Access to Polyfunctionalized Chiral Piperidines through Enantioselective Addition–Carbocyclization Cascade Reaction Catalyzed by a Rhodium(I)–Diene Complex

ARTICLE *in* ORGANIC LETTERS · OCTOBER 2015

Impact Factor: 6.36 · DOI: 10.1021/acs.orglett.5b02858

Organic LETTERS

Letter

pubs.acs.org/OrgLett

Access to Polyfunctionalized Chiral Piperidines through Enantioselective Addition–Carbocyclization Cascade Reaction Catalyzed by a Rhodium(I)–Diene Complex

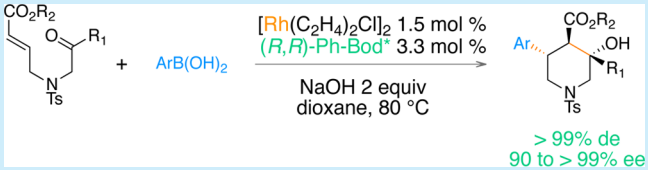
Fabien Serpier,[†] Jean-Louis Brayer,[‡] Benoît Folléas,[‡] and Sylvain Darses*[,†]

[†]PSL Research University, Chimie ParisTech - CNRS, Institut de Recherche de Chimie Paris, 11 rue Pierre et Marie Curie, 75005, Paris, France

[‡]Diverchim, ZAC du Moulin, 6 rue du Noyer, 95700 Roissy-en-France, France

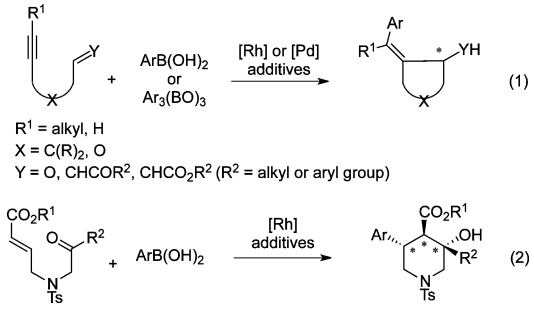
Supporting Information

ABSTRACT: A new addition–carbocyclization cascade reaction initiated by arylboronic acids and catalyzed by a rhodium/chiral diene complex is described. Starting from *N*-bridged oxoenoate derivatives, highly functionalized piperidines bearing three contiguous stereogenic centers were obtained with excellent enantio- and diastereoselectivities.



N-Heterocyclic compounds are found in many natural molecules and drugs[1] and are a class of compounds that exhibits interesting biological activities. As a consequence, several metal-catalyzed approaches have been developed in the past decade to access such functionalized scaffolds both in racemic and enantioselective versions, mainly cycloaddition,[2] hydroamination,[3] cycloisomerization,[4] ring-closing methathesis,[5] hydrogenation,[6] and reductive cyclization.[7] Formation of 5-membered saturated cycles (pyrrolidine) are by far the most studied compared to the 6-membered saturated analogues (piperidines). As a part of the reductive cyclization methods, the rhodium- or palladium-catalyzed carbocyclization reactions, initiated by the addition of organoboron reagents, represent a powerful approach for the formation of diversely substituted carbo- and heterocyclic compounds.[8] In most of the described examples, alkyne-tethered electron-deficient olefins, alkynals, or alkynones are the substrate of choice in such reactions and react via hydroarylation of the alkyne followed by intramolecular carbocyclization, leading to carbo- and *O*-heterocycles bearing one stereogenic center (Scheme 1, eq 1).[9,10] Although few approaches have been recently published to access pyrrolidines with high enantioselectivities,[11] the majority of the examples concern the formation of racemic nitrogen-containing five- and six-membered rings,[12] and only one method for the formation of chiral piperidines has been recently reported by our group.[11c]

Scheme 1. Addition–Carbocyclization Reactions Triggered by the Addition of Boron Derivatives



To extend the usefulness of carbocyclization reactions triggered by organoboron species, we wondered if chiral piperidines could be obtained in one step starting from the *N*-bridged oxoenoate derivatives (Scheme 1, eq 2), combining an α,β-unsaturated ester moiety as the entry point and a ketone as a secondary electrophilic function.

This approach would allow the formation of new piperidine derivatives with three stereogenic centers, including one quaternary center. A similar approach has been developed by Krische et al. for the formation of chiral carbocyclic compounds and also for the desymmetrization of prochiral diketones using a rhodium(I)/(*R*)-BINAP complex via an intramolecular conjugate addition/aldol cyclization sequence.[13] Even though this strategy was very effective for the formation of 5- and 6-membered carbocycles, the formation of optically active piperidines had not been explored, and the cyclization did not occur with α,β-unsaturated esters.

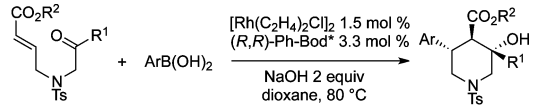
In our continuous interest in rhodium-catalyzed reactions with organoboron compounds,[14] we report for the first time the enantio- and diastereoselective rhodium-catalyzed arylative cyclization of nitrogen-tethered keto-enoate to provide chiral piperidines bearing three stereogenic centers (Scheme 2).

After some short investigations, we were pleased to find the reaction of substrate **1a** with phenylboronic acid (**2a**) was catalyzed by a chiral rhodium catalyst, generated in situ in the presence of the chiral C_2-symmetric diene (*R*,*R*)-Ph-Bod*,[15] using NaOH as a base and conducting the reaction at 80 °C (Table 1, entry 1). Two equivalents of sodium hydroxide was

Received: October 5, 2015
Published: October 15, 2015

DOI: 10.1021/acs.orglett.5b02858
Org. Lett. 2015, 17, 5496–5499

Scheme 2. Chiral Piperidines from Rhodium-Catalyzed Cascade Reactions



R^1 = Me, R^2 = Me (**1a**), R^1 = Me, R^2 = *i*Pr (**1b**), R^1 = Me, R^2 = *t*Bu (**1c**), R^1 = Ph, R^2 = *t*Bu (**1d**)

Ar = C_6H_5 (**2a**), 4-$CF_3C_6H_4$ (**2b**), 4-MeC_6H_4 (**2c**), 4-FC_6H_4 (**2d**), 4-$CF_3OC_6H_4$ (**2e**), 4-$NO_2C_6H_4$ (**2f**), 3-$CF_3C_6H_4$ (**2g**), 3-ClC_6H_4 (**2h**), 3-FC_6H_4 (**2i**), 3-$MeOC_6H_4$ (**2j**), 3-Cl-4-FC_6H_3 (**2k**)

Table 1. Rhodium-Catalyzed Addition−Carbocylization Reaction Triggered by $ArB(OH)_2$ on *N*-Bridged Oxoenoate Substrates[a]

entry	1	2	3	yield[e] (%)	ee[f] (%)
1	**1a**	**2a**	**3aa**	16	64
2	**1b**	**2a**	**3ba**	24	95
3	**1c**	**2a**	**3ca**	60	>99
4	**1c**	**2b**	**3cb**	60	>99
5[b]	**1c**	**2c**	**3cc**	59	99
6[b]	**1c**	**2d**	**3cd**	30	96
7[b]	**1c**	**2e**	**3ce**	67	98
8[b,c,d]	**1c**	**2f**	**3cf**	66	98
9[b]	**1c**	**2g**	**3cg**	66	98
10	**1c**	**2h**	**3ch**	68	98
11[b]	**1c**	**2i**	**3ci**	38	96
12[b]	**1c**	**2j**	**3cj**	47	98
13	**1c**	**2k**	**3ck**	35	98
14[b,d]	**1d**	**2b**	**3db**	38	90
15[b,d]	**1d**	**2e**	**3de**	55	91
16[b,d]	**1d**	**2g**	**3dg**	32	96
17[b,d]	**1d**	**2h**	**3dh**	52	91

[a]The reaction was conducted with **1** (0.3 mmol), **2** (0.6 mmol, 2 equiv), and NaOH (0.6 mmol, 2 equiv) in the presence of in situ generated chiral (*R*,*R*)-Ph-Bod*−rhodium complex (3 mol % Rh) in degassed dioxane at 80 °C. [b]Reaction performed with (*S*,*S*)-Ph-Bod* as ligand. [c]4 equiv of boronic acid was used. [d]Reaction performed at 100 °C. [e]Isolated yields. [f]Determined by HPLC analysis using a chiral stationary phase (see the Supporting Information).

necessary for the success of the reaction, and water had to be avoided to prevent the protonation of the rhodium enolate intermediate. Starting from **1a**, bearing a methyl ester moiety, the corresponding piperidine was obtained in low yield with a moderate enantioselectivity. By increasing the steric hindrance of the ester moiety (entries 2 and 3),[16] we were pleased to find that both yields and enantioselectivities were improved. Indeed, the rhodium-catalyzed cyclization of keto-enoate **1c**, bearing a *tert*-butyl ester, in the presence of phenylboronic acid (**2a**) occurred readily to afford the expected piperidine **3ca** in 60% yield as a unique diastereoisomer and an enantioselectivity above 99% (entry 3). Under identical conditions, we decided to examine the scope of the reaction using a variety of boronic acids (Table 1, entries 4−13). We were pleased to observe that the reaction of **1c** with diversely substituted arylboronic acids afforded the corresponding chiral piperidines with moderate to good yields and with high levels of both diastereoselectivity and enantioselectivity. Even if the reaction was more efficient using boronic acids containing electron-withdrawing substituents (entries 4, 7−10), these conditions proved to be quite general with all the arylboronic acids screened: enantioselectivities ranging from 96 to over 99% were observed in all cases. We also evaluated the carbocyclization of substrate **1d**, possessing a phenyl ketone (Table 1, entries 14−17). In order to occur, the reaction needed to be heated to 100 °C to observe a full conversion of the starting material and avoid the formation of a mixture of the desired piperidine **3** and the 1,4-addition adduct. Under these more forcing conditions, cyclization of substrate **1d** afforded diversely substituted chiral piperidines with a slight decrease in both yields and enantioselectivities (90−96% ee).

The structure of piperidine **3ca** was confirmed unambiguously by single-crystal X-ray analysis (Figure 1). The absolute

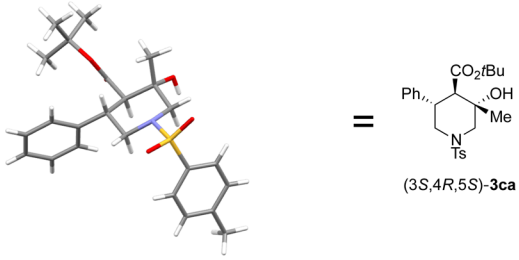


Figure 1. X-ray crystal structure of (3*S*, 4*R*, 5*S*)-**3ca**.

configuration of the three stereogenic centers of **3ca** was determined to be (3*S*,4*R*,5*S*) when (*R*,*R*)-Ph-Bod* was used as ligand. Indeed, assuming an analogous reaction pathway, the absolute configuration of the other described piperidines is supposed to be the same. The *syn* relationship between the ester and the methyl substituent is opposite to that observed by Krische et al. where the ketone and the methyl were *anti*.[13a]

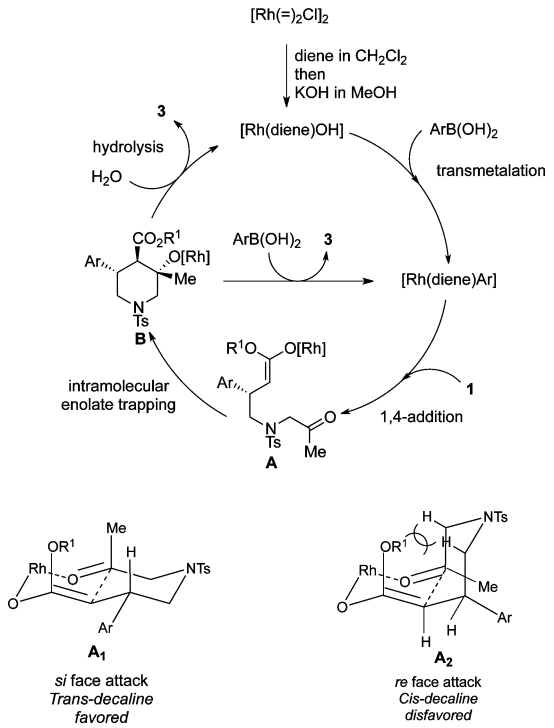
The overall mechanism is believed to involve transmetalation of the arylboron reagent to the in situ generated hydroxorhodium(I) complex followed by asymmetric 1,4-addition, providing the first stereogenic center and generating an oxa-π-allyl rhodium intermediate **A** (Scheme 3). The diastereoselective intramolecular trapping of the rhodium−enolate by the ketone functional group generated an alkoxorhodium(I) species **B**. For the regeneration of an active rhodium species, two pathways can be envisioned: direct transmetalation of the boronic acid to the alkoxorhodium(I) **B**, generating the arylrhodium complex, or protonation of the alkoxorhodium intermediate by water, arising from dehydration of boronic acid to boroxine, or boronic acid itself, generating the hydroxorhodium complex.

The excellent diastereoselectivity observed in this reaction could be explained by considering the transition state of the intramolecular rhodium−enolate trapping by the keto functional group. This transition state could be assumed to be represented as a Zimmermann−Traxler-type transition state involving the formation of decalins (Scheme 3). If the rhodium attacks on the *si* face of the ketone, a *trans*-decalin transition state is involved ($\mathbf{A_1}$), whereas a *cis*-decalin transition state is involved with an attack on the *re* face ($\mathbf{A_2}$). As the *cis*-decalin is destabilized by 1,3-diaxial interactions, the reaction must occur preferentially on the *si* face and provides the piperidines with the observed diastereoselectivity.

We next examined the reactivity of the piperidines, which can further be functionalized thanks to their versatile functional groups such as *tert*-butyl ester and tertiary hydroxyl groups. As an illustration, the reactivity of the tertiary alcohol function has been studied: the fluorination of compound **3ca** using DAST[17] (diethylaminosulfur trifluoride) gave the corresponding chiral

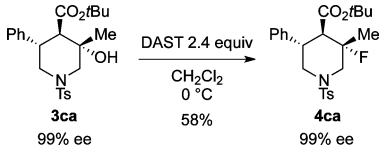
DOI: 10.1021/acs.orglett.5b02858
Org. Lett. 2015, 17, 5496−5499

Scheme 3. Possible Reaction Mechanism and Models for the Observed Diastereoselectivity



piperidine **4ca** in 58% yield and an enantiomeric excess of 99% (Scheme 4).

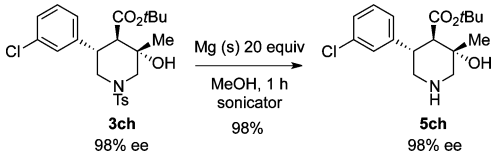
Scheme 4. Access to Chiral Fluorinated Piperidines



In this process, a quaternary stereogenic center with a carbon−fluoride bond was formed. Retention of the configuration of this stereocenter has been confirmed by NOESY experiments, showing that the reaction mechanism should involve an S_N1-type reaction.[18] To enhance the versatility of the chiral piperidines, we have also shown that the tosylated protecting group could be easily removed under mild conditions. Indeed, treatment of **3ch** with magnesium in anhydrous methanol under ultrasonic conditions[19] afforded deprotected piperidine **5ch** in 98% yield and unchanged enantioselectivity (Scheme 5).

In summary, we have developed an efficient atom-economic cascade reaction for the formation of new chiral piperidine derivatives with high levels of enantio- and diastereoselectivities. The compounds have been obtained through the first reported example of a rhodium-catalyzed asymmetric carbocyclization of *N*-tethered keto-enoate induced by boronic acids. The prepared piperidines are versatile, and the hydroxy substituent could be easily replaced by a fluorine, affording chiral fluorinated piperidines. Moreover, the tosyl protecting substituent could be easily removed under mild conditions, enhancing again the versatility of this rhodium-catalyzed cascade reaction for the formation of polyfunctionnalized chiral piperidine derivatives.

Scheme 5. Cleavage of the Tosyl Protecting Group



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02858.

X-ray diffraction data for **3ca** (CIF)

Experimental procedures, descriptions of the compounds, and ^1H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sylvain.darses@chimie-paristech.fr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Fabien Serpier thanks Diverchim for a grant.

■ REFERENCES

(1) (a) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435−446. (b) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845−5858.

(2) For reviews on catalytic dipolar cycloaddition, see: (a) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765−2810. (b) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484−4517.

(3) For reviews on hydroamination, see: (a) Hannedouche, J.; Schulz, E. *Chem. - Eur. J.* **2013**, *19*, 4972−4985. (b) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795−3892. (c) Chemler, S. R. *Org. Biomol. Chem.* **2009**, *7*, 3009−3019. (d) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−704.

(4) For reviews on cycloisomerization, see: (a) Trost, B. M.; Krische, M. J. *Synlett* **1998**, *1998*, 1−16. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813−834. (c) Fairlamb, I. J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1048−1052. (d) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271−2296.

(5) For reviews on ring-closing metathesis, see: (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238. (b) Hoveyda, A. H.; Malcolmson, S. J.; Meek, S. J.; Zhugralin, A. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 34−44.

(6) For a review on hydrogenation reactions of heteroaromatic compounds, see: Zhou, Y. *Acc. Chem. Res.* **2007**, *40*, 1357−1366.

(7) For selected examples of reductive cyclizations, see: (a) Rhee, J. U.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 10674−10675. (b) Tanaka, R.; Noguchi, K.; Tanaka, K. *J. Am. Chem. Soc.* **2010**, *132*, 1238−1239. (c) Masuda, K.; Sakiyama, N.; Tanaka, R.; Noguchi, K.; Tanaka, K. *J. Am. Chem. Soc.* **2011**, *133*, 6918−6921.

(8) For reviews on tandem reaction initiated by organoborons, see: (a) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217−224. (b) Youn, S. W. *Eur. J. Org. Chem.* **2009**, *2009*, 2597−2605. (c) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354−366.

(9) Carbocycle formation: (a) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54−55. (b) Miura, T.; Shimada, M.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1094−1095. (c) Shintani, R.; Tsurusaki, A.; Okamoto, K.;

DOI: 10.1021/acs.orglett.5b02858
Org. Lett. 2015, 17, 5496−5499

Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3909−3912. (d) Matsuda, T.; Makino, M.; Murakami, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4608−4611. (e) Miura, T.; Sasaki, T.; Harumashi, T.; Murakami, M. *J. Am. Chem. Soc.* **2006**, *128*, 2516−2517. (f) Shintani, R.; Isobe, S.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3795−3798. (g) Shen, K.; Han, X.; Lu, X. *Org. Lett.* **2012**, *14*, 1756−1759.

(10) Oxygen-containing heterocycle formation: (a) Song, J.; Shen, Q.; Xu, F.; Lu, X. *Org. Lett.* **2007**, *9*, 2947−2950. (b) Fang, X.; Li, C.; Tong, X. *Chem. Commun.* **2009**, 5311−5313. (c) Han, X.; Lu, X. *Org. Lett.* **2010**, *12*, 108−111. (d) Keilitz, J.; Newman, S. G.; Lautens, M. *Org. Lett.* **2013**, *15*, 1148−1151.

(11) (a) Tsukamoto, H.; Matsumoto, T.; Kondo, Y. *Org. Lett.* **2008**, *10*, 1047−1050. (b) Li, Y.; Xu, M. *Org. Lett.* **2014**, *16*, 2712−2715. (c) Serpier, F.; Flamme, B.; Brayer, J.-L.; Folléas, B.; Darses, S. *Org. Lett.* **2015**, *17*, 1720−1723.

(12) (a) Tsukamoto, H.; Ueno, T.; Kondo, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1406−1407. (b) Miura, T.; Takahashi, Y.; Murakami, M. *Org. Lett.* **2007**, *9*, 5075−5077. (c) Youn, S. W.; Song, J.; Jung, D. *J. Org. Chem.* **2008**, *73*, 5658−5661. (d) Williams, F. J.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 4459−4462. (e) Tsukamoto, H.; Kondo, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 4851−4854. For the formation of chiral tetrahydroquinolines, see: Zhang, X.; Han, X.; Lu, X. *Org. Lett.* **2015**, *17*, 3910−3913.

(13) (a) Cauble, D. F.; Gipson, J. D.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 1110−1111. (b) Bocknack, B. M.; Wang, L.-C.; Krische, M. J. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5421−5424.

(14) (a) Navarre, L.; Martinez, R.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* **2008**, *130*, 6159−6169. (b) Chuzel, O.; Roesch, A.; Genet, J.-P.; Darses, S. *J. Org. Chem.* **2008**, *73*, 7800−7802. (c) Gendrineau, T.; Demoulin, N.; Navarre, L.; Genet, J.-P.; Darses, S. *Chem. - Eur. J.* **2009**, *15*, 4710−4715. (d) Lefevre, N.; Brayer, J.-L.; Folléas, B.; Darses, S. *Org. Lett.* **2013**, *15*, 4274−4276.

(15) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584−13585.

(16) For some similar influence of the steric hindrance of the ester moiety in 1,4-addition reactions, see: Shintani, R.; Hayashi, T. *Org. Lett.* **2011**, *13*, 350−352.

(17) (a) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214−8264. (b) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, 2561−2578. (c) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574−578.

(18) Shellhamer, D. F.; Briggs, A. A.; Miller, B. M.; Prince, J. M.; Scott, D. H.; Heasley, V. L. *J. Chem. Soc., Perkin Trans. 2* **1996**, 973−977.

(19) Nyasse, B.; Grehn, L.; Ragnarsson, U. *Chem. Commun.* **1997**, 1017−1018.

DOI: 10.1021/acs.orglett.5b02858
Org. Lett. 2015, 17, 5496−5499