H, H₁₆), 3.73 (s, 6H, H₁₁), 3.72 (s, 2H, H₅), 3.60 – 3.41 (m, 4H, H₁₅), 3.54 (s, 2H, H₆).

¹³C NMR (75 MHz, CDCl₃) δ 171.8 (C₂), 159.0 (C₉), 153.1 (C₆), 151.2 (C₁₀), 139.9 (C₁₁), 128.4 (C₁₂), 128.3 (C₁₃), 128.3 (C₁₄), 123.2 (C₇), 101.5 (C₈), 67.0 (C₁₆), 60.5 (C₃), 53.2 (C₁), 46.0 (C₁₅), 40.5 (C₄), 39.6 (C₃).

NOESY (400 MHz, CDCl₃) H₁₂ (7.81 – 7.78 ppm) correlates to H₅ (3.72 ppm), H₈ (6.52 ppm) correlate to H₁₅ (3.60 – 3.41 ppm) and H₄ (3.54 ppm).


<table>
<thead>
<tr>
<th>Di-tert-butyl 3-morpholino-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (196)</th>
</tr>
</thead>
</table>

This compound was obtained following the general procedure M. Starting from diyne 114 (146 mg, 0.5 mmol), 4-cyanomorpholine 155 (112 mg, 1.0 mmol, 2.0 equiv) and
Experimental part

Cp*Ru(CH\textsubscript{3}CN\textsubscript{3})\textsubscript{3}PF\textsubscript{6} (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate 80/20) afforded \textit{196} (198 mg, 98\%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10\textsuperscript{-3} mbar, 90 °C for 10 minutes). m.p. 135 – 137 °C.

\textbf{Rf} = 0.23 (Petroleum ether/Ethyl acetate; 85/15, KMnO\textsubscript{4}, UV).

\textbf{\textsuperscript{1}H NMR} (300 MHz, CDCl\textsubscript{3}) \(\delta\) 8.00 (s, 1H), 6.51 (s, 1H), 3.89 – 3.72 (m, 4H), 3.50 – 3.40 (m, 4H), 3.38 (s, 4H), 1.44 (s, 18H).

\textbf{\textsuperscript{13}C NMR} (75 MHz, CDCl\textsubscript{3}) \(\delta\) 170.2, 159.4, 152.3, 143.0, 127.0, 102.8, 81.8, 67.0, 61.8, 46.4, 40.3, 37.3, 28.0.

\textbf{HRMS} (ESI\textsuperscript{+}): calcd. for C\textsubscript{22}H\textsubscript{33}N\textsubscript{2}O\textsubscript{5} [M+H]\textsuperscript{+}: 405.2384, found 405.2385.

\textbf{Diisopropyl 3-morpholino-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (197)}

This compound was obtained following the general procedure \textbf{N}. Starting from diyne \textit{115} (132 mg, 0.5 mmol), 4-cyanomorpholine \textit{155} (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH\textsubscript{3}CN\textsubscript{3})\textsubscript{3}PF\textsubscript{6} (2.5 mg, 0.005 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 70/30) afforded \textit{197} (152 mg, 81\%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10\textsuperscript{-3} mbar, 90 °C for 10 minutes). m.p. 115 – 117 °C.

\textbf{Rf} = 0.11 (Petroleum ether/Ethyl acetate; 85/15, KMnO\textsubscript{4}, UV).

\textbf{\textsuperscript{1}H NMR} (300 MHz, CDCl\textsubscript{3}) \(\delta\) 8.01 (s, 1H), 6.51 (s, 1H), 5.03 (dt, \(J =\) 12.5, 6.3 Hz, 2H), 3.86 – 3.74 (m, 4H), 3.50 – 3.38 (m, 8H), 1.23 (d, \(J =\) 6.3 Hz, 12H).

\textbf{\textsuperscript{13}C NMR} (75 MHz, CDCl\textsubscript{3}) \(\delta\) 170.9, 159.4, 152.0, 143.1, 126.7, 102.8, 69.4, 67.0, 60.8, 46.3, 40.4, 37.4, 21.6.

\textbf{HRMS} (ESI\textsuperscript{+}): calcd. for C\textsubscript{20}H\textsubscript{29}N\textsubscript{2}O\textsubscript{5} [M+H]\textsuperscript{+}: 377.2071, found 377.2071.
Experimental part

**Methyl 3-morpholino-6-phenyl-6,7-dihydro-5H-cyclopenta[c]pyridine-6-carboxylate (198)**

This compound was obtained following the general procedure N. Starting from diyne **116** (113 mg, 0.5 mmol), 4-cyanomorpholine **155** (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH3CN)3PF6 (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 70/30) afforded **198** (154 mg, 91%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes). m.p. 178 – 180 °C.

**Rf = 0.1** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

**¹H NMR** (300 MHz, CDCl₃) δ 8.07 (s, 1H), 7.45 – 7.22 (m, 5H), 6.59 (s, 1H), 4.00 – 3.74 (m, 6H), 3.60 (s, 3H), 3.50 – 3.33 (m, 4H), 3.23 (dd, J = 19.8, 15.7 Hz, 2H).

**¹³C NMR** (75 MHz, CDCl₃) δ 175.6, 159.4, 152.9, 142.9, 142.2, 128.7, 127.6, 127.4, 126.7, 103.1, 67.0, 60.0, 52.9, 46.3, 42.9, 39.5.


**Methyl 6-cyano-3-morpholino-6,7-dihydro-5H-cyclopenta[c]pyridine-6-carboxylate (199)**

This compound was obtained following the general procedure M. Starting from diyne **117** (87.5 mg, 0.5 mmol), 4-cyanomorpholine **155** (112 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 40 min. Purification on silica gel (Cyclohexane/Ethyl acetate 80/20) afforded **199** (125 mg, 87%) as a pale yellow oil.
Experimental part

**Rf = 0.1** (Petroleum ether/Ethyl acetate; 85/15, KMnO₄, UV).

**¹H NMR** (300 MHz, CDCl₃) δ 8.05 (s, 1H), 6.53 (s, 1H), 3.85 (s, 3H), 3.83 – 3.74 (m, 4H), 3.65 – 3.39 (m, 8H).

**¹³C NMR** (75 MHz, CDCl₃) δ 168.7, 159.7, 149.9, 143.5, 124.0, 120.1, 102.6, 66.8, 54.1, 47.6, 46.0, 42.9, 40.6.


<table>
<thead>
<tr>
<th>3-Morpholino-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarbonitrile (200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Chemical Structure]</td>
</tr>
<tr>
<td>Chemical Formula: C₁₄H₁₄N₄O</td>
</tr>
<tr>
<td>Exact Mass: 254.1168</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure N. Starting from diyne 118 (71 mg, 0.5 mmol), morpholine-4-carbonitrile 155 (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (5 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 2 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 50/50) afforded 200 (64 mg, 50%) as a white solid. m.p. 176 – 178 °C.

**Rf = 0.4** (Petroleum ether/Ethyl acetate; 50/50, KMnO₄, UV).

**¹H NMR** (400 MHz, CDCl₃) δ 8.12 (s, 1H), 6.56 (s, 1H), 3.85 – 3.76 (m, 4H), 3.65 (s, 2H), 3.61 (s, 2H), 3.55 – 3.40 (m, 4H).

**¹³C NMR** (75 MHz, CDCl₃) δ 159.9, 147.7, 144.0, 121.8, 116.0, 102.6, 66.7, 45.9, 44.6, 42.0, 34.0.

**MS** (CI, NH₃): m/z = 255 [M + H]⁺.

| 3-Morpholino-5,7-dihydropyrro[5,6-d]pyridine-6,2'-indene-1',3'-dione (201) |
This compound was obtained following the general procedure N. Starting from diyne \textbf{119} (111 mg, 0.5 mmol), 4-cyanomorpholine \textbf{155} (67 mg, 0.6 mmol, 1.2 equiv) and \textbf{Cp*Ru(CH3CN)3PF6} (2.5 mg, 0.005 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 50/50) afforded \textbf{201} (162 mg, 97\%) as a pale yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10^{-3} mbar, 90 °C for 10 minutes). m.p. 194 – 196 °C.

**Rt** = 0.1 (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

\textbf{1H NMR} (300 MHz, CDCl₃) \(\delta\) 8.08 – 7.95 (m, 3H), 7.93 – 7.81 (m, 2H), 6.54 (s, 1H), 3.89 – 3.72 (m, 4H), 3.54 – 3.37 (m, 4H), 3.24 (s, 2H), 3.23 (s, 2H).

\textbf{13C NMR} (75 MHz, CDCl₃) \(\delta\) 202.5, 159.6, 152.5, 143.0, 141.5, 136.1, 126.7, 123.8, 102.7, 66.9, 59.1, 46.3, 39.7, 38.4.

**HRMS** (ESI\(^{+}\)): calcd. for C\(_{20}\)H\(_{19}\)N\(_2\)O\(_3\) [M+H]\(^{+}\): 335.1390, found 335.1392.

(3-Morpholino-6,7-dihydro-5H-cyclopenta[c]pyridine-6,6-diyl)dimethanol (\textbf{202})

This compound was obtained following the general procedure M. Starting from diyne \textbf{120} (76 mg, 0.5 mmol), 4-cyanomorpholine \textbf{155} (112 mg, 1.0 mmol, 2.0 equiv) and \textbf{Cp*Ru(CH3CN)3PF6} (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Pure ethyl acetate followed by DCM/MeOH 9/1) afforded \textbf{202} (115 mg, 87\%) as a white solid. m.p. 158 – 160 °C.

**Rt** = 0.2 (Pure ethyl acetate, KMnO₄, UV).
Experimental part

$^1$H NMR (300 MHz, MeOD) $\delta$ 7.89 (s, 1H), 6.71 (s, 1H), 4.89 (s, 2H, OH), 3.83 – 3.74 (m, 4H), 3.54 (s, 4H), 3.41 – 3.33 (m, 4H), 2.77 (s, 2H), 2.71 (s, 2H).

$^{13}$C NMR (75 MHz, MeOD) $\delta$ 160.7, 156.5, 143.8, 130.6, 105.7, 67.8, 66.2, 51.6, 47.9, 38.8, 35.3.

HRMS (ESI$^+$): calcd. for C$_{14}$H$_{21}$N$_2$O$_3$ [M+H]$^+$: 265.1547, found 265.1546.

<table>
<thead>
<tr>
<th>2',2'-Dimethyl-3-morpholino-5,7-dihydrospiro[cyclopenta[c]pyridine-6,5'-[1,3]dioxane] (203)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="" alt="Chemical structure" /></td>
</tr>
</tbody>
</table>
| Chemical Formula: C$_{14}$H$_{21}$N$_2$O$_3$
| Exact Mass: 304.1787 |

This compound was obtained following the general procedure M. Starting from diyne 121 (96 mg, 0.5 mmol), 4-cyanomorpholine 156 (112 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH$_3$CN)$_3$PF$_6$ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 10 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 60/40) afforded 203 (132 mg, 87%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10$^{-3}$ mbar, 90 °C for 10 minutes). m.p. 125 – 127 °C.

Rf = 0.1 (Petroleum ether/Ethyl acetate; 80/20, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.00 (s, 1H), 6.51 (s, 1H), 3.84 – 3.77 (m, 4H), 3.70 (tt, $J$ = 11.3, 5.8 Hz, 4H), 3.46 – 3.35 (m, 4H), 2.83 (s, 2H), 2.72 (s, 2H), 1.45 (d, $J$ = 2.8 Hz, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 159.3, 153.3, 143.8, 127.8, 103.7, 98.2, 68.7, 66.9, 46.4, 42.8, 40.2, 36.4, 24.7, 23.2.

HRMS (ESI$^+$): calcd. for C$_{17}$H$_{25}$N$_2$O$_3$ [M+H]$^+$: 305.1860, found 305.1861.

<table>
<thead>
<tr>
<th>4-(2-Tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)morpholine (204)</th>
</tr>
</thead>
</table>
Experimental part

This compound was obtained following the general procedure N. Starting from diyne 122 (123.5 mg, 0.5 mmol), 4-cyanomorpholine 155 (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH3CN)3PF6 (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 2/1 to 0/1) afforded 204 (174 mg, 97%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes). m.p. 202 – 204 °C

Rf = 0.1 (Petroleum ether/Ethyl acetate; 70/30, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.01 (s, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 6.43 (s, 1H), 4.52 (s, 4H), 3.87 – 3.67 (m, 4H), 3.50 – 3.30 (m, 4H), 2.41 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 159.5, 147.8, 144.0, 142.1, 133.8, 130.0, 127.7, 122.5, 100.5, 66.8, 53.5, 51.4, 46.0, 21.7.


<table>
<thead>
<tr>
<th>tert-Butyl 6-morpholino-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxylate (205)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Formula: C₁₄H₁₈N₄O₃</td>
</tr>
<tr>
<td>Exact Mass: 305.1739</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure N. Starting from diyne 123 (96.5 mg, 0.5 mmol), 4-cyanomorpholine 155 (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH3CN)3PF6 (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 7/3 to 0/1) afforded 205 (151 mg, 99%) as a white solid. m.p. 195 – 197 °C.

Rf = 0.1 (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).
**Experimental part**

**1H NMR** (400 MHz, CDCl₃, 55 °C) δ 8.09 (s, 1H), 6.51 (s, 1H), 4.57 (s, 4H), 3.89 – 3.68 (m, 4H), 3.53 – 3.35 (m, 4H), 1.51 (s, 9H).

**13C NMR** (101 MHz, CDCl₃, 55 °C) δ 159.6, 154.6, 148.7, 142.2, 124.1, 100.8, 80.1, 66.9, 52.0, 49.8, 46.4, 28.7.


This compound was obtained following the general procedure N. Starting from diyne 109 (104 mg, 0.5 mmol), pyrrolidine-1-carbonitrile 156 (57 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 2 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 70/30) afforded 207 (144 mg, 90%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 3.0x10⁻³ mbar, 80 °C for 10 minutes). The analytical data were identical to the literature.¹²⁸

**Rᵣ = 0.42** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

**1H NMR** (300 MHz, CDCl₃) δ 7.96 (s, 1H), 6.22 (s, 1H), 3.74 (s, 6H), 3.47 (s, 4H), 3.44 – 3.30 (m, 4H), 2.07 – 1.87 (m, 4H).

**13C NMR** (75 MHz, CDCl₃) δ 172.0, 157.1, 151.0, 143.3, 123.3, 101.8, 60.8, 53.1, 47.0, 40.5, 37.6, 25.7.

**MS** (CI, NH₃): m/z = 305 [M + H]⁺.

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**Dimethyl 3-(pyrrolidin-1-yl)-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (207)**

This compound was obtained following the general procedure N. Starting from diyne 109 (104 mg, 0.5 mmol), pyrrolidine-1-carbonitrile 156 (57 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 2 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 70/30) afforded 207 (144 mg, 90%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 3.0x10⁻³ mbar, 80 °C for 10 minutes). The analytical data were identical to the literature.¹²⁸

**Rᵣ = 0.42** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

**1H NMR** (300 MHz, CDCl₃) δ 7.96 (s, 1H), 6.22 (s, 1H), 3.74 (s, 6H), 3.47 (s, 4H), 3.44 – 3.30 (m, 4H), 2.07 – 1.87 (m, 4H).

**13C NMR** (75 MHz, CDCl₃) δ 172.0, 157.1, 151.0, 143.3, 123.3, 101.8, 60.8, 53.1, 47.0, 40.5, 37.6, 25.7.

**MS** (CI, NH₃): m/z = 305 [M + H]⁺.

---

**Dimethyl 3-(dibenzylamino)-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (208)**

This compound was obtained following the general procedure N. Starting from diyne 109 (104 mg, 0.5 mmol), pyrrolidine-1-carbonitrile 156 (57 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 2 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 70/30) afforded 207 (144 mg, 90%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 3.0x10⁻³ mbar, 80 °C for 10 minutes). The analytical data were identical to the literature.¹²⁸

**Rᵣ = 0.42** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

**1H NMR** (300 MHz, CDCl₃) δ 7.96 (s, 1H), 6.22 (s, 1H), 3.74 (s, 6H), 3.47 (s, 4H), 3.44 – 3.30 (m, 4H), 2.07 – 1.87 (m, 4H).

**13C NMR** (75 MHz, CDCl₃) δ 172.0, 157.1, 151.0, 143.3, 123.3, 101.8, 60.8, 53.1, 47.0, 40.5, 37.6, 25.7.

**MS** (CI, NH₃): m/z = 305 [M + H]⁺.
Experimental part

This compound was obtained following the general procedure N. Starting from diyne 109 (104 mg, 0.5 mmol), N,N-dibenzylcyanamide 159 (133 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH3CN)3PF6 (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 10 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 208 (163 mg, 76%) as a pale yellow oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 5x10⁻³ mbar, 150 °C for 30 minutes).

Rf = 0.37 (Petroleum ether/Ethyl acetate; 85/15, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.02 (s, 1H), 7.35 – 7.14 (m, 10H), 6.33 (s, 1H), 4.76 (s, 4H), 3.74 (s, 6H), 3.50 (s, 2H), 3.42 (s, 2H).

¹³C NMR (75 MHz, CDCl₃) δ 172.0, 158.4, 151.6, 143.1, 138.7, 128.7, 127.2, 127.0, 124.6, 101.2, 60.6, 53.1, 51.3, 40.6, 37.6.

### Dimethyl 3-(diethylamino)-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (209)

This compound was obtained following the general procedure N. Starting from diyne 109 (104 mg, 0.5 mmol), N,N-diethylcyanamide 160 (59 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH3CN)3PF6 (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 10 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 209 (132 mg, 86%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0 x 10⁻³ mbar, 80 °C for 10 minutes). The analytical data were identical to the literature.¹²⁸

Rf = 0.22 (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).
Experimental part

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.95 (s, 1H), 6.32 (s, 1H), 3.74 (s, 6H), 3.54 – 3.40 (m, 8H), 1.15 (t, $J = 7.0$ Hz, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 172.1, 157.3, 151.1, 143.2, 123.0, 100.8, 60.7, 53.1, 42.8, 40.6, 37.6, 13.1.

MS (Cl, NH$_3$): m/z = 307 [M + H]$^+$

<table>
<thead>
<tr>
<th>Dimethyl 3-(dipropylamino)-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Chemical Structure]</td>
</tr>
<tr>
<td>Chemical Formula: C$<em>{18}$H$</em>{27}$N$_2$O$_4$</td>
</tr>
<tr>
<td>Exact Mass: 334.1893</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure N. Starting from diyne 109 (104 mg, 0.5 mmol), N,N-dipropylcyanamide 161 (76 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH$_3$CN)$_3$PF$_6$ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 210 (140 mg, 84%) as a pale yellow oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 5x10$^{-3}$ mbar, 100 °C for 10 minutes).

R$_f$ = 0.23 (Petroleum ether/Ethyl acetate; 80/20, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.94 (s, 1H), 6.27 (s, 1H), 3.74 (s, 6H), 3.51 – 3.40 (m, 4H), 3.40 – 3.28 (m, 4H), 1.68 – 1.47 (m, 4H), 0.91 (t, $J = 7.4$ Hz, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 172.1, 157.8, 151.0, 143.1, 122.9, 100.8, 60.7, 53.1, 51.0, 40.6, 37.6, 20.9, 11.6.

HRMS (ESI$^+$): calcd. for C$_{18}$H$_{27}$N$_2$O$_4$ [M+H]$^+$: 335.1965, found 335.1967.

<table>
<thead>
<tr>
<th>Dimethyl 3-(butyl(methyl)amino)-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (211)</th>
</tr>
</thead>
</table>
This compound was obtained following the general procedure N. Starting from diyne 109 (104 mg, 0.5 mmol), N-butyl-N-methylcyanamide 164 (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 70/30) afforded 211 (130 mg, 81\%) as a colorless oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes).

R_f = 0.24 (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.96 (s, 1H), 6.33 (s, 1H), 3.74 (s, 6H), 3.52 – 3.38 (m, 6H), 3.00 (s, 3H), 1.59 – 1.48 (m, 2H), 1.42 – 1.30 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 172.0, 158.4, 151.2, 143.0, 123.3, 101.0, 60.8, 53.1, 50.4, 40.6, 37.5, 36.7, 29.6, 20.4, 14.2.


Dimethyl 3-(methyl(phenyl)amino)-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (212)

This compound was obtained following the general procedure N. Starting from diyne 109 (104 mg, 0.5 mmol), N-methyl-N-phenylcyanamide 162 (79 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 10 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 212 (153 mg, 90\%) as a pale yellow solid. The analytical data were identical to the literature.¹³⁵a

R_f = 0.24 (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).
**Experimental part**

**$^1$H NMR** (300 MHz, CDCl$_3$) $\delta$ 8.04 (s, 1H), 7.51 – 7.32 (m, 2H), 7.31 – 7.13 (m, 3H), 6.40 (s, 1H), 3.73 (s, 6H), 3.49 (s, 2H), 3.44 (s, 3H), 3.37 (s, 2H).

**$^{13}$C NMR** (75 MHz, CDCl$_3$) $\delta$ 171.9, 158.5, 150.8, 147.3, 142.8, 129.8, 126.3, 125.7, 125.3, 104.8, 60.7, 53.1, 40.4, 38.9, 37.6.

**MS** (Cl, NH$_3$): $m/z = 341$ [M + H]$^+$

<table>
<thead>
<tr>
<th>Dimethyl 3-(benzyl(methyl)amino)-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (213)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C$<em>{20}$H$</em>{23}$N$_2$O$_4$</td>
</tr>
<tr>
<td>Exact Mass: 354.1580</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure N. Starting from diyne 109 (104 mg, 0.5 mmol), $N$-benzyl-$N$-methylcyanamide 158 (88 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH$_3$CN)$_3$PF$_6$ (2.5 mg, 0.005 mmol). The reaction mixture was stirred at room temperature for 2 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 70/30) afforded 213 (168 mg, 95%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0 x $10^{-3}$ mbar, 120 °C for 20 minutes). m.p. 136 – 138 °C.

$R_f$ = 0.17 (Petroleum ether/Ethyl acetate; 80/20, KMnO$_4$, UV).

**$^1$H NMR** (300 MHz, CDCl$_3$) $\delta$ 8.00 (s, 1H), 7.36 – 7.15 (m, 5H), 6.38 (s, 1H), 4.78 (s, 2H), 3.75 (s, 6H), 3.49 (s, 2H), 3.47 (s, 2H), 3.03 (s, 3H).

**$^{13}$C NMR** (75 MHz, CDCl$_3$) $\delta$ 172.0, 158.7, 151.5, 143.1, 139.1, 128.6, 127.2, 126.9, 124.1, 101.1, 60.7, 53.7, 53.1, 40.6, 37.6, 36.5.

**HRMS** (ESI$^+$): calcd. for C$_{20}$H$_{23}$N$_2$O$_4$ [M+H]$^+$: 355.1652, found 355.1654.

<table>
<thead>
<tr>
<th>N-Benzyl-$N$,4,7-trimethyl-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-amine (214)</th>
</tr>
</thead>
</table>
Experimental part

This compound was obtained following the general procedure N. Starting from diyne 108 (137.5 mg, 0.5 mmol), N-benzyl-N-methylcyanamide 158 (88 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH3CN)3PF6 (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 214 (203 mg, 97%) as a pale brown solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 120 °C for 20 minutes). m.p. 132 – 134 °C.

Rf = 0.3 (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.81 – 7.70 (m, 2H), 7.39 – 7.27 (m, 6H), 7.26 – 7.19 (m, 1H), 4.53 – 4.90 (m, 4H), 4.26 (s, 2H), 2.68 (s, 3H), 2.42 (s, 3H), 2.28 (s, 3H), 2.13 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 161.7, 147.2, 146.7, 143.9, 139.6, 134.0, 130.0, 128.4, 128.1, 127.7, 127.0, 124.0, 116.0, 58.1, 53.4, 52.5, 39.8, 21.7, 14.8.

HRMS (ESI⁺): calcd. for C₂₄H₂₈N₃O₂S [M+H]⁺: 422.1897, found 422.1890.

| 4-Methyl-6-morpholino-1,3-dihydrofuro[3,4-c]pyridine (217) |

This compound was obtained following the general procedure N. Starting from diyne 127 (54 mg, 0.5 mmol), 4-cyanomorpholine 155 (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH3CN)3PF6 (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 60/40) afforded 217 (95 mg, 86%, ratio > 99:1) as a pale yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes). m.p. 90 – 92 °C.
Experimental part

\( R_f = 0.17 \) (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

\( ^1H \) NMR (400 MHz, CDCl₃) \( \delta \) 6.33 (s, 1H, H₁), 5.02 – 4.97 (m, 4H, H₃, H₄, H₉), 3.87 – 3.77 (m, 4H, H₁₀), 3.49 – 3.42 (m, 4H, H₂), 2.31 (s, 3H, H₇).

\( ^13C \) NMR (101 MHz, CDCl₃) \( \delta \) 159.6 (C₈), 151.0 (C₂), 149.4 (C₆), 123.8 (C₃), 96.5 (C₁), 73.5 (C₄), 71.8 (C₉), 66.9 (C₁₀), 46.4 (C₉), 22.4 (C₇).

NOESY (400 MHz, CDCl₃) H₁ (6.33 ppm) correlate to H₃ (5.02 – 4.97 ppm) and H₉ (3.49 – 3.42 ppm), H₄ (5.02 – 4.97 ppm) correlates to H₇ (2.31 ppm), H₇ (6.33 ppm) does not correlates to H₉ (3.49 – 3.42 ppm).

HRMS (ESI⁺): calcd. for C₁₂H₁₇N₂O₂ [M+H]⁺: 221.1285, found 221.1285.

<table>
<thead>
<tr>
<th>4-(4-Methyl-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)morpholine (218)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C₁₉H₂₃N₃O₃S</td>
</tr>
<tr>
<td>Exact Mass: 373.1460</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure N. Starting from diyne 128 (130.5 mg, 0.5 mmol), 4-cyanomorpholine 155 (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 70/30) afforded 218 (168 mg, 90%, ratio > 99:1) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes), m.p. 169 – 172 °C.

\( R_f = 0.13 \) (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

\( ^1H \) NMR (400 MHz, CDCl₃) \( \delta \) 7.78 – 7.72 (m, 2H, H₄), 7.34 – 7.28 (m, 2H, H₃), 6.24 (s, 1H, H₁₃), 4.51 (s, 2H, H₆), 4.45 (s, 2H, H₇), 3.81 – 3.75 (m, 4H, H₁₅), 3.45 – 3.39 (m, 4H, H₁₄), 2.41 (s, 3H, H₁), 2.26 (s, 3H, H₁₁).
Experimental part

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 159.5 (C$_{12}$), 150.9 (C$_{10}$), 147.5 (C$_8$), 143.9 (C$_2$), 133.8 (C$_5$), 130.0 (C$_3$), 127.6 (C$_4$), 120.6 (C$_9$), 97.7 (C$_{13}$), 66.8 (C$_{15}$), 53.8 (C$_6$), 51.8 (C$_7$), 46.1 (C$_{14}$), 22.1 (C$_{11}$), 21.7 (C$_1$).

NOESY (400 MHz, CDCl$_3$) H$_{13}$ (6.24 ppm) correlate to H$_6$ (4.51 ppm) and H$_{14}$ (3.45 – 3.39 ppm), H$_7$ (4.45 ppm) correlates to H$_{11}$ (2.26 ppm), H$_{11}$ (2.26 ppm) does not correlates to H$_{14}$ (3.45 – 3.39 ppm).


### Dimethyl 1-bromo-4-methyl-3-morpholino-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (220)

![Chemical Structure]

This compound was obtained following the general procedure M. Starting from diyne 129 (150 mg, 0.5 mmol), 4-cyanomorpholine 155 (112 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH$_3$CN)$_3$PF$_6$ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 60 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 220 (161 mg, 78%, ratio = 96:4) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (condition: 1.0x10$^{-3}$ mbar, 90 °C for 10 minutes). m.p. 118 – 120 °C.

$R_t = 0.36$ (Petroleum ether/Ethyl acetate; 80/20, KMnO$_4$, UV).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.85 – 3.79 (m, 4H, H$_{12}$), 3.77 (s, 6H, H$_1$), 3.55 (s, 2H, H$_5$), 3.54 (s, 2H, H$_4$), 3.11 – 3.06 (m, 4H, H$_{11}$), 2.12 (s, 3H, H$_{13}$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.6 (C$_2$), 160.9 (C$_9$), 152.6 (C$_7$), 132.6 (C$_{10}$), 131.3 (C$_6$), 119.8 (C$_8$), 67.1 (C$_{12}$), 58.9 (C$_3$), 53.4 (C$_1$), 50.5 (C$_{11}$), 40.8 (C$_4$), 40.5 (C$_3$), 14.6 (C$_{13}$).

NOESY (400 MHz, CDCl$_3$) H$_{13}$ (2.12 ppm) correlate to H$_4$ (3.54 ppm) and H$_{11}$ (3.11 – 3.06 ppm).

<table>
<thead>
<tr>
<th>4-Bromo-7-methyl-6-morpholino-1,3-dihydrofuro[3,4-c]pyridine (221)</th>
</tr>
</thead>
</table>

This compound was obtained following the general procedure N. Starting from diyne 130 (93 mg, 0.5 mmol), 4-cyanomorpholine 155 (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₅PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at 50 °C for 2 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 221 (124 mg, 83%, ratio = 98:2) as a pale yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (condition: 1.0x10⁻³ mbar, 90 °C for 10 minutes). m.p. 108 – 110°C.

Rr = 0.19 (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

^1H NMR (400 MHz, CDCl₃) δ 5.07 (s, 2H, H₄), 5.03 – 4.95 (m, 2H, H₅), 3.88 – 3.77 (m, 4H, H₁₀), 3.18 – 3.08 (m, 4H, H₉), 2.10 (s, 3H, H₁).

^13C NMR (101 MHz, CDCl₃) δ 161.2 (C₈), 152.4 (C₃), 130.5 (C₆), 129.0 (C₇), 117.1 (C₂), 73.9 (C₄), 73.6 (C₅), 67.0 (C₁₀), 50.5 (C₉), 14.8 (C₁).

NOESY (400 MHz, CDCl₃) H₁ (2.10 ppm) correlate to H₄ (5.07 ppm) and H₉ (3.18 – 3.08 ppm).


<table>
<thead>
<tr>
<th>4-Bromo-6-morpholino-1,3-dihydrofuro[3,4-c]pyridine (222)</th>
</tr>
</thead>
</table>

Chemical Formula: C₁₁H₁₃BrN₂O₂  
Exact Mass: 284.0160
Experimental part

This compound was obtained following the general procedure N. Starting from diyne 131 (89 mg, 0.5 mmol), 4-cyanomorpholine 155 (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 2 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 60/40) afforded 222 (95 mg, 65%, ratio = 98:2) as a pale yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (condition: 1.0x10⁻³ mbar, 90 °C for 10 minutes). m.p. 122 – 124 °C.

Rᵣ = 0.1 (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (400 MHz, CDCl₃) δ 6.40 (s, 1H, H₁), 5.06 (dd, J = 2.7, 1.8 Hz, 2H, H₃), 4.94 (t, J = 1.8 Hz, 2H, H₄), 3.83 – 3.75 (m, 4H, H₉), 3.53 – 3.41 (m, 4H, H₈).

¹³C NMR (101 MHz, CDCl₃) δ 159.6 (C₇), 153.1 (C₂), 132.7 (C₆), 126.0 (C₅), 97.7 (C₁), 74.1 (C₃), 72.8 (C₄), 66.7 (C₉), 45.9 (C₈).

NOESY (400 MHz, CDCl₃) H₁ (6.40 ppm) correlate to H₃ (5.06 ppm) and H₈ (3.53 – 3.41 ppm).


\[\text{N-Benzyl-4-bromo-N,7-dimethyl-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-amine (223)}\]

This compound was obtained following the general procedure N. Starting from diyne 132 (169.5 mg, 0.5 mmol), N-benzyl-N-methylcyanamide 158 (88 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at 50 °C for 2 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 85/15) afforded 223 (182 mg, 75%, ratio = 98:2) as a white solid. m.p. 138-140 °C.

Rᵣ = 0.46 (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).
### Experimental part

**1H NMR** (400 MHz, CDCl$_3$) δ 7.80 – 7.72 (m, 2H, H$_4$), 7.40 – 7.35 (m, 2H, H$_3$), 7.35 – 7.29 (m, 4H, H$_{17,18}$), 7.29 – 7.22 (m, 1H, H$_{19}$), 4.51 (s, 2H, H$_6$), 4.53 – 4.49 (m, 2H, H$_7$), 4.29 (s, 2H, H$_{15}$), 2.72 (s, 3H, H$_{14}$), 2.43 (s, 3H, H$_1$), 2.09 (s, 3H, H$_{13}$).

**13C NMR** (101 MHz, CDCl$_3$) δ 162.1 (C$_{11}$), 148.8 (C$_8$), 144.2 (C$_2$), 138.6 (C$_{16}$), 133.6 (C$_{15}$), 130.1 (C$_{3,10}$), 128.5 (C$_{18}$), 128.0 (C$_{17}$), 127.7 (C$_4$), 127.2 (C$_{19}$), 126.5 (C$_9$), 117.4 (C$_{12}$), 57.8 (C$_{15}$), 54.1 (C$_6$), 53.7 (C$_7$), 39.6 (C$_{14}$), 21.7 (C$_1$), 15.0 (C$_{13}$).

**NOESY** (400 MHz, CDCl$_3$) H$_{13}$ (2.09 ppm) correlate to H$_6$ (4.51 ppm), H$_{15}$ (4.29 ppm) and H$_{14}$ (2.72 ppm).

### Dimethyl 1-iodo-4-methyl-3-morpholino-5,7-dihydro-6H-cyclopenta[e]pyridine-6,6-dicarboxylate (224)

![Chemical structure of Dimethyl 1-iodo-4-methyl-3-morpholino-5,7-dihydro-6H-cyclopenta[e]pyridine-6,6-dicarboxylate (224)]

This compound was obtained following the general procedure N. Starting from diyne 133 (174 mg, 0.5 mmol), 4-cyanomorpholine 155 (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH$_3$CN)$_3$PF$_6$ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at 50 °C for 30 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 224 (190 mg, 83%, ratio > 99:1) as a brown solid. The excess of cyanamide was removed by bulb to bulb distillation (condition: 1.0x10$^{-3}$ mbar, 90 °C for 10 minutes). m.p. 126 – 128°C.

**Rt = 0.14** (Petroleum ether/Ethyl acetate; 80/20, KMnO$_4$, UV).

**1H NMR** (400 MHz, CDCl$_3$) δ 3.84 – 3.79 (m, 4H, H$_{13}$), 3.77 (s, 6H, H$_1$), 3.57 (s, 2H, H$_6$), 3.49 (s, 2H, H$_5$), 3.10 – 3.03 (m, 4H, H$_{12}$), 2.11 (s, 3H, H$_{11}$).

**13C NMR** (101 MHz, CDCl$_3$) δ 171.6 (C$_2$), 160.9 (C$_9$), 150.6 (C$_6$), 136.4 (C$_7$), 120.1 (C$_{10}$), 109.8 (C$_8$), 67.1 (C$_{13}$), 58.3 (C$_3$), 53.4 (C$_1$), 50.5 (C$_{12}$), 43.3 (C$_5$), 41.0 (C$_4$), 14.6 (C$_{11}$).

**NOESY** (400 MHz, CDCl$_3$) H$_{11}$ (2.11 ppm) correlate to H$_4$ (3.57 ppm) and H$_{12}$ (3.10 – 3.03 ppm).
Experimental part

**HRMS (ESI+):** calcd. for C_{17}H_{21}N_{2}O_{5}Na [M+Na]^+: 483.0387, found 483.0385.

<table>
<thead>
<tr>
<th>3-(7-Methyl-6-morpholo-1,3-dihydrofuro[3,4-c]pyridin-4-yl)oxazolidin-2-one (225)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C_{18}H_{19}N_{3}O_{4}</td>
</tr>
<tr>
<td>Exact Mass: 305.1376</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure N. Starting from diyne 134 (96.5 mg, 0.5 mmol), morpholine-4-carbonitrile 155 (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH_{3}CN)_{3}PF_{6} (12.5 mg, 0.025 mmol). The reaction mixture was stirred at 50 °C for 16 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 60/40 to 50/50) afforded 225 (120 mg, 79%, ratio > 99:1) as a white solid. m.p. 202 – 204 °C.

**R_{f}** = 0.21 (Petroleum ether/Ethyl acetate; 50/50, KMnO_{4}, UV).

**^{1}H NMR** (300 MHz, CDCl_{3}) \(\delta 5.19 (s, 2H), 4.96 (s, 2H), 4.48 (t, J = 7.8 Hz, 2H), 4.22 (t, J = 7.9 Hz, 2H), 3.89 – 3.74 (m, 4H), 3.15 – 3.01 (m, 4H), 2.12 (s, 3H).

**^{13}C NMR** (75 MHz, CDCl_{3}) \(\delta 159.0, 155.1, 154.0, 140.1, 120.4, 114.5, 73.4, 72.5, 67.1, 62.9, 50.4, 44.9, 14.4.

**MS (CI, NH_{3}):** m/z = 306 [M + H]^+.

<table>
<thead>
<tr>
<th>3-(7-Methyl-6-(pyrrolidin-1-yl)-1,3-dihydrofuro[3,4-c]pyridin-4-yl)oxazolidin-2-one (226)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C_{18}H_{19}N_{3}O_{3}</td>
</tr>
<tr>
<td>Exact Mass: 289.1426</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure M. Starting from diyne 134 (96.5 mg, 0.5 mmol), pyrrolidine-1-carbonitrile 156 (96.1 mg, 1.0 mmol, 2.0 equiv) and
Cp*Ru(CH$_3$CN)$_3$PF$_6$ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at 50 °C for 2 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 60/40 to 50/50) afforded 226 (135 mg, 93%, ratio > 99:1) as a white solid. m.p. 177 – 179 °C.

**Rt = 0.6** (Petroleum ether/Ethyl acetate; 50/50, KMnO$_4$, UV).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.16 (s, 2H), 4.95 (s, 2H), 4.45 (t, $J = 7.9$ Hz, 2H), 4.21 (t, $J = 7.9$ Hz, 2H), 3.52 – 3.40 (m, 4H), 2.14 (s, 3H), 1.93 – 1.84 (m, 4H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 157.4, 155.2, 153.6, 139.2, 115.8, 109.3, 73.4, 72.6, 62.8, 50.1, 44.9, 25.6, 15.8.

**MS (Cl, NH$_3$):** m/z = 290 [M + H]$^+$. 


**Dimethyl 3-morpholino-1-vinyl-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (227)**

This compound was obtained following the general procedure N. Starting from diyne 135 (70 mg, 0.3 mmol), morpholine-4-carbonitrile 155 (40 mg, 0.36 mmol, 1.2 equiv) and Cp*Ru(CH$_3$CN)$_3$PF$_6$ (7.6 mg, 0.015 mmol). The reaction mixture was stirred at room temperature for 10 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 227 (94 mg, 90%, ratio > 99:1) as a white solid. m.p. 119 – 121 °C.

**Rt = 0.18** (Petroleum ether/Ethyl acetate; 80/20, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.70 (dd, $J = 17.1$, 10.6 Hz, 1H), 6.45 (s, 1H), 6.25 (dd, $J = 17.1$, 2.2 Hz, 1H), 5.42 (dd, $J = 10.6$, 2.2 Hz, 1H), 3.86 – 3.75 (m, 4H), 3.74 (s, 6H), 3.55 (s, 2H), 3.53 – 3.44 (m, 6H).
**Experimental part**

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.8, 158.8, 152.3, 147.9, 134.0, 124.1, 118.6, 102.3, 67.0, 60.3, 53.2, 46.1, 40.5, 37.7.

HRMS (ESI$^+$): calcd. for C$_{18}$H$_{23}$N$_2$O$_5$ [M+H]$^+$: 347.1601, found 347.1603.

<table>
<thead>
<tr>
<th>Dimethyl 3-(benzyl(methyl)amino)-1-vinyl-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (228)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure Diagram" /></td>
</tr>
</tbody>
</table>
| Chemical Formula: C$_{22}$H$_{26}$N$_4$O$_4$
| Exact Mass: 380.1736 |

This compound was obtained following the general procedure N. Starting from diyne 135 (70 mg, 0.3 mmol), N-benzyl-N-methylcyanamide 158 (53 mg, 0.36 mmol, 1.2 equiv) and Cp*Ru(CH$_3$CN)$_3$PF$_6$ (7.6 mg, 0.015 mmol). The reaction mixture was stirred at room temperature for 30 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 228 (105 mg, 92%, ratio > 99:1) as a white solid. m.p. 146 – 148 °C.

R$_r$ = 0.33 (Petroleum ether/Ethyl acetate; 80/20, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.35 – 7.18 (m, 5H), 6.72 (dd, $J$ = 17.1, 10.6 Hz, 1H), 6.33 (s, 1H), 6.27 (dd, $J$ = 17.1, 2.3 Hz, 1H), 5.39 (dd, $J$ = 10.6, 2.3 Hz, 1H), 4.83 (s, 2H), 3.75 (s, 6H), 3.56 (s, 2H), 3.47 (d, $J$ = 1.1 Hz, 2H), 3.05 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 172.0, 158.1, 152.1, 147.7, 139.4, 134.2, 128.6, 127.4, 126.9, 122.1, 118.2, 100.9, 60.3, 53.5, 53.2, 40.5, 37.6, 36.3.

MS (Cl, NH$_3$): m/z = 381 [M + H]$^+$.

<table>
<thead>
<tr>
<th>4-(2-Tosyl-4-vinyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)morpholine (229)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure Diagram" /></td>
</tr>
</tbody>
</table>
| Chemical Formula: C$_{20}$H$_{22}$N$_3$O$_3$S
| Exact Mass: 385.1460 |
This compound was obtained following the general procedure M. Starting from diyne 136 (136.5 mg, 0.5 mmol), morpholine-4-carbonitrile 155 (112 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH$_3$CN)$_3$PF$_6$ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 3 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 60/40) afforded 229 (145 mg, 75%, ratio > 99:1) as a white solid. m.p. 168 – 170 °C.

$R_f = 0.1$ (Petroleum ether/Ethyl acetate; 80/20, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.75 (d, $J = 8.3$ Hz, 2H), 7.31 (d, $J = 7.9$ Hz, 2H), 6.52 (dd, $J = 17.2$, 10.7 Hz, 1H), 6.35 (s, 1H), 6.18 (dd, $J = 17.2$, 1.9 Hz, 1H), 5.46 (dd, $J = 10.6$, 1.9 Hz, 1H), 4.56 (s, 2H), 4.51 (s, 2H), 3.85 – 3.70 (m, 4H), 3.53 – 3.40 (m, 4H), 2.40 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 159.0, 148.3, 147.3, 144.0, 133.8, 133.6, 130.0, 127.6, 120.1, 119.7, 99.9, 66.8, 53.4, 51.5, 45.9, 21.6.

MS (CI, NH$_3$): $m/z = 386$ [M + H]$^+$. 


8-Methyl-6-morpholino-3,4-dihydro-1H-pyrano[3,4-c]pyridine (230)

This compound was obtained following the general procedure N. Starting from diyne 138 (61 mg, 0.5 mmol), morpholine-4-carbonitrile 155 (112 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH$_3$CN)$_3$PF$_6$ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at 50 °C for 2 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 70/30) afforded 230 (95 mg, 81%, ratio > 99:1) as a white solid. m.p. 140 – 142 °C.

$R_f = 0.2$ (Petroleum ether/Ethyl acetate; 80/20, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.23 (s, 1H), 4.63 (s, 2H), 3.89 (t, $J = 5.6$ Hz, 2H), 3.85 – 3.75 (m, 4H), 3.48 – 3.35 (m, 4H), 2.76 (dt, $J = 5.8$, 2.9 Hz, 2H), 2.22 (s, 3H).
Experimental part

\[ ^{13}C \text{NMR} (75 \text{ MHz, CDCl}_3) \delta 158.0, 152.0, 144.1, 119.1, 104.0, 67.0, 65.8, 64.6, 46.2, 28.9, 21.1. \]

HRMS (ESI\(^+\)): calcd. for C\(_{13}\)H\(_{19}\)N\(_2\)O\(_2\) [M+H]\(^+\): 235.1441, found 235.1440.

<table>
<thead>
<tr>
<th>8-Methyl-6-(pyrrolidin-1-yl)-3,4-dihydro-1H-pyrano[3,4-c]pyridine (231)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical structure of 8-Methyl-6-(pyrrolidin-1-yl)-3,4-dihydro-1H-pyrano[3,4-c]pyridine" /></td>
</tr>
<tr>
<td>Chemical Formula: C(<em>{13})H(</em>{18})N(_2)O</td>
</tr>
<tr>
<td>Exact Mass: 218.1419</td>
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</tbody>
</table>

This compound was obtained following the general procedure N. Starting from diyne 138 (61 mg, 0.5 mmol), pyrrolidine-1-carbonitrile 156 (96.1 mg, 1.0 mmol, 2.0 equiv) and Cp\(^*\)Ru(CH\(_3\)CN)\(_3\)PF\(_6\) (12.5 mg, 0.025 mmol). The reaction mixture was stirred at 50 °C for 4 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 231 (50 mg, 46%, ratio > 99:1) as a white solid. m.p. 110 – 112 °C.

R\(_f\) = 0.28 (Petroleum ether/Ethyl acetate; 80/20, KMnO\(_4\), UV).

\[ ^1H \text{NMR} (400 \text{ MHz, CDCl}_3) \delta 5.96 (s, 1H), 4.64 (s, 2H), 3.89 (t, J = 5.7 Hz, 2H), 3.49 – 3.33 (m, 4H), 2.75 (t, J = 5.7 Hz, 2H), 2.22 (s, 3H), 2.03 – 1.91 (m, 4H). \]

\[ ^{13}C \text{NMR} (101 \text{ MHz, CDCl}_3) \delta 155.9, 151.9, 143.4, 115.9, 103.1, 66.0, 64.7, 46.8, 28.9, 25.7, 21.1. \]

MS (CI, NH\(_3\)): m/z = 219 [M + H]\(^+\).

<table>
<thead>
<tr>
<th>N-benzyl-N,8-dimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridin-6-amine (232)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical structure of N-benzyl-N,8-dimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridin-6-amine" /></td>
</tr>
<tr>
<td>Chemical Formula: C(<em>{17})H(</em>{20})N(_2)O</td>
</tr>
<tr>
<td>Exact Mass: 268.1576</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure N. Starting from diyne 138 (61 mg, 0.5 mmol), N-benzyl-N-methylcyanamide 158 (146 mg, 1.0 mmol, 2.0 equiv) and
Experimental part

Cp*Ru(CH\textsubscript{3}CN)\textsubscript{3}PF\textsubscript{6} (12.5 mg, 0.025 mmol). The reaction mixture was stirred at 50 °C for 4 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 232 (45 mg, 34%, ratio > 99:1) as a white solid m.p. 78 – 79 °C.

R\textsubscript{t} = 0.47 (Petroleum ether/Ethyl acetate; 75/25, KMnO\textsubscript{4}, UV).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 7.37 – 7.26 (m, 2H), 7.27 – 7.15 (m, 3H), 6.11 (s, 1H), 4.81 (s, 2H), 4.65 (s, 2H), 3.89 (t, J = 5.7 Hz, 2H), 3.00 (s, 3H), 2.85 – 2.62 (m, 2H), 2.23 (s, 3H).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 157.2, 151.7, 143.8, 139.4, 128.5, 127.4, 126.9, 116.7, 102.3, 65.9, 64.7, 53.0, 36.0, 29.0, 21.2.

MS (Cl, NH\textsubscript{3}): m/z = 269 [M + H]\textsuperscript{+}.

<table>
<thead>
<tr>
<th>4-(1-Methyl-7-tosyl-5,6,7,8-tetrahydro-2,7-naphthyridin-3-yl)morpholine (233)</th>
</tr>
</thead>
</table>

This compound was obtained following the general procedure N. Starting from diyne 139 (82.5 mg, 0.3 mmol), morpholine-4-carbonitrile 155 (67 mg, 0.6 mmol, 2.0 equiv) and Cp*Ru(CH\textsubscript{3}CN)\textsubscript{3}PF\textsubscript{6} (7.6 mg, 0.015 mmol). The reaction mixture was stirred at room temperature for 2 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 60/40) afforded 233 (100 mg, 86%, ratio > 99:1) as a white solid. m.p. 136 – 138 °C.

R\textsubscript{t} = 0.2 (Petroleum ether/Ethyl acetate; 80/20, KMnO\textsubscript{4}, UV).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 7.72 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 6.17 (s, 1H), 4.06 (s, 2H), 3.86 – 3.72 (m, 4H), 3.48 – 3.35 (m, 4H), 3.30 (t, J = 5.8 Hz, 2H), 2.82 (t, J = 5.7 Hz, 2H), 2.42 (s, 3H), 2.27 (s, 3H).

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 157.9, 153.4, 143.9, 143.8, 133.6, 129.9, 127.8, 116.1, 103.7, 66.9, 46.0, 45.0, 43.0, 29.5, 21.7.

MS (Cl, NH\textsubscript{3}): m/z = 388 [M + H]\textsuperscript{+}.
Experimental part

[Chemical Structure: (8R,9S,13S,14S,17S)-3-Methoxy-4',13-dimethyl-6'-morpholino-6,7,8,9,11,12,13,14,15,16-decahydro-3'H-spirocyclopenta[a]phenanthrene-17,1'-furo[3,4-c]pyridine (237)]

This compound was obtained following the general procedure N. Starting from diyne 143 (72.4 mg, 0.2 mmol), morpholine-4-carbonitrile 155 (27 mg, 0.24 mmol, 1.2 equiv) and Cp*Ru(CH$_3$CN)$_3$PF$_6$ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at 50°C for 2 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 237 (48.5 mg, 51%, ratio = 10:1) as a white solid. m.p. 208 – 210°C.

R$_f$ = 0.14 (Petroleum ether/Ethyl acetate; 90/10, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.12 (d, $J$ = 8.6 Hz, 1H), 6.68 (dd, $J$ = 8.6, 2.8 Hz, 1H), 6.62 (d, $J$ = 2.8 Hz, 1H), 6.30 (s, 1H), 4.93 – 4.78 (m, 2H), 3.91 – 3.80 (m, 4H), 3.77 (s, 3H), 3.61 – 3.35 (m, 4H), 2.98 – 2.78 (m, 2H), 2.31 (s, 3H), 2.28 – 2.17 (m, 1H), 2.15 – 1.94 (m, 4H), 1.87 – 1.78 (m, 1H), 1.74 – 1.55 (m, 3H), 1.46 – 1.26 (m, 4H), 1.06 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 159.8, 157.6, 156.9, 149.0, 137.9, 132.4, 126.4, 124.8, 114.0, 111.6, 98.9, 98.3, 69.9, 67.0, 55.3, 49.9, 48.3, 46.6, 43.9, 39.3, 36.3, 33.6, 30.0, 27.7, 26.4, 23.7, 22.2, 15.5.

MS (Cl, NH$_3$): m/z = 475 [M + H]$^+$. 

[Chemical Structure: 1-Butyl-3-morpholino-9H-indeno[2,1-c]pyridin-9-one (240)]
This compound was obtained following the general procedure M. Starting from diyne 29 (105 mg, 0.5 mmol), 4-cyanomorpholine 155 (112 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH3CN)3PF6 (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 10 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 240 (142 mg, 92%, ratio > 99:1) as a light yellow solid. m.p. 106 – 108 °C.

Rf = 0.12 (Petroleum ether/Ethyl acetate; 90/10, KMnO4, UV).

1H NMR (400 MHz, CDCl3) δ 7.69 – 7.64 (m, 1H, H1), 7.54 (dd, J = 7.3, 0.9 Hz, 1H, H4), 7.47 (td, J = 7.4, 1.2 Hz, 1H, H3), 7.40 (td, J = 7.4, 1.1 Hz, 1H, H2), 6.62 (s, 1H, H10), 3.86 – 3.81 (m, 4H, H18), 3.81 – 3.73 (m, 4H, H17), 3.09 – 3.01 (m, 2H, H13), 1.74 – 1.65 (m, 2H, H14), 1.50 – 1.36 (m, 2H, H15), 0.95 (t, J = 7.3 Hz, 3H, H16).

13C NMR (101 MHz, CDCl3) δ 191.3 (C7), 163.0 (C12), 161.0 (C11), 154.1 (C9), 140.8 (C5), 136.9 (C6), 133.3 (C3), 130.8 (C2), 123.6 (C1), 120.7 (C4), 116.1 (C8), 95.5 (C10), 66.8 (C18), 45.3 (C17), 34.1 (C13), 30.9 (C14), 22.8 (C15), 14.2 (C16).

NOESY (400 MHz, CDCl3) H10 (6.62 ppm) correlates to H17 (3.81 – 3.73 ppm).


<table>
<thead>
<tr>
<th>1-Butyl-3-(pyrrolidin-1-yl)-9H-indeno[2,1-c]pyridin-9-one (241)</th>
</tr>
</thead>
</table>

This compound was obtained following the general procedure M. Starting from diyne 29 (105 mg, 0.5 mmol), pyrrolidine-1-carbonitrile 156 (96.1 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH3CN)3PF6 (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 10 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 241 (133 mg, 87%, ratio > 99:1) as a light yellow solid. m.p. 90 – 91 °C.
**Experimental part**

\[ R_f = 0.4 \] (Petroleum ether/Ethyl acetate; 80/20, KMnO\(_4\), UV).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.70 – 7.61 (m, 1H, H\(_1\)), 7.58 – 7.52 (m, 1H, H\(_4\)), 7.49 – 7.43 (m, 1H, H\(_3\)), 7.42 – 7.35 (m, 1H, H\(_2\)), 6.37 (s, 1H, H\(_{10}\)), 3.62  (br, 4H, H\(_{17}\)), 3.07  (t, \( J = 7.6 \) Hz, 2H, H\(_{13}\)), 2.03  (br, 4H, H\(_{18}\)), 1.78 – 1.65 (m, 2H, H\(_{14}\)), 1.52 – 1.36 (m, 2H, H\(_{15}\)), 0.95 (t, \( J = 7.4 \) Hz, 3H, H\(_{16}\)).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 191.3 (C\(_7\)), 163.8 (C\(_{12}\)), 159.2 (C\(_{11}\)), 153.1 (C\(_9\)), 140.8 (C\(_5\)), 137.4 (C\(_8\)), 132.9 (C\(_3\)), 130.5 (C\(_2\)), 123.3 (C\(_1\)), 120.7 (C\(_4\)), 114.8 (C\(_8\)), 96.2 (C\(_{10}\)), 47.4 (C\(_{17}\)), 34.2 (C\(_{13}\)), 31.0 (C\(_{14}\)), 25.5(C\(_{17}\)), 22.9 (C\(_{15}\)), 14.2 (C\(_{16}\)).

NOESY (400 MHz, CDCl\(_3\)) H\(_{10}\) (6.37 ppm) correlates to H\(_{17}\) (3.62 ppm).

HRMS (ESI\(^+\)): calcd. for C\(_{20}\)H\(_{23}\)N\(_2\)O\(_1\) [M+H]\(^+\): 307.1805, found 307.1805.

This compound was obtained following the general procedure N. Starting from diyne 29 (105 mg, 0.5 mmol), N-benzyl-N-methylcyanamide 158 (88 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH\(_3\)CN)\(_3\)PF\(_6\) (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 30 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded 242 (142 mg, 80%, ratio > 99:1) as a yellow solid. m.p. 106 – 108 °C.

\[ R_f = 0.34 \] (Petroleum ether/Ethyl acetate; 90/10, KMnO\(_4\), UV).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.67 (dt, \( J = 7.1, 1.1 \) Hz, 1H), 7.58 – 7.50 (m, 1H, H\(_1\)), 7.50 – 7.38 (m, 2H), 7.38 – 7.24 (m, 5H), 6.57 (s, 1H), 4.99 (s, 2H), 3.20 (s, 3H), 3.15 – 3.04 (m, 2H), 1.80 – 1.67 (m, 2H), 1.52 – 1.40 (m, 2H), 0.93 (t, \( J = 7.3 \) Hz, 3H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 191.2, 163.2, 161.1, 154.0, 140.9, 138.1, 137.2, 133.0, 130.6, 128.8, 127.5, 127.4, 123.5, 120.7, 115.6, 95.1, 53.5, 36.5, 34.1, 30.8, 22.8, 14.2.

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3-(Benzyl(methyl)amino)-1-butyl-9H-indeno[2,1-c]pyridin-9-one (242)
HRMS (ESI\(^+\)): calcd. for C\(_{24}\)H\(_{25}\)N\(_2\)O\(_1\) [M+H]\(^+\): 357.1961, found 357.1961.

**1-Butyl-3-(piperidin-1-yl)-9H-indeno[2,1-c]pyridin-9-one (243)**

This compound was obtained following the general procedure N. Starting from diyne 29 (105 mg, 0.5 mmol), piperidine-1-carbonitrile 157 (66 mg, 0.6 mmol, 1.2 equiv) and Cp\(^*\)Ru(CH\(_3\)CN)\(_3\)PF\(_6\) (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 99/1 to 98/2) afforded 243 (125 mg, 78\%, ratio > 99:1) as a yellow solid. m.p. 100 – 102 °C.

R\(_f\) = 0.4 (Petroleum ether/Ethyl acetate; 90/10, KMnO\(_4\), UV).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.65 (dt, \(J\) = 7.1, 1.0 Hz, 1H), 7.55 (dt, \(J\) = 7.5, 1.0 Hz, 1H), 7.46 (td, \(J\) = 7.4, 1.3 Hz, 1H), 7.38 (td, \(J\) = 7.3, 1.2 Hz, 1H), 6.64 (s, 1H), 3.86 – 3.68 (m, 4H), 3.06 (t, \(J\) = 7.5 Hz, 2H), 1.78 – 1.60 (m, 8H), 1.52 – 1.31 (m, 2H), 0.95 (t, \(J\) = 7.3 Hz, 3H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 191.0, 163.3, 160.7, 153.7, 141.0, 137.3, 132.9, 130.5, 123.4, 120.6, 115.0, 95.4, 46.3, 34.2, 30.8, 25.9, 24.9, 22.8, 14.2.


**1-butyl-3-morpholino-9H-indeno[2,1-c]pyridin-9-ol (244)**

This compound was obtained following the general procedure M. Starting from diyne 28 (106 mg, 0.5 mmol), 4-cyanomorpholine 155 (112 mg, 1.0 mmol, 2.0 equiv) and
Experimental part

Cp*Ru(CH$_3$CN)$_3$PF$_6$ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 244 (110 mg, 68%, ratio > 99:1) as a light yellow solid. m.p. 156 – 158 ºC.

R$\text{f} = 0.18$ (Petroleum ether/Ethyl acetate; 80/20, KMnO$_4$, UV).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.67 – 7.52 (m, 2H, H$_1,4$), 7.46 – 7.32 (m, 2H, H$_2,3$), 6.58 (d, $J = 1.5$ Hz, 1H, H$_{10}$), 5.58 (s, 1H, H$_7$), 3.82 – 3.70 (m, 4H, H$_{18}$), 3.52 – 3.35 (m, 4H, H$_{17}$), 2.98 – 2.75 (m, 2H, H$_{13}$), 2.37 (br, 1H, OH), 1.80 – 1.65 (m, 2H, H$_{14}$), 1.50 – 1.35 (m, 2H, H$_{15}$), 0.96 (t, $J = 7.3$ Hz, 3H, H$_{16}$).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 160.2 (C$_{11}$), 158.2 (C$_{12}$), 150. 1 (C$_9$), 147.6 (C$_6$), 138.4 (C$_5$), 129.8 (C$_3$), 129.0 (C$_2$), 127.7 (C$_8$), 125.6 (C$_1$), 120.9 (C$_4$), 95.2 (C$_{10}$), 73.8 (C$_7$), 66.8 (C$_{18}$), 46.0 (C$_{17}$), 34.5 (C$_{13}$), 31.1 (C$_{14}$), 22.9 (C$_{15}$), 14.3 (C$_{16}$).

NOESY (400 MHz, CDCl$_3$) H$_{10}$ (6.58 ppm) correlates to H$_{17}$ (3.52 – 3.35 ppm).

HRMS (ESI$^+$): calcd. for C$_{20}$H$_{25}$N$_2$O$_2$ [M+H]$^+$: 325.1911, found 325.1912.

1-Butyl-3-(pyrrolidin-1-yl)-9H-indeno[2,1-c]pyridin-9-ol (245)

![Chemical Structure Image]

This compound was obtained following the general procedure N. Starting from diyne 28 (106 mg, 0.5 mmol), pyrrolidine-1-carbonitrile 156 (58 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH$_3$CN)$_3$PF$_6$ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 1 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 245 (124 mg, 81%, ratio > 99:1) as a yellow solid. m.p. 170 – 171 ºC.

R$\text{f} = 0.23$ (Petroleum ether/Ethyl acetate; 80/20, KMnO$_4$, UV).
Experimental part

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.68 – 7.52 (m, 2H), 7.46 – 7.29 (m, 2H), 6.26 (s, 1H), 5.58 (s, 1H), 3.45 – 3.24 (m, 4H), 3.11 – 2.63 (m, 2H), 2.42 (br, 1H), 1.95 – 1.81 (m, 4H), 1.80 – 1.67 (m, 2H), 1.49 – 1.34 (m, 2H), 0.95 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 158.6, 158.0, 149.4, 147.9, 138.8, 129.4, 128.7, 125.5, 124.7, 120.8, 94.7, 73.9, 46.9, 34.6, 31.4, 25.5, 23.0, 14.3.


### 1-Butyl-3-(pyrrolidin-1-yl)-5H-indeno[1,2-c]pyridin-5-ol (246)

This compound was obtained following the general procedure N. Starting from diyne 149 (106 mg, 0.5 mmol), pyrrolidine-1-carbonitrile 156 (58 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH$_3$CN)$_3$PF$_6$ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded 246 (110 mg, 71%, ratio = 99:1) as a slight pink solid. m.p. 140 – 142 °C.

Rf = 0.2 (Petroleum ether/Ethyl acetate; 90/10, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.66 – 7.55 (m, 1H), 7.44 (d, $J = 7.7$ Hz, 1H), 7.34 (td, $J = 7.5$, 1.2 Hz, 1H), 7.19 (td, $J = 7.4$, 1.0 Hz, 1H), 6.20 (s, 1H), 5.33 (s, 1H), 3.78 – 3.50(br, 1H), 3.37 – 3.10 (m, 4H), 2.91 – 2.61 (m, 2H), 1.86 – 1.59 (m, 6H), 1.53 – 1.37(m, 2H), 0.96 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 156.3, 155.3, 144.7, 139.7, 129.0, 125.3, 125.2, 121.1, 100.4, 74.50, 46.7, 36.0, 30.4, 25.2, 22.9, 14.2.

MS (Cl, NH$_3$): m/z = 309 [M + H]$^+$.

### 1-Cyclopropyl-3-(pyrrolidin-1-yl)-5H-indeno[1,2-c]pyridin-5-ol (247)
This compound was obtained following the general procedure N. Starting from diyne 152 (56 mg, 0.3 mmol), pyrrolidine-1-carbonitrile 156 (35 mg, 0.36 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (7.5 mg, 0.015 mmol). The reaction mixture was stirred at room temperature for 3 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 60/40 to 50/50) afforded 247 (68 mg, 78%, ratio > 99:1) as a white solid. m.p. 210 – 212 °C.

Rf = 0.23 (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (400 MHz, DMSO-d₆) δ 7.82 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 7.3 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.18 (t, J = 7.4 Hz, 1H), 6.46 (s, 1H), 5.85 (d, J = 7.4 Hz, 1H), 5.37 (d, J = 7.4 Hz, 1H), 3.40 (s, 4H), 2.50 – 2.41 (m, 1H), 2.01 – 1.82 (m, 4H), 1.19 – 1.01 (m, 2H), 1.01 – 0.87 (m, 2H).

¹³C NMR (101 MHz, DMSO-d₆) δ 157.6, 155.6, 153.7, 145.3, 139.2, 128.4, 125.0, 124.9, 121.0, 120.7, 99.8, 73.0, 46.3, 25.0, 14.6, 8.4, 7.9.

HRMS (ESI⁺): calcd. for C₁₉H₂₁N₂O₁ [M+H]⁺: 293.1648, found 293.1649.

1-Cyclopropyl-3-(pyrrolidin-1-yl)-5H-indeno[1,2-c]pyridin-5-one (248)

This compound was obtained following the general procedure N. Starting from diyne 153 (58.2 mg, 0.3 mmol), pyrrolidine-1-carbonitrile 156 (58 mg, 0.6 mmol, 2.0 equiv) and Cp*Ru(CH₃CN)₃PF₆ (7.6 mg, 0.015 mmol). The reaction mixture was stirred at room temperature for 10 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from
98/2 to 90/10 afforded 248 (77 mg, 89%, ratio = 94:6) as a dark purple solid. m.p. 162 – 163 °C.

Rt = 0.6 (Petroleum ether/Ethyl acetate; 90/10, KMnO₄, UV).

**¹H NMR** (300 MHz, CDCl₃) δ 7.73 – 7.58 (m, 2H, H₄,₁), 7.49 – 7.37 (m, 1H, H₃), 7.17 – 7.02 (m, 1H, H₂), 6.50 (s, 1H, H₁₄), 3.56 – 3.36 (m, 4H, H₁₅), 2.35 – 2.19 (m, 1H, H₁₁), 2.04 – 1.88 (m, 4H, H₁₆), 1.24 – 1.15 (m, 2H, H₁₂), 1.02 – 0.91 (m, 2H, H₁₂).

**¹³C NMR** (75 MHz, CDCl₃) δ 194.8, 157.2, 155.5, 147.0, 143.3, 135.5, 133.8, 126.0, 124.9, 121.82, 121.6, 99.2, 47.0, 25.5, 15.0, 8.4.

**NOESY** (400 MHz, CDCl₃) H₄ (7.73 – 7.58 ppm) correlates to H₁₁ (2.35 – 2.19 ppm), H₁₄ (6.50 ppm) correlates to H₁₅ (3.56 – 3.36 ppm).


### 4. Formation of enantioenriched 1,3-dihydroisobenzofuran derivatives

#### 4.1. Synthesis of prochiral triynes

**General procedure O:**

![Chemical structure](image)

In an oven-dried Argon-filled round bottom flask, n-butyl lithium (2 equiv) was added slowly to a solution of alkyne (2 equiv) in THF (5 M) at -50 °C, and the resulting mixture was stirred at -50 °C for 1 h. Acetyl chloride (1 equiv) was added at the same temperature, and the resulting mixture was allowed to warm to room temperature for 14-18 h. The reaction was quenched with water and extracted with ethyl acetate (×3). The combined organic layers were washed with water and brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desired compound.

**General procedure P:**

---

325
Experimental part

To a stirred mixture of 2-butyn-1,4-diol 52 (1 equiv) and pyridine (2.5 equiv) in DCM (0.5 M) was cooled at 0 °C in an ice bath. Acyl chloride (3 equiv) was then added in DCM (0.5 M). The reaction mixture was stirred at room temperature for 18 h until completion (TLC monitoring). The organic layer was washed with water (×3) and brine (×3), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desired compound.

3-Methyl-1,5-diphenylpenta-1,4-diyn-3-ol (249)

This compound was obtained following the general procedure O. Starting from acetyl chloride (0.89 mL, 12.5 mmol), phenylacetylene (2.75 mL, 25 mmol, 2 equiv) and nBuLi (25 mmol, 2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate; 90/10) afforded 249 (2.2 g, 70%) as a white solid. m.p. 110 – 112 °C.

Rf = 0.4 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.54 – 7.44 (m, 4H), 7.37 – 7.28 (m, 6H), 2.80 – 2.73 (m, 1H), 1.97 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 132.0, 128.8, 128.4, 122.2, 90.2, 82.8, 61.0, 32.1.

MS (Cl, NH₃): m/z = 229 [M - H₂O + H]+.

1-Phenyl-3-(phenylethynyl)hex-1-yn-3-ol (250)
This compound was obtained following the general procedure O. Starting from butyl chloride (0.52 mL, 5 mmol), phenylacetylene (1.09 mL, 10 mmol, 2 equiv) and nBuLi (10 mmol, 2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded \(\textbf{250}\) (1.17 g, 85%) as a white solid. m.p. 73 – 75 °C.

\[ R_f = 0.4 \] (Cyclohexane/Ethyl acetate; 90/10, KMnO\(_4\), UV).

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 7.51 – 7.44 (m, 4H), 7.36 – 7.28 (m, 6H), 2.66 (s, 1H), 2.12 – 2.03 (m, 2H), 1.82 – 1.69 (m, 2H), 1.05 (t, \(J = 7.4\) Hz, 3H).

\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \(\delta\) 132.0, 128.8, 128.4, 122.3, 89.5, 83.7, 64.7, 46.3, 18.3, 14.1.

\(\text{MS (Cl, NH}_3\)): m/z = 257 [M - H\(_2\)O + H]^+.

<table>
<thead>
<tr>
<th>3-(\textit{tert}-Butyl)-1,5-diphenylpenta-1,4-diyn-3-ol (251)</th>
</tr>
</thead>
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<tr>
<td><img src="image" alt="Chemical Structure" /></td>
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<tr>
<td>Chemical Formula: C(<em>{23})H(</em>{20})O</td>
</tr>
<tr>
<td>Exact Mass: 288.1514</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure O. Starting from pivaloyl chloride (1.23 mL, 10 mmol), phenylacetylene (2.2 mL, 20 mmol, 2 equiv) and nBuLi (20 mmol, 2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate; 95/5) afforded \(\textbf{251}\) (2.6 g, 90%) as a white solid. m.p. 83 – 85 °C.

\[ R_f = 0.5 \] (Cyclohexane/Ethyl acetate; 90/10, KMnO\(_4\), UV).

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 7.54 – 7.46 (m, 4H), 7.36 – 7.30 (m, 6H), 2.64 – 2.60 (m, 1H), 1.29 (s, 9H).

\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \(\delta\) 132.0, 128.7, 128.4, 122.6, 88.9, 84.4, 71.8, 40.8, 25.1.

\(\text{MS (Cl, NH}_3\)): m/z = 271 [M - H\(_2\)O + H]^+.

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<th>1,3,5-Triphenylpenta-1,4-diyn-3-ol (252)</th>
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<td>Exact Mass: 414.1703</td>
</tr>
</tbody>
</table>

327
Experimental part

This compound was obtained following the general procedure O. Starting from benzoyl chloride (1.16 mL, 10 mmol), phenylacetylene (2.2 mL, 20 mmol, 2 equiv) and nBuLi (20 mmol, 2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate; 90/10) afforded 252 (3.06 g, 99%) as a yellow oil. The analytical data were identical to the literature.206

R<sub>f</sub> = 0.33 (Cyclohexane/Ethyl acetate; 90/10, KMnO<sub>4</sub>, UV).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.01 – 7.88 (m, 2H), 7.60 – 7.27 (m, 13H), 3.09 (br, 1H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 143.5, 131.8, 129.4, 129.1, 128.7, 128.6, 126.0, 121.9, 91.3, 83.8, 64.7.

MS (Cl, NH<sub>3</sub>): m/z = 291 [M – H<sub>2</sub>O + H]<sup>+</sup>.

<table>
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<tr>
<th>7-Phenyltrideca-5,8-diyn-7-ol (253)</th>
</tr>
</thead>
<tbody>
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<td><img src="" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure O. Starting from benzoyl chloride (1.16 mL, 10 mmol), 1-hexyne (2.3 mL, 20 mmol, 2 equiv) and nBuLi (20 mmol, 2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 253 (2.45 g, 91%) as a colorless oil.

R<sub>f</sub> = 0.3 (Cyclohexane/Ethyl acetate; 90/10, KMnO<sub>4</sub>, UV).

Experimental part

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.86 – 7.72 (m, 2H), 7.46 – 7.27 (m, 3H), 2.73 (s, 1H), 2.29 (t, $J = 7.0$ Hz, 4H), 1.59 – 1.33 (m, 8H), 0.92 (t, $J = 7.2$ Hz, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 143.2, 128.4, 125.9, 85.9, 81.3, 65.4, 30.6, 22.1, 18.7, 13.7.

**MS** (Cl, NH$_3$): m/z = 251 [M - H$_2$O + H]$^+$.  

(3-Methyl-3-(prop-2-yn-1-yloxy)penta-1,4-diyne-1,5-diyldibenzene (254)

This compound was obtained following the general procedure F. Starting from 3-methyl-1,5-diphenylpenta-1,4-diyne-3-ol 249 (1 g, 4.1 mmol), propargyl bromide (0.58 mL, 5.3 mmol, 1.3 equiv) and sodium hydride (0.22 g, 5.3 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 254 (1 g, 87%) as a white solid. m.p. 50 – 52 °C.

$R_t = 0.6$ (Cyclohexane/Ethyl acetate; 90/10, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.55 – 7.44 (m, 4H), 7.39 – 7.28 (m, 6H), 4.59 – 4.53 (m, 2H), 2.52 – 2.46 (m, 1H), 1.99 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 132.0, 128.9, 128.4, 122.1, 87.3, 85.0, 80.3, 74.3, 67.3, 54.3, 31.1.

**MS** (Cl, NH$_3$): m/z = 229 [M – C$_3$H$_4$O + H]$^+$.  

(3-(But-2-yn-1-yloxy)-3-methylpenta-1,4-diyne-1,5-diyldibenzene (255)
Experimental part

This compound was obtained following the general procedure F. Starting from 3-methyl-1,5-diphenylpenta-1,4-diyn-3-ol 249 (3.2 g, 13.1 mmol), 1-bromo-2-butyne (1.4 mL, 16 mmol, 1.2 equiv) and sodium hydride (0.64 g, 16 mmol, 1.2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 255 (3 g, 76%) as a white solid. m.p. 110 – 112 °C.

Rf = 0.6 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

ⁱH NMR (300 MHz, CDCl₃) δ 7.52 – 7.45 (m, 4H), 7.37 – 7.30 (m, 6H), 4.52 (q, J = 2.4 Hz, 2H), 1.98 (s, 3H), 1.88 (t, J = 2.4 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 132.0, 128.9, 128.4, 122.2, 87.5, 84.8, 82.6, 75.4, 66.9, 54.9, 31.2, 4.0.

MS (Cl, NH₃): m/z = 229 [M - C₄H₆O + H]⁺.

(3-(But-2-yn-1-yloxy)-3-propylpenta-1,4-diyne-1,5-diyl)dibenzene (256)

This compound was obtained following the general procedure F. Starting from 1-phenyl-3-(phenylethynyl)hex-1-yn-3-ol 250 (0.27 g, 1 mmol), 1-bromo-2-butyne (0.1 mL, 1.2 mmol, 1.2 equiv) and sodium hydride (0.052 g, 1.3 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded 256 (0.24 g, 74%) as a pale yellow sticky oil. The melting point was difficult to determine.

Rf = 0.65 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.57 – 7.41 (m, 4H), 7.38 – 7.28 (m, 6H), 4.53 (q, J = 2.4 Hz, 2H), 2.18 – 2.06 (m, 2H), 1.87 (t, J = 2.4 Hz, 3H), 1.83 – 1.71 (m, 2H), 1.03 (t, J = 7.4 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 132.0, 128.8, 128.4, 122.4, 87.0, 85.6, 82.4, 75.6, 70.8, 54.7, 45.4, 18.2, 14.1, 4.0.
Experimental part

**MS** (CI, NH₃): m/z = 257 [M - C₆H₆O + H]⁺.

<table>
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<tr>
<th>(3-(But-2-yn-1-yloxy)-3-(tert-butyl)penta-1,4-diyne-1,5-diyl)dibenzene (257)</th>
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This compound was obtained following the general procedure F. Starting from 3-(tert-butyl)-1,5-diphenylpenta-1,4-diyne-3-ol 251 (2.6 g, 9 mmol), 1-bromo-2-butyne (0.95 mL, 11 mmol, 1.2 equiv) and sodium hydride (0.44 g, 11 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded 257 (2.15 g, 70%) as a white solid. m.p. 82 – 84 °C.

**Rf** = 0.5 (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

**¹H NMR** (300 MHz, CDCl₃) δ 7.45 – 7.35 (m, 4H), 7.29 – 7.12 (m, 6H), 4.45 (q, J = 2.4 Hz, 2H), 1.78 (t, J = 2.4 Hz, 3H), 1.18 (s, 9H).

**¹³C NMR** (75 MHz, CDCl₃) δ 132.0, 128.7, 128.4, 122.6, 86.5, 86.2, 81.8, 78.0, 76.1, 55.1, 41.0, 25.5, 4.0.

**MS** (CI, NH₃): m/z = 271 [M - C₆H₆O + H]⁺.

<table>
<thead>
<tr>
<th>(3-(But-2-yn-1-yloxy)penta-1,4-diyne-1,3,5-triyl)tribenzene (258)</th>
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<tr>
<td><img src="image" alt="Chemical structure" /></td>
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<tr>
<td>Chemical Formula: C₃₀H₂₄O</td>
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<td>Exact Mass: 360.1514</td>
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This compound was obtained following the general procedure F. Starting from 1,3,5-triphenylpenta-1,4-diyne-3-ol 252 (3.06 g, 10 mmol), 1-bromo-2-butyne (1.05 mL, 12 mmol, 1.2 equiv) and sodium hydride (0.52 g, 13 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate; 95/5) afforded 258 (3.23 g, 90%) as a pale yellow solid.
Experimental part

**Rf = 0.5** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

**¹H NMR** (300 MHz, CDCl₃) δ 7.98 – 7.87 (m, 2H), 7.58 – 7.47 (m, 4H), 7.47 – 7.28 (m, 9H), 4.53 (q, J = 2.4 Hz, 2H), 1.85 (t, J = 2.4 Hz, 3H).

**¹³C NMR** (75 MHz, CDCl₃) δ 140.4, 132.1, 129.0, 128.5, 128.4, 127.0, 122.2, 87.4, 86.5, 82.7, 75.4, 72.2, 54.7, 4.0.

**MS** (CI, NH₃): m/z = 291 [M - C₄H₆O + H]⁺.

<table>
<thead>
<tr>
<th>(7-(But-2-yn-1-yloxy)trideca-5,8-diyn-7-yl)benzene (259)</th>
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<td><img src="image" alt="Chemical Structure" /></td>
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</tbody>
</table>

This compound was obtained following the general procedure F. Starting from 7-phenyltrideca-5,8-diyn-7-ol 253 (1.34 g, 5 mmol), 1-bromo-2-butyne (0.57 mL, 6.5 mmol, 1.3 equiv) and sodium hydride (0.26 g, 6.5 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded 259 (1.4 g, 88%) as a colorless oil.

**Rf = 0.5** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

**¹H NMR** (300 MHz, CDCl₃) δ 7.85 – 7.70 (m, 2H), 7.42 – 7.27 (m, 3H), 4.32 (q, J = 2.4 Hz, 2H), 2.30 (t, J = 7.0 Hz, 4H), 1.83 (t, J = 2.4 Hz, 3H), 1.61 – 1.48 (m, 4H), 1.48 – 1.35 (m, 4H), 0.92 (t, J = 7.2 Hz, 6H).

**¹³C NMR** (75 MHz, CDCl₃) δ 141.2, 128.5, 128.2, 126.9, 87.9, 82.1, 78.4, 75.7, 71.5, 54.0, 30.6, 22.1, 18.7, 13.7, 3.9.

**MS** (CI, NH₃): m/z = 251 [M - C₄H₆O + H]⁺.

<table>
<thead>
<tr>
<th>Trimethyl(3-((3-methyl-1,5-diphenylpenta-1,4-diyn-3-yl)oxy)prop-1-yn-1-yl)silane (260)</th>
</tr>
</thead>
</table>

332
To a solution of (3-methyl-3-(prop-2-yn-1-yloxy)penta-1,4-diyne-1,5-diyl)dibenzene 254 (0.43 g, 1.5 mmol) in anhydrous THF (4 mL) was slowly added nBuLi (2.3 M in hexane, 0.72 mL, 1.65 mmol, 1.1 equiv) at -70 °C. The solution was stirred at the same temperature for 30 min. To the resulting mixture was added chlorotrimethylsilane (0.14 mL, 1.65 mmol, 1.1 equiv) at -70 °C, and the reaction mixture was allowed to warm to room temperature and stirred for additional 1.5 h. The reaction was quenched with saturated aqueous NH₄Cl (1.0 mL). The aqueous layer was extracted with diethyl ether (3×20 mL), and the combined organic layers were washed with brine, dried with MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) to afford 260 (0.5 g, 93%) as a pale yellow solid. m.p. 70 – 72 °C.

Rᵣ = 0.3 (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.55 – 7.41 (m, 4H), 7.39 – 7.27 (m, 6H), 4.59 (d, J = 0.8 Hz, 2H), 1.99 (d, J = 0.8 Hz, 3H), 0.18 (d, J = 0.7 Hz, 9H).

¹³C NMR (75 MHz, CDCl₃) δ 132.1, 128.9, 128.4, 122.2, 101.9, 91.1, 87.4, 85.0, 67.2, 55.0, 31.1, 0.0.

MS (Cl, NH₃): m/z = 229 [M – C₆H₁₁OSi + H]⁺.

4.2. Synthesis of internal alkynes

But-2-yne-1,4-diyl diacetate (262)
Experimental part

This compound was obtained following the general procedure P. Starting from 2-butyne-1,4-diol 52 (1.72 g, 20 mmol), acetyl chloride (4.3 mL, 60 mmol, 3 equiv) and pyridine (4 mL, 50 mmol, 2.5 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate; 80/20) afforded 262 (3.25 g, 96%) as a colorless oil. The analytical data were identical to the literature.\textsuperscript{207}

$$R_f = 0.4 \text{(Cyclohexane/Ethyl acetate; 70/30, KMnO}_4, \text{ UV)}.$$  

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.69 (s, 4H), 2.07 (s, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.2, 80.8, 52.1, 20.7.

<table>
<thead>
<tr>
<th>But-2-yne-1,4-diy I bis(2,2-dimethylpropanoate) (263)</th>
</tr>
</thead>
</table>
| \[
\text{HO-} \underset{\text{R}}{\text{C=CH=CH}} \text{-OH}
\]
| $\text{DMAP \, 5 \text{ mol \%}}$ \text{iPr$_2$NEt \, 4 \text{ equiv}}$ |
| \[
\text{O} \underset{\text{O}}{\text{C-Cl}}
\]
| DCM, 0 °C to rt, 3 h |
| $\text{R}_\text{Bu}$ |
| $\text{O}$ $\text{O}$ |
| $\text{R}_\text{Bu}$ |
| $\text{C}_4\text{H}_8\text{O}_4$ |
| But-2-yne-1,4-diy I dibenzoate (264) |

To a stirred mixture of 2-butyne-1,4-diol 52 (0.86 g, 10 mmol, 1 equiv) and iPr$_2$NEt (6.7 mL, 40 mmol, 4 equiv) in DCM (20 mL) was cooled at 0 °C in an ice bath. DMAP (0.1 g, 0.5 mmol, 5 mol %) and pivaloyl chloride (3.69 mL, 30 mmol, 3 equiv) in DCM (20 mL) were then introduced. The reaction mixture was stirred at room temperature for 3 h until completion (TLC monitoring). The organic layer was washed with water (3×30 mL) and brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/Ethyl acetate; 80/20) to afford 263 (2.5 g, 98%) as a colorless oil.

$$R_f = 0.3 \text{(Cyclohexane/Ethyl acetate; 90/10, KMnO}_4, \text{ UV)}.$$  

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.69 (s, 4H), 1.21 (s, 18H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 177.8, 80.8, 52.3, 38.9, 27.2.

This compound was obtained following the general procedure P. Starting from 2-butyne-1,4-diol 52 (1.72 g, 20 mmol), benzoyl chloride (5.8 mL, 50 mmol, 2.5 equiv) and pyridine (4 mL, 50 mmol, 2.5 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate; 90/10) afforded 264 (5.6 g, 95%) as a white solid. m.p. 80 – 82 °C.

\[ \text{Rf} = 0.3 \text{ (Cyclohexane/Ethyl acetate; 90/10, KMnO}_4, \text{ UV).} \]

\[^1\text{H NMR} \text{ (300 MHz, CDCl}_3\text{)} \delta 8.13 – 8.02 \text{ (m, 4H), 7.63 – 7.51 \text{ (m, 2H), 7.51 – 7.39 \text{ (m, 4H), 5.00 \text{ (s, 4H).} } }\]

\[^{13}\text{C NMR} \text{ (75 MHz, CDCl}_3\text{)} \delta 165.9, 133.5, 130.0, 129.6, 128.6, 81.1, 52.8.\]

\[^{\text{MS}} \text{ (Cl, NH}_3\text{): m/z = 312 [M + NH}_4\text{]}^+.\]

<table>
<thead>
<tr>
<th>But-2-yne-1,4-diyl bis(4-methylbenzenesulfonate) (265)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>

In a round bottom flask, 2-butyne-1,4-diol 52 (2.15 g, 25.0 mmol) was dissolved in THF (50 mL) and combined with NaOH (3.5 g, 87 mmol, 3.5 equiv) in water (50 mL). The flask was cooled to 0 °C (ice bath), and a solution of p-toluenesulfonyl chloride (10.5 g, 55.0 mmol, 2.2 equiv) in THF (50 mL) was added dropwise. The resulting mixture was stirred at 0 °C for 2 h until complete reaction. The product was then extracted with ethyl acetate (2×50 mL) and washed with saturated NaHCO\textsubscript{3} (3×30 mL), water (2×50 mL), and brine (50 mL). The organic layer was dried over anhydrous MgSO\textsubscript{4}, filtered and concentrated under reduced pressure to
Experimental part

give the product 265 as a grey solid (8.2 g, 83%). m.p. 98-100 °C. The analytical data were identical to the literature.208

\[ R_f = 0.21 \] (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

\(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.81 – 7.71 (m, 4H), 7.39 – 7.30 (m, 4H), 4.58 (s, 4H), 2.45 (s, 6H).

\(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 145.5, 133.0, 130.0, 128.2, 81.1, 57.2, 21.8.

4.3. Rhodium-catalyzed [2+2+2] cycloaddition of triynes and alkynes

General procedure Q:

In a vacuum line, an oven-dried Schlenk tube was degassed and purged with argon three times. Rh(cod)₂BF₄ (5 mol %) and (R)-BINAP (5 mol%) were introduced under argon. The Schlenk flask was then degassed and purged with argon three additional times. Under argon, freshly distilled and degassed DCM (1.0 mL) was added and the mixture was allowed to stir at room temperature for 30 min. A solution of the corresponding alkyne (2 equiv) in distilled DCM (1.0 mL) was then introduced under argon. The Schlenk flask was tightly sealed and allowed to stir at room temperature for additional 10 minutes. A solution of the corresponding triyne (1 equiv) in distilled DCM (1.0 mL) was finally added dropwise at room temperature. The reaction mixture allowed to stir at 40 °C for 20-24 h, concentrated under reduced pressure, and the residue was purified by flash chromatography to afford the desired product.

| (1,4-Dimethyl-7-phenyl-1-(phenylethynyl)-1,3-dihydroisobenzofuran-5,6-diyl)bis (methylene) diacetate (266) |

---

This compound was obtained following the general procedure Q. Starting from (3-(but-2-yn-1-yloxy)-3-methylpenta-1,4-diyne-1,5-diyl)dibenzene 255 (119 mg, 0.4 mmol), but-2-yn-1,4-diyldiacetate 262 (136 mg, 0.8 mmol, 2 equiv), Rh(cod)₂BF₄ (8 mg, 0.02 mmol, 5 mol %), and (R)-BINAP (12.4 mg, 0.02 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 20 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 80/20) afforded 266 (95 mg, 50%) as a white solid. m.p. 112 – 114 °C.

Rₐ = 0.4 (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.42-7.20 (m, 10H), 5.28 (d, J = 1.8 Hz, 2H), 5.17 (AB₃sys, J = 9.3 Hz, 2H), 4.93 (AB₃sys, J = 9.1 Hz, 2H), 2.34 (s, 3H), 2.09 (s, 3H), 1.96 (s, 3H), 1.38 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 170.7, 170.2, 141.7, 139.9, 136.7, 136.0, 134.0, 133.9, 131.9, 131.4, 130.7, 130.1, 128.3, 128.2, 127.9, 127.7, 127.6, 122.7, 90.8, 85.2, 82.1, 70.5, 61.0, 60.3, 28.2, 20.9, 20.8, 15.8.

SFC: ee = 50%, Chiralpak OD-H, scCO₂/MeOH 90/10, P = 150 bar, flow = 4.0 mL/min, 215nm, tₘajor = 2.82 min, tₘinor = 3.57 min.

MS (CI, NH₃): m/z = 486 [M + NH₄]⁺.

| (1,4-Dimethyl-7-phenyl-1-(phenylethynyl)-1,3-dihydroisobenzofuran-5,6-diyl)bis(methylene) bis(2,2-dimethylpropanoate) (267) |

This compound was obtained following the general procedure Q. Starting from (3-(but-2-yn-1-yloxy)-3-methylpenta-1,4-diyne-1,5-diyl)dibenzene 255 (89 mg, 0.3 mmol), but-2-yn-1,4-diyl
Experimental part

bis(2,2-dimethylpropanoate) 263 (152 mg, 0.6 mmol, 2 equiv), Rh(cod)\(_2\)BF\(_4\) (6.1 mg, 0.015 mmol, 5 mol %), and \((R)\)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 20 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 99/1 to 95/5) afforded 267 (35 mg, 20%) as a colorless oil.

\(\text{Rr} = 0.4\) (Cyclohexane/Ethyl acetate; 95/5, KMnO\(_4\), UV).

\(^1^H\text{NMR}\) (300 MHz, CDCl\(_3\)) \(\delta 7.50 – 7.40\) (m, 1H), \(7.40 – 7.23\) (m, 8H), \(7.23 – 7.13\) (m, 1H), \(5.21\) (d, \(J = 1.2\) Hz, 2H), \(5.17\) (AB\(_{sys}\), \(J = 12.3\) Hz, 2H), \(4.85\) (AB\(_{sys}\), \(J = 12.0\) Hz, 2H), \(2.31\) (s, 3H), \(1.39\) (s, 3H), \(1.22\) (s, 9H), \(1.14\) (s, 9H).

\(^{13}^C\text{NMR}\) (75 MHz, CDCl\(_3\)) \(\delta 178.5, 177.9, 141.4, 139.8, 136.7, 136.3, 134.7, 134.2, 131.9, 131.6, 130.9, 130.4, 128.3, 128.0, 127.8, 127.6, 122.9, 91.2, 85.3, 82.3, 70.7, 61.2, 60.6, 39.1, 38.7, 28.5, 27.4, 27.3, 16.0.

SFC: \(ee = 36\%\), Chiralpak OD-H, scCO\(_2\)/MeOH 90/10, \(P = 150\) bar, flow = 4.0 mL/min, 215nm, \(t_{\text{major}} = 2.03\) min, \(t_{\text{minor}} = 2.54\) min.

MS (ESI, NH\(_3\)): \(m/z = 570\) [M + NH\(_4\)]\(^+\).

This compound was obtained following the general procedure Q. Starting from (3-(but-2-yn-1-yloxy)-3-methylpenta-1,4-diyne-1,5-diyl)dibenzene 255 (89 mg, 0.3 mmol), but-2-yne-1,4-diyldibenzoate 264 (176.4 mg, 0.6 mmol, 2 equiv), Rh(cod)\(_2\)BF\(_4\) (6.1 mg, 0.015 mmol, 5 mol %), and \((R)\)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 24 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 268 (50 mg, 28%) as a colorless oil.

\(\text{Rr} = 0.5\) (Cyclohexane/Ethyl acetate; 80/20, KMnO\(_4\), UV).
**Experimental part**

\[ ^1H \text{ NMR} \ (300 \text{ MHz, CDCl}_3) \ \delta \ 8.00 - 7.93 \ (m, 2H), 7.93 - 7.84 \ (m, 2H), 7.57 - 7.41 \ (m, 3H), 7.39 - 7.22 \ (m, 13H), 5.60 \ (s, 2H), 5.39 - 5.12 \ (m, 4H), 2.44 \ (s, 3H), 1.42 \ (s, 3H). \]

\[ ^{13}C \text{ NMR} \ (75 \text{ MHz, CDCl}_3) \ \delta \ 166.4, 166.0, 141.8, 140.0, 136.9, 136.2, 134.5, 134.5, 133.6, 132.9, 132.2, 131.6, 130.9, 130.4, 129.9, 129.8, 129.7, 128.4, 128.3, 128.1, 127.9, 127.8, 122.9, 91.1, 85.4, 82.3, 70.8, 61.8, 61.1, 28.4, 16.1. \]

**SFC**: ee = 46%, Chiralpak OD-H, scCO\(_2\)/MeOH 90/10, P = 150 bar, flow = 4.0 mL/min, 215nm, \( t_{\text{major}} = 13.09 \) min, \( t_{\text{minor}} = 18.56 \) min.

**MS** (CI, NH\(_3\)): \( m/z = 610 \ [M + NH_4]^+ \).

### 5,6-Diethyl-1,4-dimethyl-7-phenyl-1-(phenylethynyl)-1,3-dihydroisobenzofuran (269)

![Chemical Structure](attachment:chemical_structure.png)

This compound was obtained following the general procedure Q. Starting from (3-(but-2-yn-1-yloxy)-3-methylpenta-1,4-diyne-1,5-diyl)dibenzene 255 (89 mg, 0.3 mmol), 3-hexyne 53 (50 mg, 0.6 mmol, 2 equiv), Rh(cod)_2BF\(_4\) (6.1 mg, 0.015 mmol, 5 mol %), and (R)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 20 h. Purification on silica gel (Cyclohexane/Ethyl acetate; 99/1) afforded 269 (92 mg, 79%) as a white solid. m.p. 114-118 °C.

**Rt = 0.35** (Cyclohexane/Ethyl acetate; 95/5, KMnO\(_4\), UV).

\[ ^1H \text{ NMR} \ (300 \text{ MHz, CDCl}_3) \ \delta \ 7.49 - 7.31 \ (m, 6H), 7.31 - 7.19 \ (m, 4H), 5.25 - 5.02 \ (m, 2H), 2.84 - 2.66 \ (m, 2H), 2.54 - 2.34 \ (m, 2H), 2.26 \ (s, 3H), 1.41 - 1.32 \ (m, 3H), 1.20 \ (td, J = 7.5, 2.1 Hz, 3H), 0.95 \ (td, J = 7.6, 2.5 Hz, 3H). \]

\[ ^{13}C \text{ NMR} \ (75 \text{ MHz, CDCl}_3) \ \delta \ 140.9, 140.6, 138.4, 138.2, 136.2, 134.6, 131.6, 131.4, 130.6, 128.9, 128.2, 128.1, 127.6, 127.4, 127.2, 123.4, 92.0, 84.6, 82.3, 70.9, 28.8, 23.0, 22.5, 16.0, 14.8. \]
**Experimental part**

**SFC:** *ee* = 21%, Chiralpak OD-H, scCO$_2$/MeOH 95/5, *P* = 150 bar, flow = 4.0 mL/min, 215nm, t$_{\text{major}}$ = 4.15 min, t$_{\text{minor}}$ = 5.51 min.

**MS** (CI, NH$_3$): m/z = 398 [M + NH$_4$]$^+$.  

<table>
<thead>
<tr>
<th>5,6-Bis(methoxymethyl)-1,4-dimethyl-7-phenyl-1-(phenylethynyl)-1,3-dihydroisobenzofuran (270)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="" alt="Chemical structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C$<em>{24}$H$</em>{28}$O$_3$</td>
</tr>
<tr>
<td>Exact Mass: 412.2038</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure Q. Starting from (3-(but-2-yn-1-yloxy)-3-methylpenta-1,4-diyne-1,5-diyl)dibenzene 255 (89 mg, 0.3 mmol), 1,4-dimethoxybut-2-yne 51 (68.4 mg, 0.6 mmol, 2 equiv), Rh(cod)$_2$BF$_4$ (6.1 mg, 0.015 mmol, 5 mol %), and (R)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 20 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 270 (78 mg, 63%) as a colorless oil.

**Rf** = 0.35 (Cyclohexane/Ethyl acetate; 90/10, KMnO$_4$, UV).

**$^1$H NMR** (300 MHz, CDCl$_3$) δ 7.52 – 7.45 (m, 1H), 7.45 – 7.31 (m, 5H), 7.31 – 7.24 (m, 4H), 5.15 (AB$_{\text{sys}}$, *J* = 12.3 Hz, 2H), 4.62 (d, *J* = 3.0 Hz, 1H), 4.18 (AB$_{\text{sys}}$, *J* = 10.2 Hz, 2H), 3.50 (s, 3H), 3.17 (s, 3H), 2.35 (s, 3H), 1.36 (d, 3H).

**$^{13}$C NMR** (75 MHz, CDCl$_3$) δ 140.7, 139.1, 137.2, 136.1, 135.7, 131.5, 131.0, 130.5, 128.2, 128.1, 127.5, 127.3, 123.0, 91.4, 85.0, 82.1, 70.6, 68.7, 68.3, 58.9, 58.3, 28.3, 15.7.

**SFC:** *ee* = 32%, Chiralpak OD-H, scCO$_2$/MeOH 95/5, *P* = 150 bar, flow = 3.0 mL/min, 215nm, t$_{\text{major}}$ 5.78 min, t$_{\text{minor}}$ = 6.78 min.

**MS** (CI, NH$_3$): m/z = 430 [M + NH$_4$]$^+$.  

<table>
<thead>
<tr>
<th>Dimethyl 1,4-dimethyl-7-phenyl-1-(phenylethynyl)-1,3-dihydroisobenzofuran-5,6-dicarboxylate (271)</th>
</tr>
</thead>
</table>

340
This compound was obtained following the general procedure Q. Starting from (3-(but-2-yn-1-yloxy)-3-methylpenta-1,4-diyne-1,5-diyl)dibenzene 255 (89 mg, 0.3 mmol), dimethyl but-2-ynedioate 261 (85 mg, 0.6 mmol, 2 equiv), Rh(cod)2BF4 (6.1 mg, 0.015 mmol, 5 mol %), and (R)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 24 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 271 (67 mg, 51%) as a colorless oil.

\[ R_t = 0.13 \] (Cyclohexane/Ethyl acetate; 80/20, KMnO4, UV).

\(^1\)H NMR (300 MHz, CDCl3) \( \delta \) 7.71 – 7.45 (m, 1H), 7.45 – 7.23 (m, 8H), 7.22 – 7.14 (m, 1H), 5.16 (ABsys, \( J = 12.9 \text{ Hz} \), 2H), 3.88 (s, 3H), 3.44 (s, 3H), 2.36 (s, 3H), 1.38 (s, 3H).

\(^{13}\)C NMR (75 MHz, CDCl3) \( \delta \) 168.3, 168.1, 143.2, 141.3, 135.7, 134.6, 133.5, 131.7, 131.6, 130.6, 130.3, 129.7, 128.5, 128.3, 128.1, 127.6, 122.7, 90.5, 85.9, 82.1, 70.4, 52.6, 52.1, 28.0, 16.7.

SFC: ee = 47%, Chiralpak OD-H, scCO2/MeOH 90/10, P = 150 bar, flow = 4.0 mL/min, 215nm, \( t_{\text{major}} = 2.74 \text{ min} \), \( t_{\text{minor}} = 3.48 \text{ min} \).

MS (Cl, NH\(_3\)): m/z = 458 [M + NH\(_4\)]\(^+\).

| (4-Methyl-7-phenyl-1-(phenylethynyl)-1-propyl-1,3-dihydroisobenzofuran-5,6-diyl)bis(methylene) diacetate (274) |

| Chemical Formula: C\(_{38}\)H\(_{28}\)O\(_5\) |
| Exact Mass: 496.2250 |

This compound was obtained following the general procedure Q. Starting from (3-(but-2-yn-1-yloxy)-3-propylpenta-1,4-diyne-1,5-diyl)dibenzene 256 (98 mg, 0.3 mmol), but-2-yn-1,4-diyl
Experimental part

diacetate 262 (102 mg, 0.6 mmol, 2 equiv), Rh(cod)$_2$BF$_4$ (6.1 mg, 0.015 mmol, 5 mol %), and (R)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 20 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 80/20) afforded 274 (68 mg, 46%) as a colorless oil.

Rr = 0.2 (Cyclohexane/Ethyl acetate; 85/15, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.51 – 7.22 (m, 9H), 7.22 – 7.10 (m, 1H), 5.26 (d, $J = 3.6$ Hz, 2H), 5.16 (AB$_{sys}$, $J = 12.6$ Hz, 2H), 4.91 (AB$_{sys}$, $J = 12.3$ Hz, 2H), 2.33 (s, 3H), 2.09 (s, 3H), 1.96 (s, 3H), 1.76 – 1.60 (m, 1H), 1.46 – 1.20 (m, 2H), 1.20 – 1.01 (m, 1H), 0.73 (t, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.8, 170.3, 140.6, 140.2, 136.8, 136.2, 134.1, 131.9, 131.6, 131.0, 129.6, 128.3, 128.1, 127.8, 127.7, 123.0, 91.1, 85.6, 71.3, 61.2, 60.5, 42.1, 21.0, 21.0, 17.2, 16.0, 13.9.

SFC: $ee = 51\%$, Chiralpak OD-H, scCO$_2$/MeOH 95/5, P = 150 bar, flow = 4.0 mL/min, 215nm, $t_{major} = 4.91$ min, $t_{minor} = 5.78$ min.

MS (Cl, NH$_3$): m/z = 514 [M + NH$_4$]$^+$.  

<table>
<thead>
<tr>
<th>(1-(tert-Butyl)-4-methyl-7-phenyl-1-(phenylethynyl)-1,3-dihydroisobenzofuran-5,6-diyl)bis(methylene) diacetate (275)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image_url" alt="Chemical structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C$<em>{23}$H$</em>{14}$O$_5$</td>
</tr>
<tr>
<td>Exact Mass: 510.2406</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure Q. Starting from (3-(but-2-yn-1-yloxy)-3-(tert-butyl)penta-1,4-diyn-1,5-diyl) dibenzene 257 (102 mg, 0.3 mmol), but-2-yn-1,4-diyl diacetate 262 (102 mg, 0.6 mmol, 2 equiv), Rh(cod)$_2$BF$_4$ (6.1 mg, 0.015 mmol, 5 mol %), and (R)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 24 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 275 (80 mg, 51%) as a pale yellow oil.
Experimental part

R<sub>f</sub> = 0.16 (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

<sup>1</sup>H NMR (300 MHz, CDCl₃) δ 7.51 (dt, J = 8.2, 1.3 Hz, 1H), 7.43 – 7.18 (m, 8H), 7.18 – 7.06 (m, 1H), 5.24 (AB<sub>sys</sub>, J = 12.3 Hz, 2H), 5.19 (d, J = 3.9 Hz, 2H), 4.80 (AB<sub>sys</sub>, J = 12.0 Hz, 2H), 2.30 (s, 3H), 2.08 (s, 3H), 1.96 (s, 3H), 0.79 (s, 9H).

<sup>13</sup>C NMR (75 MHz, CDCl₃) δ 170.9, 170.3, 142.0, 139.3, 138.5, 137.7, 134.7, 134.5, 132.0, 131.6, 128.3, 127.9, 127.3, 127.2, 123.2, 93.3, 91.2, 87.7, 72.4, 61.7, 60.5, 42.6, 26.6, 21.0, 15.8.

SFC: ee = 38%, Chiralpak OD-H, scCO₂/MeOH 90/10, P = 150 bar, flow = 4.0 mL/min, 215nm, t<sub>major</sub> = 2.59 min, t<sub>minor</sub> = 3.03 min.

MS (ESI, NH₃): m/z = 528 [M + NH₄]<sup>+</sup>.

<table>
<thead>
<tr>
<th>(4-Methyl-1,7-diphenyl-1-(phenylethynyl)-1,3-dihydroisobenzofuran-5,6-diyl)bis (methylene) diacetate (276)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="https://example.com/structure.png" alt="Chemical structure" /></td>
</tr>
<tr>
<td>Chemical Formula: C₃₉H₃₀O₅</td>
</tr>
<tr>
<td>Exact Mass: 590.2093</td>
</tr>
</tbody>
</table>

This compound was obtained following the general procedure Q. Starting from (3-(but-2-yn-1-yloxy)penta-1,4-diyn-1,3,5-triyl)tribenzene 258 (108 mg, 0.3 mmol), but-2-yne-1,4-diyl diacetate 262 (102 mg, 0.6 mmol, 2 equiv), Rh(cod)₂BF₄ (6.1 mg, 0.015 mmol, 5 mol %), and (R)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 24 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 80/20) afforded 276 (75 mg, 48%) as a pale yellow oil.

R<sub>f</sub> = 0.22 (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

<sup>1</sup>H NMR (300 MHz, CDCl₃) δ 7.51 – 7.40 (m, 2H), 7.38 – 7.20 (m, 5H), 7.19 – 7.02 (m, 6H), 6.81 – 6.71 (m, 1H), 6.09 – 6.00 (m, 1H), 5.40 (s, 2H), 5.34 – 5.22 (m, 2H), 4.82 (AB<sub>sys</sub>, J = 12.0 Hz, 2H), 2.43 (s, 3H), 2.11 (s, 3H), 1.91 (s, 3H).
Experimental part

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.8, 170.2, 142.8, 141.7, 139.8, 137.6, 135.5, 134.6, 134.3, 131.8, 131.6, 130.6, 129.5, 128.6, 128.4, 127.8, 127.7, 127.3, 127.1, 122.8, 89.3, 88.4, 87.0, 72.0, 61.1, 60.5, 21.0, 20.9, 16.1.

SFC: $ee = 41\%$, Chiralpak OD-H, scCO$_2$/MeOH 90/10, $P = 150$ bar, flow = 4.0 mL/min, 215nm, $t_{major} = 7.36$ min, $t_{minor} = 13.03$ min.

MS (ESI, NH$_3$): m/z = 548 [M + NH$_4$]$^+$.  

(7-Butyl-1-(hex-1-yn-1-yl)-4-methyl-1-phenyl-1,3-dihydroisobenzofuran-5,6-diyl)bis(methylene) diacetate (277)

This compound was obtained following the general procedure Q. Starting from (7-(but-2-yn-1-yloxy)trideca-5,8-diyn-7-yl)benzene 259 (96 mg, 0.3 mmol), but-2-yne-1,4-diyl diacetate 262 (102 mg, 0.6 mmol, 2 equiv), Rh(cod)$_2$BF$_4$ (6.1 mg, 0.015 mmol, 5 mol %), and (R)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 $^\circ$C for 20 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded 277 (80 mg, 54%) as a pale yellow oil.

$R_f = 0.27$ (Cyclohexane/Ethyl acetate; 80/20, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.63 – 7.46 (m, 2H), 7.36 – 7.26 (m, 3H), 5.26 – 5.20 (m, 4H), 5.18 (s, 2H), 2.53 (td, $J = 13.2, 12.8, 4.7$ Hz, 1H), 2.42 – 2.30 (m, 3H), 2.29 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H), 1.65 – 1.52 (m, 2H), 1.52 – 1.37 (m, 2H), 1.19 – 0.97 (m, 2H), 0.93 (t, $J = 7.2$ Hz, 3H), 0.88 – 0.78 (m, 1H), 0.66 (t, $J = 7.3$ Hz, 3H), 0.55 – 0.33 (m, 1H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.9, 170.8, 142.8, 140.1, 136.2, 134.9, 134.4, 130.0, 128.4, 128.3, 127.4, 90.5, 86.9, 79.1, 72.1, 60.6, 60.2, 32.8, 30.7, 29.2, 23.3, 22.2, 21.0, 19.0, 15.9, 13.7.
Experimental part

SFC: ee = 24%, Chiralpak OD-H, scCO$_2$/MeOH 90/10, P = 150 bar, flow = 4.0 mL/min, 215nm, $t_{\text{minor}}$ = 3.21 min, $t_{\text{major}}$ = 5.86 min.

MS (ESI, NH$_3$): m/z = 508 [M + NH$_4$]$^+$. 

(1-Methyl-7-phenyl-1-(phenylethynyl)-4-(trimethylsilyl)-1,3-dihydroisobenzofuran-5,6-diyl)bis(methylene) diacetate (278)

This compound was obtained following the general procedure Q. Starting from trimethyl(3-(3-methyl-1,5-diphenylpenta-1,4-diyn-3-yl)oxy)prop-1-yn-1-yl)silane 260 (107 mg, 0.3 mmol), but-2-yn-1,4-diyl diacetate 262 (102 mg, 0.6 mmol, 2 equiv), Rh(cod)$_2$BF$_4$ (6.1 mg, 0.015 mmol, 5 mol %), and (R)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 24 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 80/20) afforded 278 (42 mg, 26%) as a pale yellow oil.

$R_f$ = 0.21 (Cyclohexane/Ethyl acetate; 85/15, KMnO$_4$, UV).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.48 – 7.17 (m, 10H), 5.28 (s, 2H), 5.21 (AB$_{\text{sys}}$, $J$ = 12.6 Hz, 2H), 4.87 (AB$_{\text{sys}}$, $J$ = 12.0 Hz, 2H), 2.09 (s, 3H), 1.96 (s, 3H), 1.35 (s, 3H), 0.43 (s, 9H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.6, 170.3, 146.6, 141.7, 140.8, 140.4, 136.0, 135.1, 134.4, 131.6, 130.6, 130.0, 128.4, 128.3, 128.2, 127.9, 127.7, 122.9, 91.0, 85.3, 80.6, 72.1, 63.9, 60.8, 28.2, 21.1, 20.9, 2.3.

SFC: ee = 52%, Chiralpak OD-H, scCO$_2$/MeOH 90/10, P = 150 bar, flow = 4.0 mL/min, 215nm, $t_{\text{major}}$ = 2.13 min, $t_{\text{minor}}$ = 3.13 min.

MS (ESI, NH$_3$): m/z = 544 [M + NH$_4$]$^+$. 

345
Experimental part
Abstract
This manuscript focused on the development of eco-friendly and mild processes to access original carbocyclic and heterocyclic scaffolds of biological interest through transition-metal-catalyzed [2+2+2] cycloaddition reactions. Initially, an efficient and practical route for the preparation of highly substituted fluorenones and analogues via solventless RuCl\textsubscript{3}·nH\textsubscript{2}O-mediated [2+2+2] cycloaddition of benzyol bridged α,ω-diynes and alkynes was developed. Secondly, various functionalized 2-aminopyridine derivatives were synthesized using both neutral RuCl\textsubscript{3}·nH\textsubscript{2}O and cationic Cp*Ru(CH\textsubscript{3}CN)\textsubscript{3}PF\textsubscript{6} complexes to catalyze the [2+2+2] cycloaddition of diynes and cyanamides under solvent-free conditions. With Cp*Ru(CH\textsubscript{3}CN)\textsubscript{3}PF\textsubscript{6} as catalyst, excellent regioselectivities were achieved to provide a wide range of 2-aminopyridines of high synthetic utility involving halopyridines, vinyl pyridines and amino-aza-fluorenones. Finally, the enantioselective rhodium-catalyzed [2+2+2] cycloaddition of prochiral triynes and monoalkynes was carried out in the presence of cationic [Rh(cod)\textsubscript{2}]BF\textsubscript{4}/(R)-BINAP complex to provide enantioenriched 1,3-dihydroisobenzofuran derivatives containing a quaternary carbon stereogenic center.

Keywords: solvent-free reactions, ruthenium, rhodium, [2+2+2] cycloadditions, fluorenones, 2-aminopyridines, 1,3-dihydroisobenzofurans.

Résumé
Ce manuscrit traite de la mise au point d’une méthode d’accès éco-compatible à des squelettes carbocycliques et hétérocycliques, présents dans de nombreux composés d’intérêt biologique. Cette méthode met en œuvre une réaction de cycloaddition [2+2+2] catalysée par un métal de transition. Dans un premier temps, une voie d’accès à des fluorénones hautement substituées, ainsi qu’à des analogues a été développée. Cette voie utilise une réaction de cycloaddition [2+2+2] de diyynes-α,ω pontés par un groupe benzoyle, avec des alcynes, en présence de RuCl\textsubscript{3}·nH\textsubscript{2}O. Dans un deuxième temps, des dérivés 2-aminopyridines diversement fonctionnalisés ont été synthétisés via une catalyse au ruthénium neutre (RuCl\textsubscript{3}·nH\textsubscript{2}O) ou cationique (Cp*Ru(CH\textsubscript{3}CN)\textsubscript{3}PF\textsubscript{6}), et ce à partir de la cycloaddition [2+2+2] de diyynes et de cyanamides. Dans le cas où Cp*Ru(CH\textsubscript{3}CN)\textsubscript{3}PF\textsubscript{6} a été utilisé comme catalyseur, une excellente régiosélectivité a été observée, ce qui a permis d’isoler une grande variété de 2-aminopyridines, dont des halopyridines, des vinylpyridines, ou des amino-aza-fluorenones. Dans une dernière partie, la cycloaddition [2+2+2] énantiosélective de triynes prochiraux avec des mono alcynes a été examinée. Elle a été conduite en utilisant un catalyseur cationique au rhodium, le complexe [Rh(cod)\textsubscript{2}]BF\textsubscript{4}/(R)-BINAP, et a permis la préparation de dérivés de 1,3-dihydroisobenzofuranes énantiomériquement enrichis, contenant un carbone quaternaire stéréogène.

Mots-clés : réactions sans solvant, ruthénium, rhodium, cycloadditions [2+2+2], fluorénones, 2-aminopyridines, 1,3-dihydroisobenzofuranes.