



**HAL**  
open science

## Intermolecular Rhodium(II)-Catalyzed Allylic C(sp<sup>3</sup>)-H Amination of Cyclic Enamides

Romain Rey-Rodriguez, Grégory Jestin, Vincent Gandon, Gwendal Grelier, Pascal Retailleau, Benjamin Darses, Philippe Dauban, Isabelle Gillaizeau

► **To cite this version:**

Romain Rey-Rodriguez, Grégory Jestin, Vincent Gandon, Gwendal Grelier, Pascal Retailleau, et al.. Intermolecular Rhodium(II)-Catalyzed Allylic C(sp<sup>3</sup>)-H Amination of Cyclic Enamides. *Advanced Synthesis and Catalysis*, 2018, 360 (3), pp.513-518. 10.1002/adsc.201701188 . hal-02366212

**HAL Id: hal-02366212**

**<https://hal.science/hal-02366212>**

Submitted on 15 Nov 2019

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Intermolecular Rhodium(II)-Catalyzed Allylic C(sp<sup>3</sup>)-H Amination of Cyclic Enamides

Romain Rey-Rodriguez,<sup>a,b</sup> Grégory Jestin,<sup>a</sup> Vincent Gandon,<sup>c</sup> Gwendal Grelier,<sup>b</sup> Pascal Retailleau,<sup>b</sup> Benjamin Darses,<sup>b</sup> Philippe Dauban,<sup>b\*</sup> and Isabelle Gillaizeau<sup>a\*</sup>

<sup>a</sup> Institute of Organic and Analytical Chemistry, ICOA UMR 7311 CNRS, Université d'Orléans, rue de Chartres, 45100 Orléans, France

[e-mail: [isabelle.gillaizeau@univ-orleans.fr](mailto:isabelle.gillaizeau@univ-orleans.fr)]

<sup>b</sup> Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Université Paris-Sud, Université Paris-Saclay, avenue de la terrasse, 91198 Gif-sur-Yvette, France

[e-mail : [philippe.dauban@cnrs.fr](mailto:philippe.dauban@cnrs.fr)]

<sup>c</sup> Institut de Chimie Moléculaire et des Matériaux d'Orsay, CNRS UMR 8182, Univ. Paris-Sud, Université Paris-Saclay, 91405 Orsay, France

Received: ((will be filled in by the editorial staff))



Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.201#####>. ((Please delete if not appropriate))

**Abstract.** The intermolecular Rh(II)-catalyzed C(sp<sup>3</sup>)-H amination of enamides gives access to new 4-aminopiperidine derivatives that are useful building blocks in medicinal chemistry. This efficient transformation proceeds at room temperature with complete regio- and chemoselectivity in favor of the allylic C(sp<sup>3</sup>)-H bond, and has a broad functional group tolerance. In addition, the matched combination of the chiral Rh<sub>2</sub>(S-nta)<sub>4</sub> (nta = (S)-N-1,8-naphthoylalanine) with an optically pure (S)-sulfonimidamide allows isolation of allylic amines with excellent stereocontrol.

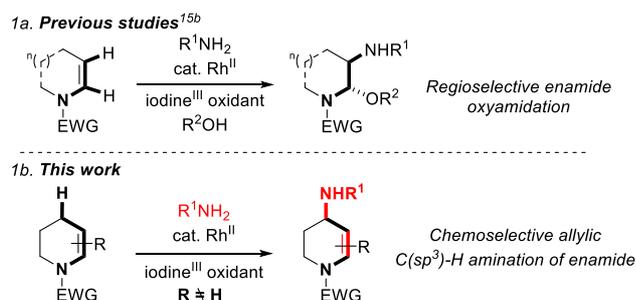
**Keywords:** Allylic amination; Enamide; Heterocycle; Nitrene; Rhodium catalysis

## Introduction

The ubiquity of nitrogen in life and material sciences is a source of inspiration for the design of selective C–N bond forming reactions. Significant achievements have been made to this end through the discovery of new processes for the direct amination of C(sp<sup>3</sup>)-H bonds.<sup>[1]</sup> Particularly, the recent development of transition metal-catalyzed nitrene C(sp<sup>3</sup>)-H insertion reactions<sup>[2]</sup> has culminated in the design of efficient methods that make catalytic C–H amination now a standard tool in the total synthesis of complex molecules.<sup>[3]</sup>

Catalytic allylic C(sp<sup>3</sup>)-H amination raises the issue of chemoselectivity because metallanitrenes are well known to add to alkenes to afford the corresponding aziridines.<sup>[2-4]</sup> Several solutions have first arisen from the use of tethered reagents that allow for delivering the metal-bound nitrene species in an intramolecular manner with high level of chemoselectivity. The development of fine-tuned Rh,<sup>[5]</sup> Ru,<sup>[6]</sup> Fe,<sup>[7]</sup> Co,<sup>[8]</sup> Ag,<sup>[9]</sup> and Mn<sup>[10]</sup> complexes has proved fruitful to

favor the functionalization of the allylic position. However, the corresponding intermolecular reaction is, by comparison, much more difficult to achieve. The first examples of efficient intermolecular chemoselective allylic C(sp<sup>3</sup>)-H amination reactions have been recently reported following the careful design of nitrene precursors and metal complexes,<sup>[11],[12]</sup> and these results demonstrate the need for further investigation to extend their scope.



**Figure 1.** Background for the study.

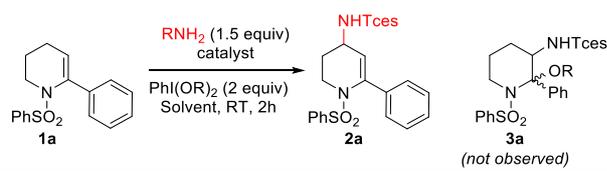
Another issue to address with catalytic C(sp<sup>3</sup>)-H amination reactions is their application to nitrogen heterocycles. Hyperconjugative effects, particularly, are responsible for the higher reactivity of C(sp<sup>3</sup>)-H bonds  $\alpha$ -to the nitrogen,<sup>[13]</sup> thereby making the remote functionalization of other sites difficult to perform, though efficient solutions have been reported.<sup>[14]</sup> We have recently demonstrated that catalytic nitrene transfers enable the regioselective intermolecular oxyamidation of various  $\pi$ -bonds.<sup>[15]</sup> Specifically, the application of rhodium-catalyzed nitrene additions<sup>[16]</sup> to enamides and enecarbamates affords oxyaminated products in high yields, that can be further transformed via the nucleophilic displacement of the resulting *N,O*-acetals (Figure 1a).<sup>[15b]</sup> However, while exploring the scope of the reaction, a different reactivity has been uncovered for C2- or C3-substituted enamides.<sup>[17]</sup> Herein, we report a novel access to 4-aminopiperidines,<sup>[18]</sup> a privileged motif in medicinal chemistry (i.e. aminobenzoquinolizine) resulting from a catalytic allylic C(sp<sup>3</sup>)-H amination (Figure 1b).

## Results and Discussion

Previous studies have shown that the use of the TcesNH<sub>2</sub> (2,2,2-Trichloroethoxysulfonamide)/Rh<sub>2</sub>(esp)<sub>2</sub> (esp:  $\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzene-dipropionate) system in the presence of olefins always affords products resulting from addition to the  $\pi$ -bond.<sup>[15,16]</sup> However, application to 2-phenyl-enamide **1a**<sup>[19]</sup> of the reaction conditions previously established for enamide oxyamidation led us to observe a complete switch in the chemoselectivity of the reaction (Table 1). Thus, instead of isolating the product resulting from functionalization of the  $\pi$ -bond, we isolated the allylic C(sp<sup>3</sup>)-H aminated derivative **2a** as the sole compound. No trace of the corresponding oxyamidated derivative **3a** was observed on the <sup>1</sup>H NMR spectrum of the crude reaction mixture. The high and unusual chemoselectivity of the transformation prompted us to undertake a systematic study as the intermolecular Rh-catalyzed allylic C(sp<sup>3</sup>)-H amination of enamide would afford a readily efficient access to relevant 1,3 diamino motifs. A rapid screening of the oxidants and their equivalents (Table 1, entries 1-3), the catalysts and their loading (entries 4-7), the solvents (entries 8-12) and the nitrene source (entry 13) in the presence of compound **1a** revealed that the best yield was obtained by using TcesNH<sub>2</sub> (1.5 equiv) as the nitrene source, in the presence of Rh<sub>2</sub>(esp)<sub>2</sub> (2 mol%) and PhI(OPiv)<sub>2</sub> (2 equiv) in toluene at room temperature (entry 1). Under these conditions, the corresponding allylic aminated enamide **2a** was isolated in 90% yield after 2 hours of reaction. Amination of toluene was observed as a side reaction when Rh<sub>2</sub>(OAc)<sub>4</sub> was used as the catalyst (entry 5).<sup>[20]</sup> No side reaction via the formation of the oxyamidated compound **3a** was observed in the presence of MeOH as a solvent (entries 11-12).<sup>[15b]</sup> By using TsNH<sub>2</sub> as the nitrene source, no reaction

occurred (entry 13). Control experiments showed no reactivity in the absence of catalyst or oxidant.

**Table 1.** Catalytic allylic C(sp<sup>3</sup>)-H amination of **1a**.<sup>[a]</sup>



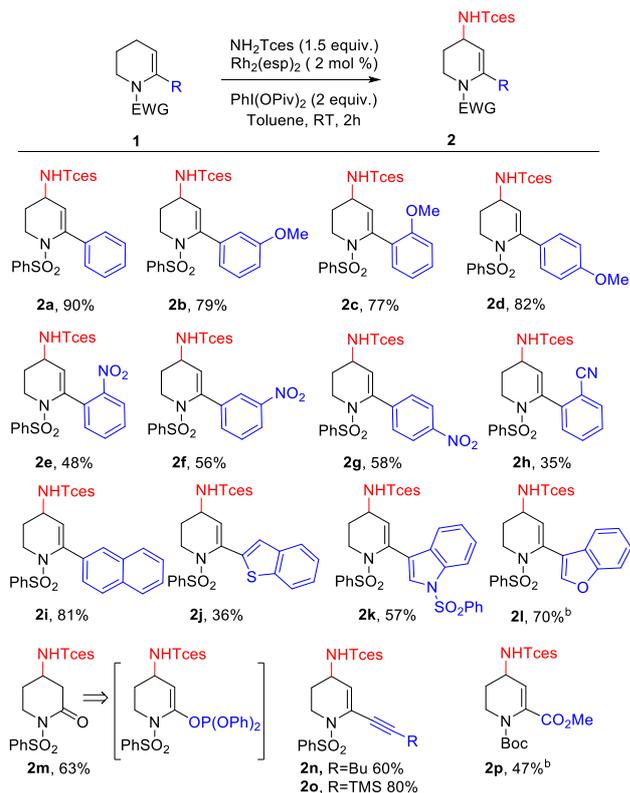
Entry	Catalyst	Oxidant	Solvent	Yield <sup>[b]</sup>
1	Rh <sub>2</sub> (esp) <sub>2</sub>	PhI(OPiv) <sub>2</sub>	Toluene	90%
2	Rh <sub>2</sub> (esp) <sub>2</sub>	PhI(OAc) <sub>2</sub>	Toluene	88 %
3 <sup>c</sup>	Rh <sub>2</sub> (esp) <sub>2</sub>	PhI(OPiv) <sub>2</sub>	Toluene	70 %
4 <sup>d</sup>	Rh <sub>2</sub> (esp) <sub>2</sub>	PhI(OPiv) <sub>2</sub>	Toluene	73 %
5 <sup>e</sup>	Rh <sub>2</sub> (OAc) <sub>4</sub>	PhI(OPiv) <sub>2</sub>	Toluene	0 %
6 <sup>d</sup>	Cu(OTf) <sub>2</sub>	PhI(OPiv) <sub>2</sub>	Toluene	0%
7 <sup>f</sup>	Cu <sub>2</sub> O, phenantroline	PhI(OPiv) <sub>2</sub>	Toluene	0 %
8	Rh <sub>2</sub> (esp) <sub>2</sub>	PhI(OPiv) <sub>2</sub>	(CH <sub>2</sub> Cl) <sub>2</sub>	45 %
9	Rh <sub>2</sub> (esp) <sub>2</sub>	PhI(OPiv) <sub>2</sub>	CH <sub>3</sub> CN	0 %
10	Rh <sub>2</sub> (esp) <sub>2</sub>	PhI(OPiv) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	85 %
11	Rh <sub>2</sub> (esp) <sub>2</sub>	PhI(OPiv) <sub>2</sub>	CCl <sub>4</sub> /MeOH (1:1)	81 %
12 <sup>g</sup>	Rh <sub>2</sub> (esp) <sub>2</sub>	PhI(OPiv) <sub>2</sub>	CCl <sub>4</sub> /MeOH(1:1)	85 %
13 <sup>h</sup>	Rh <sub>2</sub> (esp) <sub>2</sub>	PhI(OPiv) <sub>2</sub>	Toluene	0%

<sup>[a]</sup> Unless otherwise specified, all reactions were carried out using: **1a** (0.17 mmol), TcesNH<sub>2</sub> (0.25 mmol), Rh<sub>2</sub>(esp)<sub>2</sub> (2 mol%), PhI(OPiv)<sub>2</sub> (0.33 mmol) in toluene (2 ml) at rt for 2h. <sup>[b]</sup> Isolated yield. <sup>[c]</sup> 1 equiv. of oxidant was used. <sup>[d]</sup> 1 mol% of catalyst was used. <sup>[e]</sup> The compound of C(sp<sup>3</sup>)-H amination of toluene was isolated as the sole side product. <sup>[f]</sup> 1 mol% of catalyst and 2 mol% of ligand were used. <sup>[g]</sup> Reaction conducted at 0 °C. <sup>[h]</sup> TsNH<sub>2</sub> (1.5 equiv) was used as the nitrene source.

The optimized reaction conditions for C(sp<sup>3</sup>)-H amination were then applied to various C2-substituted enamides **1a-p** (Table 2).<sup>[19,21]</sup> The high chemoselectivity for allylic C(sp<sup>3</sup>)-H amination over oxyamidation was confirmed in each case. The expected allylic amines were isolated with yields of up to 90%. The reaction tolerates the presence of electron-donating or electron-withdrawing groups on the aromatic ring, the corresponding products having been isolated with yields in the 35-82% range (**2b-h**). It is worth mentioning that yields are intertwined with the electronic properties of the aryl substituents; the lowest yields being observed for electron-withdrawing substituents (**2e-h**). Given the prevalence of heterocycles in medicinal chemistry, we also evaluated the tolerance of this method to enamides bearing fused aromatic or heteroaromatic ring system at C2, such as a naphthalene (**1i**), a benzothiophene (**1j**), an indole (**1k**), or a benzofuran (**1l**). The bias of enamides **1j-l** toward allylic C(sp<sup>3</sup>)-H amination vs. oxyamidation persisted, and no product arising from the competitive functionalization of the heterocyclic double bond was detected.<sup>[15a]</sup> This result showcases the potential

application of this method to late stage diversification of biologically active compounds. An interesting result was also obtained starting from the enol phosphate **1m**. The product resulting from the C(sp<sup>3</sup>)-H amination reaction was hydrolyzed *in situ* to the corresponding 4-aminopiperidin-2-one **2m**, which could be advantageously used for further functionalization. Finally, enynes **2n** and **2o**, or enamide bearing an ester function (**2p**), which could serve as valuable synthetic intermediates, were tolerated.

**Table 2.** Rh catalyzed allylic C(sp<sup>3</sup>)-H amination of C2-substituted enamides **1**.<sup>[a]</sup>

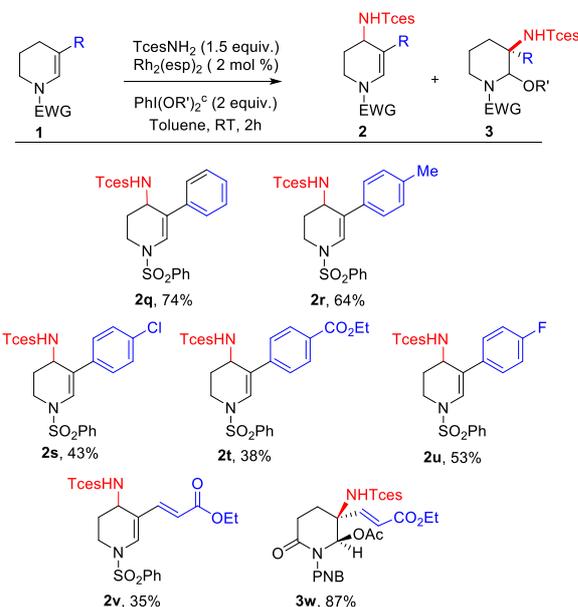


<sup>[a]</sup> Isolated yield. <sup>[b]</sup> 3 equiv. of substrate was employed.

These results then prompted us to extend the scope of the C(sp<sup>3</sup>)-H amination reaction toward C3-substituted enamides **1q-w** (Table 3).<sup>[22]</sup> Successful amination at the allylic position of **1q-v** was performed under optimized conditions to afford the corresponding new 4-amino-substituted enamides **2q-v** with complete chemoselectivity and good yields. We did not detect the formation of the corresponding oxyamidated compound **3**. Both electron-donating (**2r**) and electron-withdrawing (**2s-u**) functional groups were tolerated. As observed above, the electronic nature of aryl substituents directly impacts the reactivity of the adjacent allylic C(sp<sup>3</sup>)-H bond; electron-rich arenes provide the highest yields.<sup>[23]</sup> This trend was confirmed with dienamide **1v**. The presence of an electron-withdrawing substituent (i.e ester group) onto the dienamide reduces the reactivity of the proximal C(sp<sup>3</sup>)-H. Low yields observed in some cases were considered to be due to the instability of

product **2** under the oxidative reaction conditions. It is worth mentioning that degradation was observed starting from C2-alkyl enamides.

**Table 3.** Rh catalyzed allylic C(sp<sup>3</sup>)-H amination of C3-substituted enamides.<sup>[a]</sup>

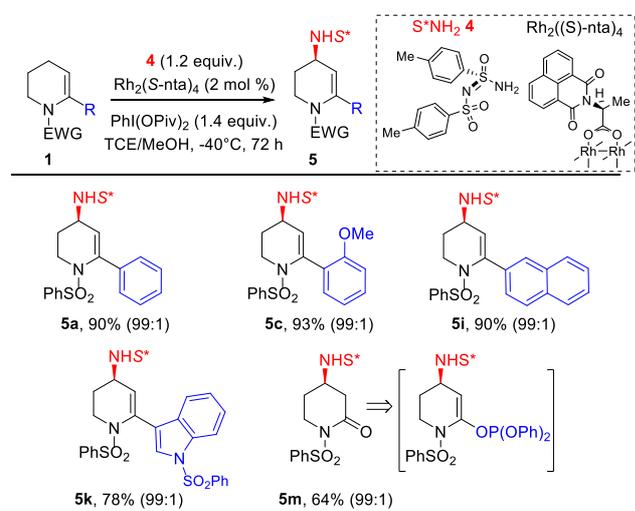


<sup>[a]</sup> Isolated yield. <sup>[b]</sup> Chemoselectivity determined by crude <sup>1</sup>H NMR. <sup>[c]</sup> PhI(OAc)<sub>2</sub> or PhI(OPiv)<sub>2</sub> was used, see Supporting Information.

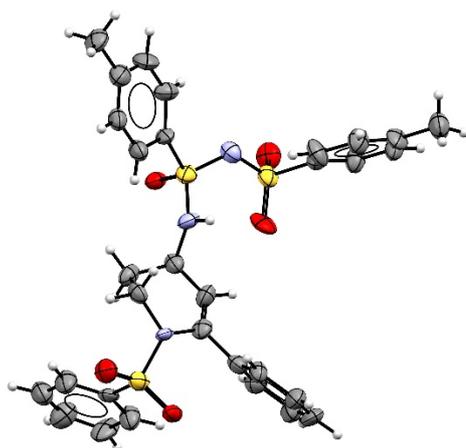
These results then prompted us to extend the scope of the C(sp<sup>3</sup>)-H amination reaction toward C3-substituted enamides **1q-w** (Table 3).<sup>[22]</sup> Successful amination at the allylic position of **1q-v** was performed under optimized conditions to afford the corresponding new 4-amino-substituted enamides **2q-v** with complete chemoselectivity and good yields. We did not detect the formation of the corresponding oxyamidated compound **3**. Both electron-donating (**2r**) and electron-withdrawing (**2s-u**) functional groups were tolerated. As observed above, the electronic nature of aryl substituents directly impacts the reactivity of the adjacent allylic C(sp<sup>3</sup>)-H bond; electron-rich arenes provide the highest yields.<sup>[23]</sup> This trend was confirmed with dienamide **1v**. The presence of an electron-withdrawing substituent (i.e ester group) onto the dienamide reduces the reactivity of the proximal C(sp<sup>3</sup>)-H. Low yields observed in some cases were considered to be due to the instability of product **2** under the oxidative reaction conditions. Moreover, these C3-substituted compounds also permitted us to assess the influence of the *N*-protecting group on the chemoselectivity of this process. Thus, allylic amination was observed starting from the *N*-(sulfonyl) dienamide **1v** whereas use of the (*p*-nitrobenzyl) endo-dienamide **1w** led to a complete switch of reactivity. Allylic amination was thus disfavored in presence of the enamide **1w**, although C3-substituted, but electronically deactivated. The oxyamidated product **3w** was isolated in 87% yield as the sole product with a complete diastereoselectivity in

favor of the *cis* isomer.<sup>[24]</sup> It is also noteworthy that no reaction occurred with 2,3-disubstituted enamide, probably due to steric hindrance.<sup>[25]</sup>

**Table 4.** Diastereoselective Rh-catalyzed C(sp<sup>3</sup>)-H amination of enamides **1**.<sup>[a]</sup>



<sup>[a]</sup> Isolated yield.



**Figure 2.** X-ray structure of **5a**.

The chemoselectivity observed for the allylic C(sp<sup>3</sup>)-H amination of enamides convinced us to consider whether we could also reach the same selectivity with the conditions previously reported for the stereoselective amination of hydrocarbons.<sup>[11b-d]</sup> This C(sp<sup>3</sup>)-H functionalization reaction involves the combination of the chiral rhodium complex Rh<sub>2</sub>(S-nta)<sub>4</sub> (*nta* = (*S*)-*N*-1,8-naphthoylalanine) with an optically pure chiral nitrene precursor, *i.e.* the (*S*)-sulfonimidamide **4** (Table 4).<sup>[26]</sup> This matched pair of reagents has been shown to promote the amination of benzylic and allylic substrates as well as that of alkanes, enol ethers and terpenes with high yields and excellent stereocontrol. If successful with enamides, it should give access to optically pure heterocyclic structures. Pleasingly, in presence of the (*S*)-

sulfonimidamide **4** and the chiral complex Rh<sub>2</sub>(S-nta)<sub>4</sub>, the 2-phenylenamide **1a** led exclusively to the chiral allylic amide **5a** isolated in 90% yield as the single (*R*)-isomer by analogy with our previous studies.<sup>[11b,26]</sup> Notably, the X-ray crystal structure of **5a** confirmed the stereochemistry of the 4-amino enamides **5** (Figure 2).<sup>[27]</sup> The 4-amino enamides **5c**, **5i**, **5k**, and **5m** were subsequently obtained with yields in the 64-93% range as single diastereoisomers. It is worth mentioning that **5m** thereby offers the possibility of performing further functionalization.<sup>[28]</sup> However, contrary to what was observed in Table 3 using the TcesNH<sub>2</sub>/Rh<sub>2</sub>(esp)<sub>2</sub> system, no reaction occurred starting from C3-substituted enamides, because the stereoselective C(sp<sup>3</sup>)-H amination with sulfonimidamides is sensitive to steric hindrance as observed in our previous studies.<sup>[11b,c]</sup>

## Conclusion

In summary, we have demonstrated that the chemoselectivity of catalytic nitrene additions can be tuned by the substitution of the alkene in the case of cyclic enamides. Thus, the presence of a C2- or a C3-substituent prevents the nitrene transfer from proceeding at the double bond, and the enamides undergo an intermolecular rhodium-catalyzed allylic C(sp<sup>3</sup>)-H amination to afford the corresponding amines with yields of up to 90%. This result underscores the ability of the sulfamate/Rh<sub>2</sub>(esp)<sub>2</sub> system to react preferentially with allylic C(sp<sup>3</sup>)-H bonds in an intermolecular process affording new C4-aminated enamides under mild conditions. Excellent reactivity and diastereoselectivity were also observed using a combination of the (*S*)-sulfonimidamide **4** and the chiral rhodium catalyst Rh<sub>2</sub>(S-nta)<sub>4</sub>. This reaction paves the way to the synthesis of complex biologically active molecules and/or for late stage diversification. Further investigations on expanding the scope and applications of this method are underway in our laboratory.

## Experimental Section

### General procedure for C4-aminated enamides **2**.

In an oven-dried sealable tube, enamide **1** (0.17 mmol, 1 equiv) was dissolved in dry toluene (2 mL). TcesNH<sub>2</sub> (57 mg, 0.25 mmol, 1.5 equiv), Rh<sub>2</sub>(esp)<sub>2</sub> (3 mg, 0.0034 mmol, 0.02 equiv), and PhI(OPiv)<sub>2</sub> (138 mg, 0.34 mmol, 2 equiv) were successively added and the reaction was stirred at room temperature for 2 hours. After completion of the reaction, the filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate) to afford the C4-aminated enamide **2**.

### General procedure for C4-aminated enamides **5**.

In an oven-dried sealable tube, enamide **1** (0.2 mmol, 1 equiv), Rh<sub>2</sub>(S-nta)<sub>4</sub> (5 mg, 0.004 mmol, 0.02 equiv), (-)-*N*-(*p*-toluenesulfonyl)-*p*-toluenesulfonimidamide **4** (78 mg, 0.24 mmol, 1.2 equiv) and 4Å molecular sieves (100 mg) were successively added, the tube was capped with rubber

septum then purged three times with argon. 1,1,2,2-tetrachloroethane (0.75 mL) and methanol (0.25 mL) were added under argon. The tube was cooled to -78°C and bis(*tert*-butylcarbonyloxy)iodobenzene (114 mg, 0.28 mmol, 1.4 equiv) was added. The reaction was stirred at -35°C for 3 days. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to give the desired product **5** isolated as unique diastereoisomer (>99:1).

## Acknowledgements

The authors thank the French National Research Agency (program n° ANR-11-IDEX-0003-02, CHARMMMAT ANR-11-LABX-0039, SynOrg ANR-11-LABX-0029, and ANR-15-CE29-0014-01) for financial support and fellowships (G. J., R. R.-R.).

## References

- [1] a) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417-424; b) F. Collet, R.H. Dodd, P. Dauban, *Chem. Commun.* **2009**, 5061-5074 ; c) D. N. Zalatan, J. Du Bois, *Top. Curr. Chem.* **2010**, *292*, 347-378; d) J. L. Jeffrey, R. Sarpong, *Chem. Sci.* **2013**, *4*, 4092-4106; e) S. Chiba, H. Chen, *Org. Biomol. Chem.* **2014**, *12*, 4051-4060 ; f) M.-L. Louillat, F. W. Patureau, *Chem. Soc. Rev.* **2014**, *43*, 901-910; g) R. R. Karimov, A. Sharma, J. F. Hartwig, *ACS Cent. Sci.* **2016**, *2*, 715-724; h) Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247-9301.
- [2] a) P. Müller, C. Fruit, *Chem. Rev.* **2003**, *103*, 2905-2960 ; b) M. M. Diaz-Requejo, P. J. Pérez, *Chem. Rev.* **2008**, *108*, 3379-3394; c) K. Huard, H. Lebel, *Chem. Eur. J.* **2008**, *14*, 6222-6230; d) S. Fantauzzi, A. Caselli, E. Gallo, *Dalton Trans.* **2009**, 5434-5443; e) T. G. Driver, *Org. Biomol. Chem.* **2010**, *8*, 3831-3846; f) J. W. W. Chang, T. M. U. Ton, P. W. H. Chan, *Chem. Rec.* **2011**, *11*, 331-357; g) J. L. Roizen, M. E. Harvey, J. Du Bois, *Acc. Chem. Res.* **2012**, *45*, 911-922; h) T. Uchida, T. Katsuki, *Chem. Rec.* **2014**, *14*, 117-129; i) R. J. Scamp, J. W. Rigoli, J. M. Schomaker, *Pure Appl. Chem.* **2014**, *86*, 381-393; j) J. Buendia, G. Grelier, P. Dauban, *Adv. Organomet. Chem.* **2015**, *64*, 77-118.
- [3] a) D. Karila, R. H. Dodd, *Curr. Org. Chem.* **2011**, *15*, 1507-1538; b) J. Egger, E. M. Carreira, *Nat. Prod. Rep.* **2014**, *31*, 449-455; c) B. Darses, R. Rodrigues, L. Neuville, M. Mazurais, P. Dauban, *Chem. Commun.* **2017**, *53*, 493-508.
- [4] L. Degennaro, P. Trinchera, R. Luisi, *Chem. Rev.* **2014**, *114*, 7881-7929.
- [5] a) D. N. Zalatan, J. Du Bois, *J. Am. Chem. Soc.* **2008**, *130*, 9220-9221 ; b) K. W. Fiori, C. G. Espino, B. H. Brodsky, J. Du Bois, *Tetrahedron* **2009**, *65*, 3042-3051.
- [6] M. E. Harvey, D. G. Musaev, J. Du Bois, *J. Am. Chem. Soc.* **2011**, *133*, 17207-17216.
- [7] S. M. Paradine, M. C. White, *J. Am. Chem. Soc.* **2012**, *134*, 2036-2039.
- [8] H. Lu, H. Jiang, Y. Hu, L. Wojtas, X. P. Zhang, *Chem. Sci.* **2011**, *2*, 2361-2366.
- [9] a) J. W. Rigoli, C. D. Weatherly, J. M. Alderson, B. T. Vo, J. M. Schomaker, *J. Am. Chem. Soc.* **2013**, *135*, 17238-17241; b) R. J. Scamp, J. G. Jirak, N. S. Dolan, I. A. Guzei, J. M. Schomaker, *Org. Lett.* **2016**, *18*, 3014-3017.
- [10] S. M. Paradine, J. R. Griffin, J. Zhao, A. L. Petronico, S. M. Miller, M. C. White, *Nat. Chem.* **2015**, *7*, 987-994.
- [11] a) N. S. Dolan, R. J. Scamp, T. Yang, J. F. Berry, J. M. Schomaker, *J. Am. Chem. Soc.* **2016**, *138*, 14658-14667; b) C. Liang, F. Collet, F. Robert-Peillard, P. Müller, R. H. Dodd, P. Dauban, *J. Am. Chem. Soc.* **2008**, *130*, 343-350; c) C. Lescot, B. Darses, F. Collet, P. Retailleau, P. Dauban, *J. Org. Chem.* **2012**, *77*, 7232-7240; d) J. Buendia, B. Darses, P. Dauban, *Angew. Chem. Int. Ed.* **2015**, *54*, 5697-5701. For a recent comprehensive review on allylic amination, see: e) R. L. Grangea, E. A. Clizbebe, P. A. Evans, *Synthesis* **2016**, *48*, 2911-2968.
- [12] For other relevant studies in the area of chemoselective intermolecular C(sp<sup>3</sup>)-H amination, see: a) J. L. Roizen, D. N. Zalatan, J. Du Bois, *Angew. Chem. Int. Ed.* **2013**, *52*, 11343-11346; b) E. N. Bess, R. J. DeLuca D. J. Tindall, M. S. Oderinde, J. L. Roizen, J. Du Bois, M. S. Sigman, *J. Am. Chem. Soc.* **2014**, *134*, 5783-5789; c) J. Wang, C. Zhao, Y. Weng, H. Xu, *Catal. Sci. Technol.*, **2016**, *6*, 5292-5303.
- [13] a) S. Toumieux, P. Compain, O. R. Martin, M. Selkti, *Org. Lett.* **2006**, *8*, 4493-4496; b) S. Wang, D. Romo, *Angew. Chem. Int. Ed.* **2008**, *47*, 1284-1286; c) M. Kono, S. Harada, T. Nemoto, *Chem. Eur. J.* **2017**, *23*, 7428-7432.
- [14] a) J. M. Howell, K. Feng, J. R. Clark, L. J. Trzepakowski, M. C. White, *J. Am. Chem. Soc.* **2015**, *137*, 1459014593; b) Y.-J. Liu, H. Xu, W.-J. Kong, M. Shang, H.-X. Dai, J.-Q. Yu *Nature* **2014**, *515*, 389-393.
- [15] a) S. Beaumont, V. Pons, P. Retailleau, R. H. Dodd, P. Dauban, *Angew. Chem. Int. Ed.* **2010**, *49*, 1634-1637; b) N. Gigant, G. Dequizez, P. Retailleau, I. Gillaizeau, P. Dauban *Chem. Eur. J.* **2012**, *18*, 90-94; c) G. Dequizez, J. Ciesielski, P. Retailleau, P. Dauban, *Chem. Eur. J.* **2014**, *20*, 8929-8933; d) J. Ciesielski, G. Dequizez, P. Retailleau, V. Gandon, P. Dauban, *Chem. Eur. J.* **2016**, *22*, 9338-9347.
- [16] a) K. Guthikonda, J. Du Bois, *J. Am. Chem. Soc.* **2002**, *124*, 13672-13673 ; b) K. W. Fiori, J. Du Bois, *J. Am. Chem. Soc.* **2007**, *129*, 562-568.
- [17] N. Gigant, L. Chausset-Boissarie, I. Gillaizeau, *Chem. Eur. J.* **2014**, *20*, 7548-7564.
- [18] P. Mattei, M. Boehringer, P. Di Giorgio, H. Fischer, M. Hennig, J. Huwyler, B. Koçer, B. Kuhn, B. M. Loeffler, A. MacDonald, R. Narquizian, *Bioorg. Med. Chem.*, **2010**, *20*, 1109-1113.
- [19] a) 2-substituted enamides **1** were synthesized by Pd cross-coupling reaction starting from enol phosphate derivatives: D. Mousset, I. Gillaizeau, J. Hassan, F. Lepifre, P. Bouyssou, G. Coudert, G. *Tetrahedron Lett.* **2005**, *21*, 3703-3705 and see Supporting Informations.

- [20] D. A. Powell, H. Fan, *J. Org. Chem.* **2010**, *75*, 2726-2729.
- [21] Various 5-, 6- and 7-membered ring cyclic enamides were prepared but the C(sp<sup>3</sup>)—H amination reaction proved successful only from the 6-membered ring compounds.
- [22] N. Gigant, L. Chausset-Boissarie, I. Gillaizeau, *Org. Lett.* **2013**, *15*, 816-819; d) N. Gigant, L. Chausset-Boissarie, M.-C. Belhomme, T. Poisson, X. Pannecoucke, I. Gillaizeau, *Org. Lett.* **2013**, *15*, 278-281; e) N. Gigant, I. Gillaizeau, *Org. Lett.* **2012**, *14*, 3304-3307.
- [23] See also: a) T. Newhouse, P. S. Baran, *Angew. Chem. Int. Ed.*, **2011**, *50*, 3362-3374; b) A. G. H. Wee, B. Liu, D. D. McLeod, *J. Org. Chem.* **1998**, *63*, 4218-4227.
- [24] The stereochemistry was unambiguously established by NMR 1D and 2D (see Supporting Information).
- [25] Molecular orbital coefficients of C2-Ph substituted enamide **1a**, C3-Ph substituted enamide **1q** and non-substituted enamide were obtained by DFT computations (see the Supporting Information), but they did not allow to rationalize the selectivity.
- [26] Our previous studies have shown that both chiral reagents are needed to secure good yields and stereocontrol. Moreover, the synthesis of known enantiopure amines and several X-ray crystallographic studies of various allylic products have demonstrated that (*R*)-enantiomers of the C-H aminated compounds are obtained by combining the (*S*)-sulfonimidamide with the (*S*)-rhodium complex. See: ref. 11b. (a) C. Liang, F. Robert-Peillard, C. Fruit, P. Müller, R. H. Dodd, P. Dauban, *Angew. Chem. Int. Ed.* **2006**, *45*, 4641-4644. (b) M. Mazurais, C. Lescot, P. Retailleau, P. Dauban, *Eur. J. Org. Chem.* **2014**, 66-79.
- [27] CCDC 1584973 (**5a**) contains the supplementary crystallographic data for this paper. This data is provided free of charge by the Cambridge Crystallographic Data Centre.
- [28] a) X.-H. Hu, X.-F. Yang, T.-P. Loh, *Angew. Chem. Int. Ed.*, **2015**, *54*, 15535-15539 and references cited herein; b) E. Claveau, I. Gillaizeau, A. Bruel, G. Coudert, *J. Org. Chem.* **2007**, *72*, 4832-4836.

Intermolecular Rhodium(II)-Catalyzed Allylic C(sp<sup>3</sup>)-H Amination of Cyclic Enamides*Adv. Synth. Catal.* **Year**, *Volume*, Page – Page

Romain Rey-Rodriguez, Grégory Jestin, Vincent Gandon, Gwendal Grelier, Pascal Retailleau, Benjamin Darses, Philippe Dauban,\* and Isabelle Gillaizeau\*

