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[Cp*Ru]-Catalyzed Selective Coupling/Hydrogenation

I. Labed.\textsuperscript{b} A. Labed.\textsuperscript{b} Y. Sun.\textsuperscript{a} F. Jiang.\textsuperscript{a} M. Achard.\textsuperscript{a}# S. Dérien.\textsuperscript{a} Z. Kabouche.\textsuperscript{b} and C. Bruneau\textsuperscript{a}

Accesses to 3,4- and 3,5-disubstituted piperidine derivatives have been achieved through [Cp*Ru]-catalyzed intermolecular coupling of allylic alcohols and propargylic amides. Tandem transformation was also possible via chemoselective [Cp*Ru]-catalyzed hydrogenation of the resulting homo-dienes.

Introduction

In regards to their applications in agrochemicals and pharmaceuticals, functionalized piperidine derivatives represent an important class of alkaloids and new methodologies for the preparation of substituted piperidine derivatives have attracted the attention of many researchers.\textsuperscript{1,2} Traditional approaches to access polyfunctionalized piperidines usually involve alkylation, arylation of piperidone derivatives, hydrogenation of substituted pyridine or cycloadditions.\textsuperscript{3-6} Multicomponent cascade transformations constitute new straightforward protocols for the syntheses of polysubstituted piperidines.\textsuperscript{6} Recently, direct functionalization of piperidines have emerged as excellent alternatives to the aforementioned methodologies. Among the latter, neutral redox processes involving the formation of transient azomethine ylides from aldehydes and amines have been efficiently used for the preparation of 2- and 2,3-(di)substituted piperidines.\textsuperscript{2f,7} The preparation of cyclic enamines or enamides containing reactive carbons at the α and β positions towards nucleophile and electrophile, respectively constitute another important approach for the preparation of 2,3-disubstituted piperidines.\textsuperscript{8} On the other hand, the use of transition metal complexes has gained increasing importance due to their ability to construct valuable N-heterocycles. Hydrogen borrowing or hydrogen autotransfer processes have been efficiently applied for the preparation of piperidine derivatives from primary amines and 1,5-pentanediols.\textsuperscript{2a,b,e,9} This methodology also allowed the postfunctionalization of cyclic amines at 2- or 3-position through metal-catalyzed redox processes.\textsuperscript{10} Cross Dehydrogenative Coupling (CDC) involving the formation of electrophilic iminium ion via oxidative processes has found broad application in α functionalization of amines.\textsuperscript{11} Metal-catalyzed C-H functionalization of cyclic enamide derivatives proved to be a powerful tool to synthesize substituted piperidines.\textsuperscript{12} Direct functionalization of saturated piperidines represents another interesting approach for either α- or β-substituted piperidines.\textsuperscript{13} Among the polysubstituted piperidines, 4-phenylpiperidine

![Figure 1 Representative examples of 4-phenylpiperidines](image-url)
derivatives such as paroxetine, femoxetine, picenadol, pethidine, terikalant, haloperidol and related structures have found broad applications as antidepressant, antipsychotic and other related biological properties (Figure 1). However, straightforward accesses to 4-phenylpiperidine derivatives through transition metal-catalysis remain scarce. 

Recently, we reported that [Cp*Ru]-based catalysts can be judiciously employed in regioselective oxidative coupling between propargylic amines and aliphatic allylic alcohols to offer straightforward accesses to dehydropiperidine derivatives. Taking advantage of this methodology by substrate scope broadening, we now disclose that [{Ru(Cp*)(CH$_3$CN)$_3$}PF$_6$]-catalyzed the chemoselective semi-hydrogenation of the resulting homodienes allowing the development of the tandem transformation.

Results and discussion

Various cyclic enamides 3f-3j were previously prepared from the corresponding linear aliphatic allylic alcohols with propargylic amides 2 through ruthenium-catalyzed coupling. However, during the coupling between cinnamyl alcohol 1a and propargylic sulphonamide 2a in the presence of catalytic amount of [{Ru(Cp*)(CH$_3$CN)$_3$}PF$_6$], results demonstrate the crucial importance of the substituents on the allylic alcohol on the reaction efficiency and side isomerization (Scheme 1).

Table 1. Synthesis of 3-methylidene-4-phenyl disubstituted enamide 3a $^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ratio 1/2</th>
<th>T (°C)</th>
<th>Conversion$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5/1</td>
<td>80</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>2.5/1</td>
<td>80</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>2/1</td>
<td>80</td>
<td>41</td>
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<tr>
<td>4</td>
<td>1.5/1</td>
<td>80</td>
<td>48</td>
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<tr>
<td>5</td>
<td>1/1</td>
<td>80</td>
<td>54</td>
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<tr>
<td>6</td>
<td>1/2</td>
<td>80</td>
<td>42</td>
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<tr>
<td>7</td>
<td>1.2/1</td>
<td>60</td>
<td>0</td>
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<td>8</td>
<td>1.2/1</td>
<td>100</td>
<td>72</td>
</tr>
<tr>
<td>9</td>
<td>1.2/1</td>
<td>125</td>
<td>58</td>
</tr>
<tr>
<td>10$^c$</td>
<td>1.2/1</td>
<td>100</td>
<td>95(74)</td>
</tr>
</tbody>
</table>

$^a$ All reactions were carried out in THF for 15 h under an inert atmosphere of argon with 2a/[Ru] in 1/0.05 molar ratio. $^b$ Conversion determined by GC. Number in parentheses is isolated yield after purification. $^c$ reactions were carried out in THF for 15 h under an inert atmosphere of argon with 2a/[Ru] in 1/0.08 molar ratio.

Our previously reported procedure involving slow addition of the protected propargylic amine 2a and 2b was found to be unsuitable highlighting faster isomerization of 1a to 3-phenylpropanal than the expected coupling (3f-j, Scheme 1). Therefore, after an initial screening of solvents, THF and DCE were found to be suitable for the
transformation. The temperature exerted a strong influence on conversion and the formation of 3a was not observed with reaction temperature below 60 °C (entry 7). Increasing the amount of alcohol 1a highlighted the side formation of undesired hemiaminal ethers presumably resulting from the nucleophilic attack of the alcohol on the cyclic enamide and side formation of aldehyde arising from the isomerisation of the allylic alcohol 1a (entries 1 to 4). A best 1.2:1 ratio of the alcohol limited these side reactions. Performing the reaction in sealed tube at 100 °C afforded up to 72% conversion (entry 8). It is noteworthy that at higher reaction temperatures above 120 °C, noticeable amount of p-toluenesulphonamide resulting from the depropargylation of 2a was detected (entry 9). Finally, with the best reaction conditions, the use of higher catalyst loading improved the transformation affording almost complete conversion and the formation of 3a in 74% isolated yield after a rapid purification by short column chromatography over neutralized silica gel to minimize degradation (entry 10). The importance of the nitrogen protecting group was next investigated with allylic alcohol 1a. Under our optimized reaction conditions, no reaction took place in the presence of propargylic aniline 2d presumably due to the stronger coordination of the nitrogen atom to the ruthenium center. To our delight, amide 2c, sulphonamide 2a and carbamate 2b functionalities were found to be suitable leading to the formation of cyclic products 3a-c in 70-87% range yields (Scheme 1). Similarly, 4-nitrocinnamyl alcohol 1b reacts cleanly with 2a affording 3d in 65% isolated yield. In contrast, under similar reaction conditions, 2-substituted allylic alcohols such as methallyl alcohol 1c was found to be less reactive and required a modified procedure involving large excess of the methallyl alcohol 1c (5 equiv.) to observe the formation of the cyclic enamide product 3e. In these cases, the lower reactivity of the resulting cyclic enamide diminished side hemiaminal ether formation in THF yielding from 2a, the 3,5-disubstituted product 3e in 84% (Scheme 1). Taken together these results demonstrated that the steric hindrance of the allylic alcohols has a strong impact on the reaction efficiency and linear aliphatic alcohols were found to be more reactive and less sensitive to side reactions in such processes (compounds 3f-3j in scheme 1). As previously observed with similar structures, it is noteworthy that performing the reaction in methanol with propargylic amines 2a and 2b in the presence of cinnamyl alcohol 1a, cleanly afforded the more stable hemiaminal ethers 4a and 4b with a 9:1 diastereoisomeric ratio (Scheme 2).20,21

Scheme 1 Access to 3,4- and 3,5-disubstituted enamides 3.

diminished side hemiaminal ether formation in THF yielding from 2a, the 3,5-disubstituted product 3e in 84% (Scheme 1). Taken together these results demonstrated that the steric hindrance of the allylic alcohols has a strong impact on the reaction efficiency and linear aliphatic alcohols were found to be more reactive and less sensitive to side reactions in such processes (compounds 3f-3j in scheme 1). As previously observed with similar structures, it is noteworthy that performing the reaction in methanol with propargylic amines 2a and 2b in the presence of cinnamyl alcohol 1a, cleanly afforded the more stable hemiaminal ethers 4a and 4b with a 9:1 diastereoisomeric ratio (Scheme 2).20,21

Scheme 2. Preparation of hemiaminal ethers 4.
Rationalization of these results was next undertaken. Upon non reductive elimination/addition, the propargylic amides $2^\text{ and allylic alcohols } 1$ react with the cationic $\text{[Cp}^*\text{Ru]}^+$ fragment to form two key intermediates $\text{I}$ and $\text{II}$ in equilibrium whereas, the presence of more nucleophilic amine such as propargylic aniline $2^\text{d}$ inhibited the formation of these proposed key intermediates presumably due to the coordination of the nitrogen atom to the ruthenium centre leading to intermediates $\text{III}$ (Figure 2). The coordination of the oxygen atom on the cationic ruthenium fragment thus facilitating the introduction of the allylic alcohol in $\text{I}$ could also explain the lower activity of the neutral $\text{[Cp}^*\text{Ru(COD)Cl]}$ in such transformations. $^{20}$ Oxidative cyclization of $\text{II}$ gave the cationic ruthenacyclopentene $\text{IV}$. The steric interaction between the $R^3$ group and the $\text{Cp}^*$ ligand thus reducing the cyclization rate might account for the lower reactivity of methallyl alcohol $1^\text{c}$ during this process. $^{22}$ Then, intermediate $\text{IV}$ undergoes $\beta$-$H$ elimination with the former allylic proton and the ruthenium affording the hydrido ruthenium(IV) $\text{V}$. Reductive elimination from $\text{V}$ gives back the active cationic $\text{[Cp}^*\text{Ru]}^+$ moiety and generates the intermediate aminoaldehyde $\text{VI}$, which releases the enamides $3$ after intramolecular condensation with elimination of water.

![Figure 2 Postulated mechanism accounting on products 3.](image)

Using methanol as solvent, the presence of an excess of cinnamyl alcohol $1^\text{a}$, led to the side formation of $3,3$-dimethoxypropyl)benzene $5$. Interestingly, we found that the complete formation of this acetal was only possible when $\text{[(Ru(Cp*)[CH_3CN]_2)PF_6]}$ along with catalytic amount of $2^\text{a}$ were used as catalytic system for this isomerisation-acetalisation sequence (Scheme 3). These last results tend to demonstrate that the generated electrophilic ruthenium species promoted acetal formation and could also play a role during the transformation of intermediate $\text{VI}$ to enamide $3$.

![Scheme 3. [Ru]-catalyzed acetal formation from allylic alcohols.](image)

Considering that products $3$ and $4$ feature a methylene group, we next investigated the postfunctionalization of these products in hydroboration-oxidation sequence to access 3-hydroxymethylpiperidine derivatives. The use of Thexylborane with $3^\text{a}$ didn’t afford the expected product. $^{23}$ To our delight, performing similar reaction with BH$_3$:DMS made possible the formation of the expected compound along with noticeable amount of side products arising from the side reaction of the endo cyclic insaturation. Finally, replacing $3^\text{a}$ by its corresponding hemiaminal ether $4^\text{a}$ afforded $5^\text{a}$ in a 75:19:6 stereoisomeric mixture and 76% isolated yield (Scheme 4).

The beneficial presence of C-Me bonds in alkaloids and heterocycles recently highlighted as the “magic methyl effect” has attracted a lot of interest and can contribute to an increase of their biological activities. The methylene moiety in products 3 could be therefore selectively reduced to a methyl group keeping intact the endo cyclic insaturation for further posfunctionalization. Selective hydrogenation of dienes into alkene in the presence of [Cp*Ru]-based catalyst have been reported by Drießen-Hölscher. During this study, it was observed that the use of organophosphorous ligand such as tris(hydroxypropyl)phosphane favoured complete hydrogenation of the diene into its corresponding alkane. We investigated the semi-hydrogenation of 3a using [{Ru(Cp*)}(CH3CN)3]PF6 as precatalyst to further perform the tandem coupling/hydrogenation transformation. Initial attempt to hydrogenate 3a without additives demonstrated that semi hydrogenation was possible at 120 °C under 45 bars of H2 but side isomerisation of the exo-insaturation occurred to afford the conjugated diene (Table 2, entry 1).

Table 2. [Ru(Cp*)]-catalyzed semi hydrogenation of enamide 3a

<table>
<thead>
<tr>
<th>Entry</th>
<th>P(bar)</th>
<th>T(°C)</th>
<th>Additive (mol%)</th>
<th>conv. (yield)b</th>
<th>7/8/9 Ratioc</th>
<th>7a cis/trans ratio d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>120</td>
<td>None</td>
<td>75</td>
<td>55/35/10</td>
<td>70/30</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>120</td>
<td>A (5%)</td>
<td>99(75)</td>
<td>100/0/0</td>
<td>70/30</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>120</td>
<td>B (5%)</td>
<td>99(70)</td>
<td>80/0/20</td>
<td>80/20</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>110</td>
<td>A (5%)</td>
<td>99</td>
<td>100/0/0</td>
<td>70/30</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>120</td>
<td>A (5%)</td>
<td>97</td>
<td>95/5/0</td>
<td>65/35</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>90</td>
<td>A (5%)</td>
<td>80</td>
<td>100/0/0</td>
<td>75/25</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>110</td>
<td>A (5%)</td>
<td>99</td>
<td>100/0/0</td>
<td>75/25</td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>110</td>
<td>B (5%)</td>
<td>99</td>
<td>90/1/9</td>
<td>80/20</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>110</td>
<td>C (5%)</td>
<td>93</td>
<td>84/2/14</td>
<td>80/20</td>
</tr>
</tbody>
</table>

a All reactions were carried out in a 20 mL reactor using THF for 15h with 3a/[Ru]/additive in 1/0.05/0.05 molar ratio. b Number in parentheses is isolated yield of 7a after purification. c Ratio 7/8/9 were determined by GC. d cis/trans ratio was determined by GC and 1H NMR.
Recently, Fehr and co-workers at Firmenich showed the beneficial role of Brönsted acid as additive to prevent isomerisation during hydrogenation of dienes for the synthesis of Santalol. 27 Thus, a set of sulfonic acid derivatives was evaluated for this transformation (Figure 3). Gratifyingly, the use of phosphine-sulfonic acids (5 mol%) such as A and B led to complete conversion and suppress the side isomerisation affording 7a in up to 70-75% isolated yield and 70:30-80:20 cis:trans ratios, respectively (entries 2 and 3). Best diastereoselectivity was obtained with additive B (entries 3 and 8). However, in these cases noticeable amount of fully reduced products 9a were also observed demonstrating that A led to the best chemoselectivity. Importantly, lower or higher amount of the acidic additive reduced the catalytic activity. The structure of the major diastereoisomer was unequivocally determined by NMR analyses where the high-field ethylenic protons appeared as a set of two doublet of doublet at 4.77 and 4.68 ppm with a 5.0 and 2.3 Hz coupling constants with the allylic proton corresponding to the cis and trans isomers, respectively (Figure 4). Further confirmation was obtained by selective crystallization of the cis isomer 7a (Figure 4). 28 Interestingly, no degradation occurred during the purification of the enamide 7a demonstrating its higher stability compared to the homodiene 3a. Performing the reactions at 110-120 °C in the presence of [Ru(Cp*)(CH3CN)3]PF6 and A showed that under lower H2 pressure although full conversions were observed, slight decrease of the cis:trans ratio of 7a were also noticed (entry 4 compared to 7 and entry 2 compared to 5). The conversion was affected by reaction temperature and only 80% was reached at 90 °C under 60 bar of molecular hydrogen (entry 6).
At this stage, we wondered if the diastereoselectivities obtained in the presence of A and B arose from the coordination of the phosphine or from simple sterical or acidic outcomes of the additive. Therefore, the use of benzene sulfonic acid C, as additive highlighted similar diastereoselectivity leading to 80:20 cis:trans ratio but with uncompleted conversion, suggesting that with these two phosphine ligands no binding to metal center of the phosphorus atom seems to occur during the hydrogenation in THF as solvent (entry 9).

Although a detailed mechanism for the ruthenium-catalysed alkene hydrogenation is yet to be established, alkene hydrogenation could occur through consecutive insertion of the coordinated alkene followed by reductive elimination on the cationic hydrido/hydrogen species [Ru(Cp*)H₂]⁺. A ionic process involving protonation by the acidic [Ru(Cp*)(η²-H₃)]⁺ followed by reduction with side generated neutral [Ru(Cp*)H] cannot totally be excluded. It should be noted that when the reactions were carried out in the presence of arene ruthenium(II) complexes featuring similar ligands complete reduction of the homodienes were selectively obtained which tend to suggest that the Cp* ligand remained intact under these reaction conditions. More important is the influence of the acidic additives in preventing the isomerization processes and toward the reaction efficiency. Recently, Grotjahn and coworkers demonstrated that cationic ruthenium(II) species bearing bifunctional ligand play an important role in isomerization through the possible intervention of allylic ruthenium species where the basic nitrogen of the imidazole facilitates the η³-allylic formation via reversible deprotonation. In contrast, the necessity of acidic additives A-B could prevent the formation of such allylic species via prior protonation/oxidative addition mechanism. On the other hand, Nozaki demonstrated that during hydroformylation of alkenes, [Ru(Cp*)H] species efficiently catalysed the isomerization through reversible insertion. Therefore acidic additives might also play a role on the catalytic activity and prevent isomerization by regenerating [Ru(Cp*)H₂]⁺ from neutral [Ru(Cp*)H] and dinuclear (μ-H) monocationic ruthenium(II) species.

With these results in hand, we investigated the possibility to perform the tandem process with additive B which afforded better diastereoselectivities. After several attempts, we found that the acidic additive must be added only at the second stage to allow the coupling of propargylic amide 2a with cinnamyl alcohol 1a. Importantly, lower amount of the sulfonic acid B was necessary demonstrating partial degradation of the catalyst during the initial coupling and required optimization of the reaction conditions to overcome this issue. Thus, initial optimization afforded 7a in 52% isolated yield and 75/25 diastereoisomeric ratio (Scheme 5).

**Scheme 5. Tandem Coupling/Hydrogenation.**

**Conclusions**

In conclusion, we demonstrated that the selective oxidative coupling between allylic alcohols and propargylic amines can be extended to cinnamyl alcohol derivatives and 2-substituted allylic alcohols. This methodology allows the access to 3,4- and 3,5-disubstituted enamides as valuable scaffolds for the preparation of 3-methylpiperidine derivatives through selective [Ru(Cp*)]-catalyzed alkene hydrogenation.

**Experimental**

**General considerations**
All reactions were carried out under an inert atmosphere with standard Schlenk techniques, unless otherwise mentioned. THF was purified by solvent purification system equipped with a series of activated filter columns. Benzene sulfonic acid was purchased from commercial sources and used as received. ligands A and B were prepared according literature protocols. Propargylic amines 2 were prepared according to reported procedures. Compounds 3f-j were already reported in reference 20. Proton magnetic resonance (1H NMR) spectra were recorded on Bruker 400 MHz spectrometer and carbon magnetic resonance (13C NMR) spectra were performed at 100 MHz. Chemical shifts (δ) are reported in parts per million relative to residual solvent signals (CD2Cl2 5.32 and 53.84; CDCl3 7.15 and 128.02, CD3OD 5.84 and 49.05). Coupling constants are reported in Hertz. 1H NMR assignment abbreviations are the following: singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), broad singlet (bs), doublet of doublets (dd), doublet of triplets (dt), and multiplet (m). All reagents were weighed and handled in air, and refilled with an inert atmosphere of argon at room temperature to prevent oxidation. HRMS were recorded on a Waters Q-Tof 2 with an ESI source.

**General Procedure for preparation of the enamides 3-4**

To a dried pressure tube under an inert atmosphere, propargylic amine 2 (0.239 mmol, 1eq), allylic alcohol substrate 1 (1.2 eq) were dissolved in THF or methanol (0.5 to 1 mL) followed by the addition of [(Ru(Cp*)(CH2CN)]PF6 (5 mol% (MeOH) or 8 mol% (THF)). The resulting solution was stirred at 100°C for 15h. Reaction completion was monitored using GC, GC-MS and TLC techniques. After concentration **in vacuo**, the crude mixture was purified by short column chromatography over dried deactivated silica gel.

**3-methylene-4-phenyl-1-tosyl-1,2,3,4-tetrahydropyridine 3a**

Prepared from N-tosyl propargylamine 2a (50 mg, 0.239 mmol) and cinnamyl alcohol 1a (0.288 mmol, 1.2 eq) in THF (0.5 mL). Chromatography on silica gel using PE/Et2O (80:20) as eluent afforded compound 3a as yellow oil, 58 mg (74%), 1H NMR (400 MHz, CD2Cl2) δ 7.69 (d, J= 8.1 Hz, 2H), 7.36 (d, J= 8.1 Hz, 2H), 7.20-7.15 (m, 3H), 6.98-6.95 (m, 2H), 6.84 (d, J= 8.0 Hz, 1H), 5.10 (dd, J= 4.4, 8.0 Hz, 1H), 4.90 (bs, 1H), 4.81 (bs, 1H), 3.96 (d, J= 13.4 Hz, 1H), 3.93 (bs, 1H), 3.67 (d, J= 12.9 Hz, 1H), 2.45 (s, 3H); 13C NMR (100 MHz, CD2Cl2) δ 144.6, 142.8, 141.4, 134.8, 130.1, 128.6, 128.2, 127.7, 127.0, 126.5, 113.7, 110.7, 48.3, 45.4, 21.7; HRMS calcd for C19H15NO2NaS [M+Na]+ 348.10342 found 348.1035 (0 ppm).

**Tert-butyl 3-methylene-4-phenyl-3,4-dihydropyridine-1(2H)-carboxylate 3b**

Prepared from N-Boc propargylamine 2b (50 mg, 0.322 mmol) and cinnamyl alcohol 1a (1.2 eq, 0.376 mmol) in THF (0.7 mL). Chromatography on silica gel using PE/Et2O (70:30) as eluent afforded compound 3b as colourless oil as a mixture of isomers in a 3:2 ratio due to the Boc protecting group, (76 mg, 87%) 1H NMR (400 MHz, CD2Cl2) δ 7.32-7.22 (m, 5H), 7.09-6.97 (2bs, 1H), 5.06-4.88 (m, 3H), 4.20-4.11 (m, 1H), 4.08 (d, J= 3.6 Hz, 1H), 3.86 (d, J= 13.6 Hz, 1H), 1.50 (bs, 9H); 13C NMR (100 MHz, CD2Cl2) δ 152.5 (I1, C=O) 152.1 (I2, C=O), 148.0, 147.8, 143.6, 143.5, 128.7, 128.3, 126.9, 125.1, 112.6 (I1, =CH2), 112.5 (I2, =CH2), 106.4, 106.1, 81.25, 47.4, 46.3, 45.8, 45.7, 28.4; GC-MS m/z (%): 271 (M+, 1%), 215, 200, 170, 142.

**3-methylene-4-phenyl-3,4-dihydropyridin-1(2H)-yl](phenyl)methanone 3c**

Prepared from N-(prop-2-ynyl)benzamide 2c (50 mg, 0.314 mmol) and cinnamyl alcohol 1a (1.2 eq, 0.41 mmol) in THF (0.6 mL). Chromatography on silica gel using PE/Et2O (70:30) as eluent afforded compound 3c as colourless oil, 61 mg (70%) 1H NMR (400 MHz, CD2Cl2) δ 7.52-7.43 (m, 5H), 7.35-7.23 (m, 5H), 6.73-6.70 (m, 1H), 5.16-5.14 (m, 1H), 5.00-4.93 (m, 2H), 4.48 (d, J= 13.4 Hz, 1H), 4.18-4.16 (m, 1H), 4.11 (d, J= 13.4 Hz, 1H); 13C NMR (100 MHz, CD3OD) δ 171.0, 144.0, 143.7, 135.9, 131.9, 129.8, 129.6, 129.2, 129.1, 128.9, 127.9, 114.0, 111.3, 47.3, 47.0; HRMS calcd. for C19H15NOa [M+Na]+ 298.12078 found 298.1207 (0 ppm).
3-methylene-4-(4-nitrophenoxy)-1-tosyl-1,2,3,4-tetrahydropyridine 3d

Prepared from N-tosyl propargylamine 2a (50 mg, 0.239 mmol) and 4-nitrocinnamyl alcohol 1a (1.2 eq, 0.288 mmol) in THF (0.5 mL). Chromatography on silica gel using PE/EtO (50:50) as eluent afforded compound 3d as colourless oil, 57 mg (65%). 1H NMR (400 MHz, CDCl3) δ 7.65 (d, J= 8.6 Hz, 2H), 7.58 (d, J= 8.2 Hz, 2H), 6.90, (dd, J= 1.6, 8.1 Hz, 1H), 6.72 (d, J= 8.2 Hz, 2H), 6.42 (d, J= 8.6 Hz, 2H), 4.49 (bs, 1H), 4.47 (dd, J= 4.4, 8.1 Hz, 1H), 4.30 (bs, 1H), 3.80 (d, J= 13.0 Hz, 1H), 3.50 (d, J= 13.0 Hz, 1H), 3.30 (d, J= 3.5 Hz, 1H), 1.88 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 149.3, 147.1, 143.8, 140.0, 135.4, 129.7, 128.6, 128.1, 127.6, 114.0, 107.9, 47.9, 44.7, 21.0; HRMS calcd for C19H18NaO2S [M+Na]+ 393.0885, found 393.0884 (0 ppm).

5-methyl-3-methylene-1-tosyl-1,2,3,4-tetrahydropyridine 3e

Prepared from N-tosyl propargylamine 2a (50 mg, 0.239 mmol) and 2-methylprop-2-en-1-ol 1c (5 eq, 1.19 mmol) in THF (1 mL). Chromatography on silica gel using DCM/PE/EtO (80:10:10) as eluent afforded compound 3e as colourless oil (53 mg, 84%); 1H NMR (400 MHz, CD3OD) δ 7.64 (d, J= 8.1 Hz, 2H), 7.35 (d, J= 8.1 Hz, 2H), 6.40 (bs, 1H), 4.82 (s, 1H), 4.81 (s, 1H), 3.83 (s, 2H), 2.56 (s, 2H), 2.41 (s, 3H), 1.67 (s, 3H); 13C NMR (100 MHz, CD3OD) δ 145.2, 138.5, 136.2, 130.6, 128.5, 120.8, 119.8, 112.5, 50.5, 35.6, 21.4, 20.3; HRMS calcd for C20H22NO4NaS [M+Na]+ 286.0787 found 286.0786 (1 ppm).

2-methoxy-5-methylene-4-phenyl-1-tosylpiperidine 4a

Prepared from N-tosyl propargylamine 2a (50 mg, 0.239 mmol) and cinnamyl alcohol 1a (1.2 eq, 0.288 mmol) in MeOH (0.5 mL). Chromatography on silica gel using PE/EtO (70:30) as eluent afforded compound 4a as yellow oil in a 93/7 diastereoisomeric mixture (70 mg, 82%); 1H NMR (400 MHz, CD2OD) δ 7.74 (d, J= 8.2 Hz, 2H), 7.06-6.98 (m, 3H), 6.79-6.77 (m, 4H), 5.26 (t, J= 0.5 Hz, 1H), 4.59 (bs, 1H), 4.27 (d, J= 14.3 Hz, 1H), 4.10 (bs, 1H), 3.84 (d, J= 14.3 Hz, 1H), 3.74-3.70 (m, 1H), 3.23 (s, 3H), 1.89 (s, 3H), 1.84 (ddd, J= 2.0, 4.1, 13.2 Hz, 1H), 1.59 (dt, J= 3.2, 13.1 Hz, 1H); 13C NMR (100 MHz, CD2OD) δ 134.8, 142.8, 141.3, 138.9, 129.5, 128.8, 128.6, 127.8, 127.0, 111.8, 84.8, 55.0, 47.6, 42.0, 36.7, 21.0; HRMS calcd for C26H26NO4S Na+[M+Na]+ 380.12964 found 380.1289 (1 ppm).

Tert-butyl 2-methoxy-5-methylene-4-phenyl-1-tosylpiperidine-1-carboxylate 4b

Prepared from N-Boc propargylamine 2b (50 mg, 0.322 mmol) and cinnamyl alcohol 1a (1.2 eq, 0.387 mmol) in MeOH (0.6 mL). Chromatography on silica gel using PE/EtO (70:30) as eluent afforded compound 4b as colourless oil, 62 mg (64%), as two isomers due to the Boc protecting group (63/37 ratio) in a 90/10 diastereoisomeric ratio. 1H NMR (400 MHz, CD2Cl2) δ 7.32 (t, J= 7.2 Hz, 2H), 7.24 (td, J= 7.2, 1.1 Hz, 1H), 7.19 (brd, J= 7.2 Hz, 2H), 5.55 (bs, 0.4 Hz), 5.44 (bs, 0.6Hz), 4.93-4.87 (m, 1H), 4.47 (d, J= 14.0 Hz, 0.6Hz), 4.35-4.32 (m, 0.4Hz), 4.13 (bs, 1H), 3.80 (dd, J= 14.0, 4.0 Hz, 1H), 3.74 (d, J= 14.0 Hz, 0.4Hz), 3.64 (d, J= 14.0 Hz, 0.6Hz), 3.30 (s, 2.6Hz), 3.28 (s, 0.4Hz), 1.48 (s, 9Hz); 13C NMR (100 MHz, CD2Cl2) δ 155.0, 154.6, 147.2, 146.9, 142.9, 141.9, 129.0, 128.8, 128.7, 128.6, 127.0, 126.8, 110.8, 110.6, 82.9, 81.9, 80.5, 80.2, 54.9, 54.8, 46.8, 45.3, 43.0, 42.5, 37.8, 37.5, 28.5, 28.4; HRMS calcd for C26H26NO4S Na+[M+Na]+ 326.17321 found 326.1728 (0 ppm).

General Procedure for preparation of the acetics 5

To a dried pressure tube under an inert atmosphere, propargylic amine 2a (5 mol%) and [{Ru(Cp*)(CHCN)3}PF6] (1 mol%) were dissolved in methanol or ethanol (1 mL) followed by the addition of cinnamyl alcohol 1a (1.0 eq). The resulting solution was stirred at 100°C overnight. After concentration in vacuo, the crude mixture was purified by short column chromatography to afford the acetal 5 as product.

(3,3-dimethoxypropyl)benzene 5a
Prepared from cinnamyl alcohol 1a (50 mg, 0.239 mmol) and MeOH (1 mL). Filtration on silica gel using PE/Et₂O (80:20) as eluent afforded compound 5a in 90% yield. ¹H NMR (400 MHz, C₆D₆) δ 7.12-6.98 (m, 5H), 4.18 (t, J = 5.6 Hz, 1H), 3.15 (s, 6H), 2.48 (t, J = 8.15 Hz, 2H), 1.74-1.69 (m, 2H).

**(6-methoxy-4-phenyl-1-tosylpiperidin-3-yl)methanol 6a**

BH₃:DMS (C= 1M, 0.3 mL) was slowly added to a solution containing 2-methoxy-5-methylene-4-phenyl-1-tosylpiperidine 4a (30 mg, 0.08 mmol) in THF (0.5 mL) at 0°C and the resulting mixture was stirred for 2 hours. H₂O₂ (30%, 0.08 mL) and NaOH (3N, 0.08 mL) were sequentially added and the stirring was maintained for 3 h at room temperature. Extraction with H₂O and CH₂Cl₂ x 3 followed by drying over sodium sulfate and concentration afforded a crude oil which was further purified by chromatography on silica gel using PE/Et₂O (80:20) as eluent to afford compound 6a as yellow oil (24 mg, 76%) in a 75:19:6 stereoisomeric ratio (*only the major compound is described*), ¹H NMR (400 MHz, C₆D₆) δ 7.74 (d, J = 8.1 Hz, 2H), 7.10-7.01 (m, 3H), 6.82-6.77 (m, 4H), 5.34 (t, J = 0.4 Hz, 1H), 4.04 (d, J = 13.0 Hz, 1H), 3.44 (t, J = 4.0, 13.0 Hz, 1H), 3.28-3.20 (m, 1H), 3.14-3.06 (m, 2H), 2.95 (s, 3H), 1.92-1.82 (m, 1H), 1.87 (s, 3H), 1.79-1.68 (m, 2H); ¹³C NMR (100 MHz, C₆D₆), δ 141.5, 141.2, 137.4, 128.1, 127.2, 126.2, 126.1, 125.2, 83.0, 56.0, 53.9, 40.6, 39.8, 35.1, 28.6, 19.7; HRMS calcd for C₂₀H₂₅NOxNaS [M+Na]^+ 398.14020 found 398.1403 (0 ppm).

**General Procedure for the semi-hydrogenation of 3a.**

In a 20 mL reactor, containing 3-methylene-4-phenyl-1-tosyl-1,2,3,4-tetrahydropyridine 3a (30 mg, 0.09 mmol), THF (2 mL) was added followed by the addition of {Ru(Cp*)(CH₃CN)}₃PF₆ and the additive (5 mol%). The autoclave was sealed, and was fast evacuated and filled with argon three times then ended with vacuum. The molecular hydrogen was introduced into the reactor at the indicated pressure. Then, the mixture was stirred at the mentioned temperature. After 15 hours the autoclave was cooled down to the room temperature and the hydrogen was then carefully released, the conversion was determined by GC, GC-MS and crude ¹H NMR. Chromatography on silica gel using PE/Et₂O (80:20) as eluent afforded compound 7a as yellow oil, as yellow oil, δ 22.5 mg (75%), (*only the cis compound is described*) ¹H NMR (400 MHz, C₆D₆) δ 7.68 (d, J = 7.8 Hz, 2H), 7.06-6.92 (m, 4H), 6.79-6.75 (m, 3H), 6.60 (d, J = 6.9 Hz, 1H), 4.77 (dd, J = 5.0, 8.2 Hz, 1H), 3.39 (dd, J = 1.7, 10.9 Hz, 1H), 2.86 (t, J = 5.0 Hz, 1H), 2.80 (t, J = 10.9 Hz, 1H), 1.88 (s, 3H), 1.76-1.68 (m, 1H), 0.29 (d, J = 6.7 Hz, 3H); ¹³C NMR (100 MHz, CD₂Cl₂) δ 144.5, 140.8, 134.9, 130.2, 129.7, 128.0, 127.6, 126.9, 125.6, 110.0, 46.7, 42.6, 30.1, 20.0, 14.3; HRMS calcd for C₁₉H₂₁NO₂SNaS [(M+Na)^+] 350.11907 found 350.119 (0 ppm).

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**Notes and References**

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