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## [Cp\*Ru]-Catalyzed Selective Coupling/Hydrogenation

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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.<sup>1,2</sup> Traditional approaches to access polyfunctionalized piperidines usually involve alkylation, arylation of piperidone derivatives, hydrogenation of substituted pyridine or cycloadditions.<sup>3-6</sup> Multicomponent cascade transformations constitute new straightforward protocols for the syntheses of polysubstituted piperidines.<sup>6</sup> 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.<sup>2f,7</sup> The preparation of cyclic enamines or enamides containing reactive carbons at the  $\alpha$  and  $\beta$  positions towards nucleophile and electrophile, respectively constitute another important approach for the preparation of 2,3-disubstituted piperidines.<sup>8</sup> 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-pentandiol.<sup>2a,b,e,9</sup> This methodology also allowed the postfunctionalization of cyclic amines at 2- or 3-position through metal-catalyzed redox processes.<sup>10</sup> Cross Dehydrogenative Coupling (CDC) involving the formation of electrophilic iminium ion *via* oxidative processes has found broad application in  $\alpha$  functionalization of amines.<sup>11</sup> Metal-catalyzed C-H functionalization of cyclic enamide derivatives proved to be a powerful tool to synthesize substituted piperidines.<sup>12</sup> Direct functionalization of saturated piperidines represents another interesting approach for either  $\alpha$ - or  $\beta$ -substituted piperidines.<sup>13</sup> Among the polysubstituted piperidines, 4-phenylpiperidine

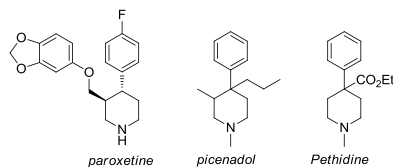


Figure 1 Representative examples of 4-phenylpiperidines

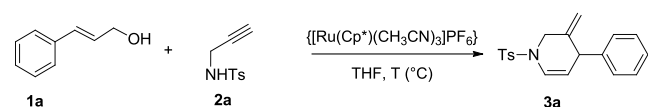
derivatives such as paroxetine, femoxetine, piconadol, pethidine, terikalant, haloperidol and related structures have found broad applications as antidepressant, antipsychotic and other related biological properties (Figure 1).<sup>4b,14-18</sup> However, straightforward accesses to 4-phenylpiperidine derivatives through transition metal-catalysis remain scarce.<sup>19</sup>

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.<sup>20</sup> Taking advantage of this methodology by substrate scope broadening, we now disclose that {[*Ru*(Cp\*)(CH<sub>3</sub>CN)<sub>3</sub>]PF<sub>6</sub>}-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.<sup>20</sup> However, during the coupling between cinnamyl alcohol **1a** and propargylic sulphonamide **2a** in the presence of catalytic amount of {[*Ru*(Cp\*)(CH<sub>3</sub>CN)<sub>3</sub>]PF<sub>6</sub>}, 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**<sup>a</sup>

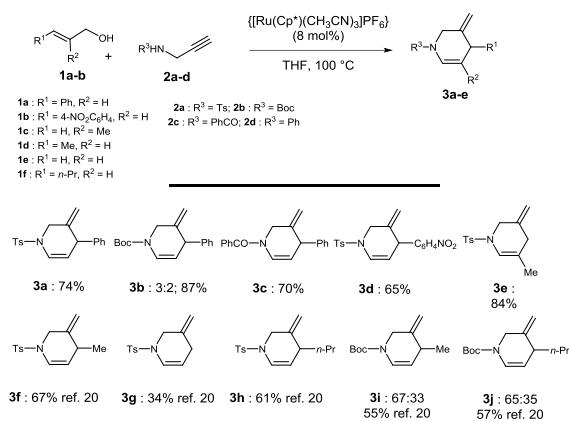


Entry	Ratio <b>1/2</b>	T (°C)	Conversion <sup>b</sup>
1	5/1	80	35
2	2.5/1	80	39
3	2/1	80	41
4	1.5/1	80	48
5	1/1	80	54
6	1/2	80	42
7	1.2/1	60	0
8	1.2/1	100	72
9	1.2/1	125	58
10 <sup>c</sup>	1.2/1	100	95(74)

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

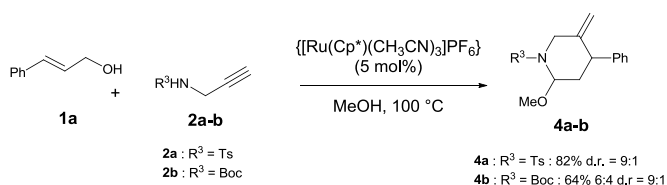
Our previously reported procedure involving slow addition of the protected propargylic amine **2a** and **2b** was found to be unsuitable highlighting faster isomerization of **1a** to 3-phenylpropanal than the expected coupling (**3f-j**, Scheme 1).<sup>20</sup> Therefore, after an initial screening 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*-toluene sulphonamide 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



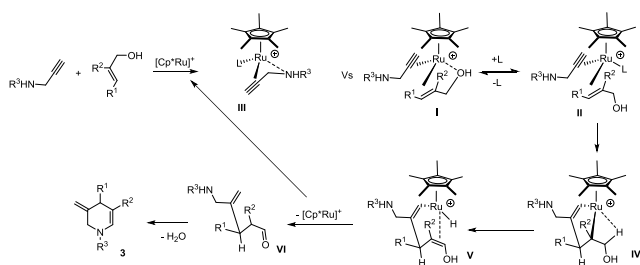
### Scheme 1 Access to 3,4- and 3,5-disubstituted enamides **3**.

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).<sup>20,21</sup>



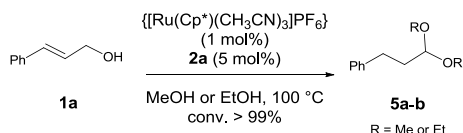
### Scheme 2 . Preparation of hemiaminal ethers **4**.

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



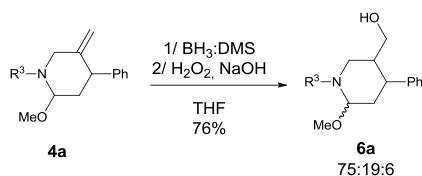
**Figure 2** Postulated mechanism accounting on products **3**.

Using methanol as solvent, the presence of an excess of cinnamyl alcohol **1a**, 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  $\{[\text{Ru}(\text{Cp}^*)(\text{CH}_3\text{CN})_3]\text{PF}_6\}$  along with catalytic amount of **2a** 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 **VI** to enamide **3**.



**Scheme 3** .  $[\text{Ru}]$ -catalyzed acetal formation from allylic alcohols.

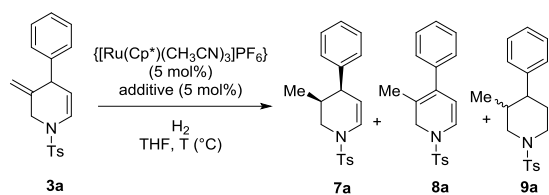
Considering that products **3** and **4** feature a methylene group, we next investigated the postfunctionalization of these products in hydroboration-oxidation sequence to access 3-hydroxymethylpiperidine derivatives. The use of Thexylborane with **3a** didn't afford the expected product.<sup>23</sup> To our delight, performing similar reaction with  $\text{BH}_3:\text{DMS}$  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 **3a** by its corresponding hemiaminal ether **4a** afforded **5a** in a 75:19:6 stereoisomeric mixture and 76% isolated yield (Scheme 4).



**Scheme 4 .** Hydroboration-Oxidation of **4a**.

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.<sup>24</sup> The methylene moiety in products **3** could be therefore selectively reduced to a methyl group keeping intact the *endo* cyclic insaturation for further postfunctionalization. Selective hydrogenation of dienes into alkene in the presence of [Cp\*Ru]-based catalyst have been reported by Drießen-Hölscher.<sup>25</sup> 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\*)(CH<sub>3</sub>CN)<sub>3</sub>]PF<sub>6</sub>} as precatalyst to further perform the tandem coupling/hydrogenation transformation.<sup>26</sup> Initial attempt to hydrogenate **3a** without additives demonstrated that semi hydrogenation was possible at 120 °C under 45 bars of H<sub>2</sub> but side isomerisation of the *exo*-insaturation occurred to afford the conjugated diene (Table 2, entry 1).

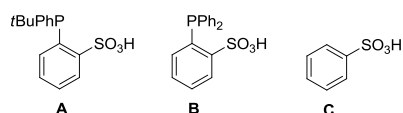
**Table 2 .** [Ru(Cp\*)]-catalyzed semi hydrogenation of enamide **3a**<sup>a</sup>



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

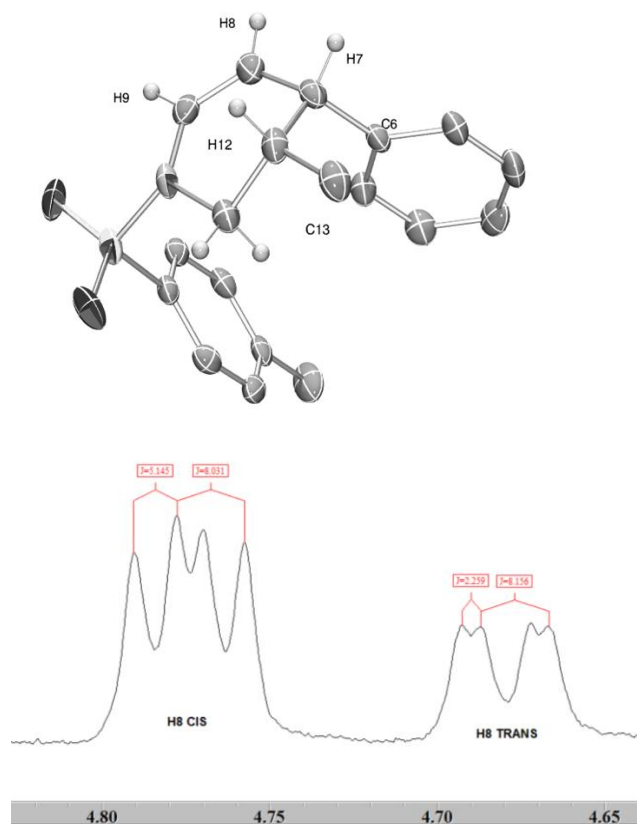
<sup>a</sup> All reactions were carried out in a 20 mL reactor using THF for 15h with **3a**/[Ru]/additive in 1/0.05/0.05 molar ratio. <sup>b</sup> Number in parentheses is isolated yield of **7a** after purification. <sup>c</sup> ratio **7/8/9** were determined by GC. <sup>d</sup> *cis/trans* ratio was determined by GC and <sup>1</sup>H NMR.

Recently, Fehr and co-workers at Firmenich showed the beneficial role of Brønsted acid as additive to prevent isomerisation during hydrogenation of dienes for the synthesis of Santalol.<sup>27</sup> 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



**Figure 3** . Additives employed during hydrogenation.

was obtained by selective crystallization of the *cis* isomer **7a** (Figure 4).<sup>28</sup> 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\*)(CH<sub>3</sub>CN)<sub>3</sub>]PF<sub>6</sub>} and **A** showed that under lower H<sub>2</sub> 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).

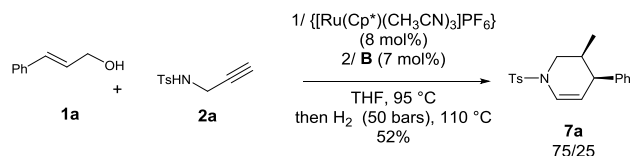


**Figure 4** . X-ray structure of the semi reduced *cis*-cyclic enamide **7a** and representative ethylenic proton signals of the two diastereoisomers.

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<sup>29</sup> 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  $[\text{Ru}(\text{Cp}^*)\text{H}_2]^+$ .<sup>30-31</sup> A ionic process involving protonation by the acidic  $[\text{Ru}(\text{Cp}^*)(\eta^2\text{-H}_2)]^+$  followed by reduction with side generated neutral  $[\text{Ru}(\text{Cp}^*)\text{H}]$  cannot totally be excluded.<sup>32</sup> 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.<sup>20</sup> More important is the influence of the acidic additives on 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  $\eta^3$ -allylic formation via reversible deprotonation.<sup>33</sup> 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,  $[\text{Ru}(\text{Cp}^*)\text{H}]$  species efficiently catalysed the isomerization through reversible insertion.<sup>34</sup> Therefore acidic additives might also play a role on the catalytic activity and prevent isomerization by regenerating  $[\text{Ru}(\text{Cp}^*)\text{H}_2]^+$  from neutral  $[\text{Ru}(\text{Cp}^*)\text{H}]$  and dinuclear ( $\mu\text{-H}$ ) monocationic ruthenium(II) species.<sup>32-35-37</sup>

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  $[\text{Ru}(\text{Cp}^*)]$ -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.<sup>38</sup> Propargylic amines **2** were prepared according to reported procedures.<sup>39</sup> Compounds **3f-j** were already reported in reference 20. Proton magnetic resonance (<sup>1</sup>H NMR) spectra were recorded on Bruker 400 MHz spectrometer and carbon magnetic resonance (<sup>13</sup>C NMR) spectra were performed at 100 MHz. Chemical shifts ( $\delta$ ) are reported in parts per million relative to residual solvent signals (CD<sub>2</sub>Cl<sub>2</sub> 5.32 and 53.84; C<sub>6</sub>D<sub>6</sub> 7.15 and 128.02, CD<sub>3</sub>OD 5.84 and 49.05). Coupling constants are reported in Hertz. <sup>1</sup>H 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\*)(CH<sub>3</sub>CN)<sub>3</sub>]PF<sub>6</sub>} (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/Et<sub>2</sub>O (80:20) as eluent afforded compound **3a** as yellow oil, 58 mg (74%), <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  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* = 12.9 Hz, 1H), 3.93 (bs, 1H), 3.67 (d, *J* = 12.9 Hz, 1H), 2.45 (s, 3H); <sup>13</sup>C NMR (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  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 C<sub>19</sub>H<sub>19</sub>NO<sub>2</sub>NaS [M+Na]<sup>+</sup> 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/Et<sub>2</sub>O (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%) <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  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); <sup>13</sup>C NMR (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  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, =CH<sub>2</sub>), 112.5 (I2, =CH<sub>2</sub>), 106.4, 106.1, 81.25, 47.4, 46.3, 45.8, 45.7, 28.4; GC-MS *m/z* (%): 271 (M<sup>+</sup>, 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/Et<sub>2</sub>O (70:30) as eluent afforded compound **3c** as colourless oil, 61 mg (70%) <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  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); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD)  $\delta$  171.0, 144.0, 143.7, 135.9, 131.9, 129.8, 129.6, 129.2, 129.1, 128.8, 127.9, 114.0, 111.3, 47.3, 47.0; HRMS calcd. for C<sub>19</sub>H<sub>17</sub>NONa [M+Na]<sup>+</sup> 298.12078 found 298.1207 (0 ppm).

### 3-methylene-4-(4-nitrophenyl)-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, 0,286 mmol) in THF (0,5 mL). Chromatography on silica gel using PE/Et<sub>2</sub>O (50:50) as eluent afforded compound **3d** as colourless oil, 57 mg (65%) <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>) 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); <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>) δ 149.3, 147.1, 143.8, 140.0, 135.4, 129.7, 128.6, 128.1, 127.6, 123.4, 114.0, 107.9, 47.9, 44.7, 21.0; HRMS calcd. for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>NaO<sub>4</sub>S [M+Na]<sup>+</sup> 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/Et<sub>2</sub>O (80:10:10) as eluent afforded compound **3e** as colourless oil (53 mg, 84%); <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) 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); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD) 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 C<sub>14</sub>H<sub>17</sub>NO<sub>2</sub>NaS [M+Na]<sup>+</sup> 286.0877 found 286.0876 (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/Et<sub>2</sub>O (70:30) as eluent afforded compound **4a** as yellow oil in a 93/7 diastereoisomeric mixture (70 mg, 82%), <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>) 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); <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>) 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 C<sub>20</sub>H<sub>23</sub>NO<sub>3</sub>NaS [M+Na]<sup>+</sup> 380.12964 found 380.1289 (1 ppm).

### Tert-butyl 2-methoxy-5-methylene-4-phenylpiperidine-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/Et<sub>2</sub>O (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. <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 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 H), 5.44 (bs, 0.6H), 4.93-4.87 (m, 1H), 4.47 (d, *J* = 14.0 Hz, 0.6H), 4.35-4.32 (m, 0.4H), 4.13 (bs, 1H), 3.80 (dd, *J* = 14.0, 4.0 Hz, 1H), 3.74 (d, *J* = 14.0 Hz, 0.4H), 3.64 (d, *J* = 14.0 Hz, 0.6H), 3.30 (s, 2.6H), 3.28 (s, 0.4H), 1.48 (s, 9H); <sup>13</sup>C NMR (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 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 C<sub>18</sub>H<sub>25</sub>NO<sub>3</sub>NaS ([M+Na]<sup>+</sup>) 326.17321 found 326.1728 (0 ppm).

### General Procedure for preparation of the acetals 5

To a dried pressure tube under an inert atmosphere, propargylic amine **2a** (5 mol%) and {[Ru(Cp\*)(CH<sub>3</sub>CN)<sub>3</sub>]PF<sub>6</sub>} (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<sup>40</sup>

Prepared from cinnamyl alcohol **1a** (50 mg, 0.239 mmol) and MeOH (1 mL). Filtration on silica gel using PE/Et<sub>2</sub>O (80:20) as eluent afforded compound **5a** in 90% yield. <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>) 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**

BH<sub>3</sub>: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. H<sub>2</sub>O<sub>2</sub> (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 H<sub>2</sub>O and CH<sub>2</sub>Cl<sub>2</sub> 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/Et<sub>2</sub>O (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*), <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>) 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* = 10.5 Hz, 1H), 3.33 (td, *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); <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>) 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 C<sub>20</sub>H<sub>25</sub>NO<sub>4</sub>NaS [M+Na]<sup>+</sup> 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\*)(CH<sub>3</sub>CN)<sub>3</sub>}PF<sub>6</sub> 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 <sup>1</sup>H NMR. Chromatography on silica gel using PE/Et<sub>2</sub>O (80:20) as eluent afforded compound **7a** as yellow oil, as yellow oil, δ 22.5 mg (75%), (*only the cis compound is described*) <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>) 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); <sup>13</sup>C NMR (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 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 C<sub>19</sub>H<sub>21</sub>NO<sub>2</sub>SNaS ([M+Na])<sup>+</sup> 350.11907 found 350.119 (0 ppm).

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