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Chiral Pyrrolidines and Piperidines from Enantioselective Rhodium-Catalyzed Cascade Arylative Cyclization

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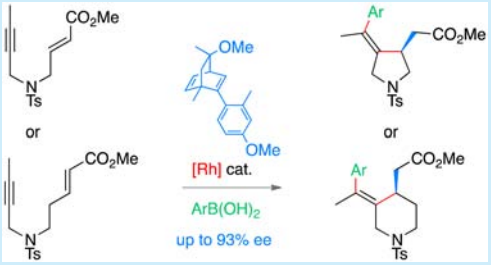
Supporting Information

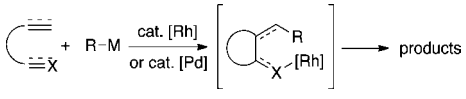
ABSTRACT: A new rhodium-catalyzed asymmetric arylative cyclization of nitrogen-tethered alkyne-enoate with arylboronic acids is described. In this process two new carbon−carbon bonds and one stereocenter are formed, providing access to pyrrolidines and piperidines with good enantioselectivities by to the use of C_1-symmetric chiral monosubstituted diene ligands.



Transition-metal catalyzed cascade reactions provide powerful methods for the elaboration of complex molecules because they involve multiple carbon−carbon or carbon−heteroatom bond formations from relatively simple substrates in an atom-economical way.[1] Among them, rhodium- and palladium-catalyzed tandem annulations triggered by the addition of organoboron reagents to activated alkenes or alkynes afford a useful strategy for the construction of cyclic compounds.[2]

In this approach, a molecule bearing two unsaturated functional groups is cyclized in the presence of Rh(I)-aryl or Pd(II)-aryl species generated *in situ* from transmetalation of the arylboron species (Scheme 1). The more reactive functional group (for example an alkyne) provides the entry point for the addition of the Rh(I)-aryl via a first intermolecular carbometalation reaction, which triggers the second intramolecular carbometalation of the less reactive functional group to construct a cyclic skeleton.

Scheme 1. Rhodium- and Palladium-Catalyzed Tandem Annulations Triggered by the Addition of Organoboron Reagents



Furthermore, in the presence of an appropriate chiral ligand, an asymmetric version can be envisioned to access chiral cyclic compounds.

Although this strategy has been used for the formation of chiral carbocyclic compounds,[3] only a few examples have been described for the formation of chiral heterocyclic compounds,[4] and particularly *N*-heterocyclic molecules.[5] The Tsukamoto group has described the enantioselective palladium-catalyzed arylative cyclization of allenyl aldehydes to provide chiral pyrrolidines.[6] Xu et al. described the preparation of pyrrolidines bearing a tertiary allylic alcohol chiral center via the rhodium-catalyzed tandem cyclization of nitrogen-bridged 5-alkynones with arylboronic acids.[7] In most of these processes, carbocyclization occurs through the addition of the generated vinyl- or alkylrhodium species to an aldehyde or ketone. We wondered if we could access *N*-heterocyclic compounds via the trapping of the vinylrhodium species with an enoate (carbocyclization of alkyne tethered enoate), an approach that has scarcely been described in the carbocyclic series,[3d,f] and recently via the desymmetrization of alkyne tethered cyclohexadiones.[4b]

In our continuous interest in rhodium-catalyzed reactions with organoboron compounds,[8] we report for the first time the enantioselective rhodium-catalyzed arylative cyclization of nitrogen-tethered alkyne-enoate to provide chiral pyrrolidines and piperidines.

As a reaction model, we first investigated the formation of pyrrolidine **3aa** via the reaction of readily available alkyne-enoate **1a** with phenylboronic acid (**2a**), in the presence of rhodium complexes and chiral ligands (Table 1).

As the reaction was very sluggish in the presence of chiral phosphane ligands (entries 1−2) we envisaged the use of chiral diene ligands that have been really useful in rhodium-catalyzed processes and other reactions.[9] In the presence of commercially available disubstituted C_2-type symmetric chiral dienes (entries 3−5), low yields and moderate enantioselectivities were achieved. However, using C_1-type symmetric dienes developed by Carreira and us,[10] better yields were obtained and the levels of enantioselectivity could be easily tuned by the nature and the

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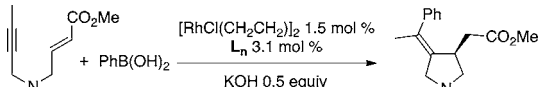
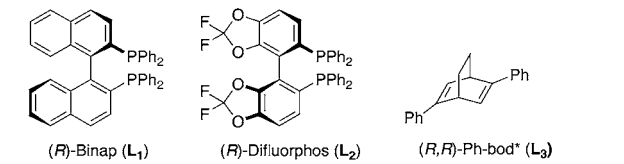
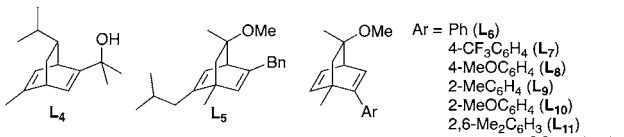
Table 1. Evaluation of Chiral for the Rh-Catalyzed Arylative Cyclization of 1a[a]



1a 3aa



(*R*)-Binap (L_1) (*R*)-Difluorphos (L_2) (*R,R*)-Ph-bod* (L_3)



L_4 L_5

Ar = Ph (L_6)
4-$CF_3C_6H_4$ (L_7)
4-$MeOC_6H_4$ (L_8)
2-MeC_6H_4 (L_9)
2-$MeOC_6H_4$ (L_{10})
2,6-$Me_2C_6H_3$ (L_{11})
2-Me-4-$MeOC_6H_3$ (L_{12})
2,4-$(MeO)_2C_6H_3$ (L_{13})

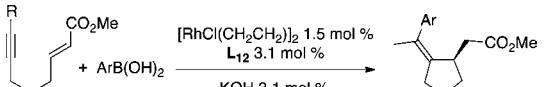
entry	L_n	yield[b] (%)	ee[c] (%)
1	L_1	<10	nd[d]
2	L_2	<10	nd[d]
3	L_3	16	72
4	L_4	16	63
5	L_5	21	68
6	L_6	48	59
7	L_7	49	40
8	L_8	72	59
9	L_9	52	89
10	L_{10}	53	90
11	L_{11}	14	16
12	L_{12}	61	90
13	L_{13}	63	88

[a]The reaction was conducted with **1a** (0.31 mmol), **2a** (0.62 mmol, 2 equiv) in the presence of an in situ generated chiral ligand−rhodium complex (3 mol % Rh) in degassed dioxane/water 10:1 at 60 °C. [b]Isolated yields of **3aa**. [c]Enantiomeric excess determined by chiral HPLC. [d]Not determined.

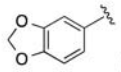
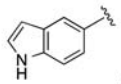
position of the substituent of the aromatic ring of the diene. Indeed, with 4-substituted chiral dienes, the levels of enantioselectivity were moderate (entries 6−8) whereas the presence of an ortho-substituent resulted in an increase of the ee up to 90% (entries 9−10). Increasing the steric hindrance in the ortho position (entry 11) was detrimental on both yield and enantioselectivity. Combining the positive effect of a 4-methoxy substituent on the yield (entry 8) with the necessity to have an ortho-substituent for high enantioselectivity, chiral dienes L_{12} and L_{13} were prepared and evaluated (entries 12−13). Good enantioselectivities were achieved and yields could be slightly increased; chiral diene L_{12} was selected for the rest of the study because of its ease of preparation. After some further optimization (solvent, amount of base) we were pleased to find that reaction of **1a** with **2a** occurred smoothly at 60 °C, in a mixture of methanol and water as solvent, in the presence of a rhodium catalyst complexed with C_1-symmetric chiral diene ligand L_{12}, affording chiral pyrrolidine **3aa** in 63% yield and an enantiomeric excess of 92% (Table 2, entry 1).

We wondered if an increase of steric hindrance at the ester moiety would result in increased enantioselectivity as observed in other rhodium-catalyzed reactions.[8a,11] However, the use of

Table 2. Chiral Pyrrolidines from Rh/Chiral Diene-Catalyzed Arylative Cyclization of 1a[a]



1a 3

entry	2 (Ar =)	3	yield[b] (%)	ee[c] (%)
1	C_6H_5 (**2a**)	**3aa**	63	92
2[d]	**2a**	**3ba**	45	91
3	4-$MeOC_6H_4$ (**2b**)	**3ab**	61	93
4	4-*t*-BuC_6H_4 (**2c**)	**3ac**	61	91
5	4-$CF_3C_6H_4$ (**2d**)	**3ad**	74	93
6	4-BrC_6H_4 (**2e**)	**3ae**	61	91
7	2-Np (**2f**)	**3af**	70	89
8	 (**2g**)	**3ag**	52	92
9	 (**2h**)	**3ah**	57	89
10	2-MeC_6H_4 (**2g**)	**3ag**	traces	nd[e]

[a]The reaction was conducted with **1a** (0.31 mmol), **2** (0.62 mmol, 2 equiv) in the presence of an in situ generated chiral diene−rhodium complex (3 mol % Rh) in degassed methanol/water 10:1 at 60 °C. [b]Isolated yields of **3**. [c]Enantiomeric excess determined by chiral HPLC. [d]Using enyne **1b** bearing an isopropyl ester instead of the methyl ester. [e]Not determined.

isopropyl ester alkyne-eneoate **1b** (entry 2) did not bring any improvement to the stereochemical outcome of the reaction, accompanied by a lower yield in carbocyclized adduct **3ba**. The optimized conditions proved to be quite general, and a variety of arylboronic acids participated in the reaction, affording a variety of chiral pyrrolidines bearing an all-carbon tetrasubstituted olefin (entries 3−11). Importantly the yields and enantiomeric excesses of pyrrolidines **3** were not influenced by the electronic properties (electron-withdrawing or -releasing substituents) of the arylboron reagent (entries 3−6). Interestingly, a bromo-substituted arylboronic acid also underwent addition to **1a**, affording highly functionalized substrate **3ae**, which can be further functionalized by palladium-catalyzed cross-coupling, providing further opportunities to access, in a straightforward way, more complex structures. The presence of an ortho-substituent on the arylboronic acid (entry 10) was detrimental, and the conversion was very low.

We next envisaged to access chiral piperidines using an analogous method, but starting from nitrogen-tethered 1,7-enynes instead of the previously used 1,6-enynes. To that end, two new nitrogen-tethered alkyne enoates were prepared and evaluated: **1c** bearing a supplementary carbon atom on the enoate moiety compared to **1a** and **1d** where a carbon atom has been added on the alkyne side (Scheme 2). We were pleased to find that, under identical conditions and using the same C_1-symmetric chiral diene ligand L_{12}, the rhodium-catalyzed arylative cyclization occurred readily on these substrates. With substrate **1c** the levels of enantioselectivity were similar to those observed for the formation of pyrrolidine derivatives. However,

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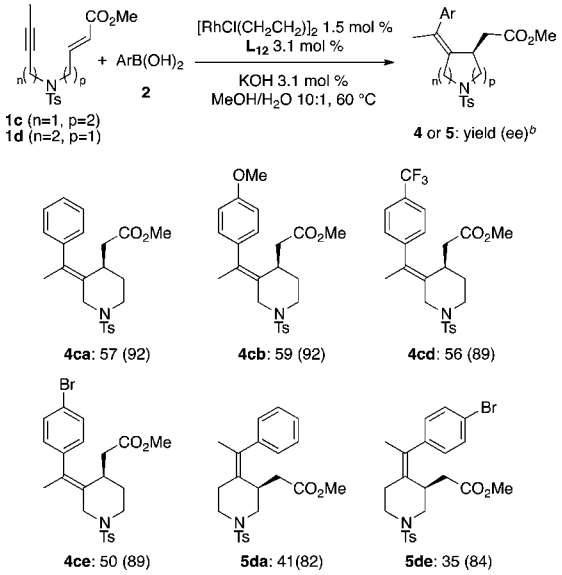
Scheme 2. Chiral Piperidines from Rh/Chiral Diene-Catalyzed Arylative Cyclization of 1b and 1c[a]



[a]The reaction was conducted with **1c** or **1d** (0.31 mmol), **2** (0.62 mmol, 2 equiv) in the presence of an in situ generated chiral diene−rhodium complex (3 mol % Rh) in degassed methanol/water 10:1 at 60 °C. [b]Isolated yields of **4** or **5** and enantiomeric excess determined by chiral HPLC.

when enyne **1d** was engaged in the rhodium-catalyzed arylative cyclization, a slight decrease in the enantioselectivity was observed (ee = 82% and 84%). Overall, it appeared that chiral piperidines could also be obtained using the same reaction conditions used for the formation of pyrrolidines.

The structure of piperidine **4ce** was confirmed unambiguously by single-crystal X-ray analysis, and the formed chiral center was determined to have the *R* configuration (Figure 1). Indeed, assuming an analogous reaction pathway, the absolute configuration of the other described pyrrolidines and piperidines is supposed to be the same.

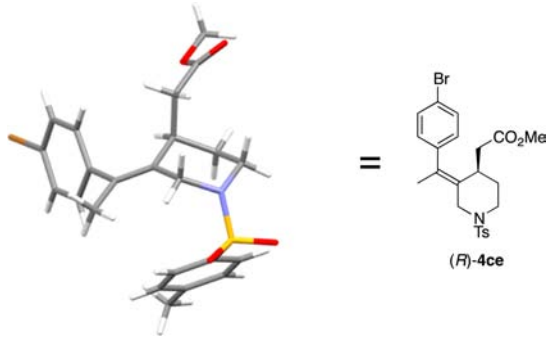
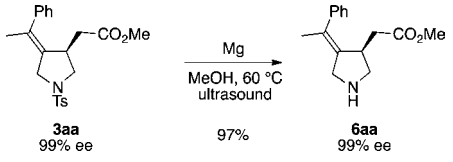


Figure 1. X-ray crystal structure of (*R*)-**4ce**.

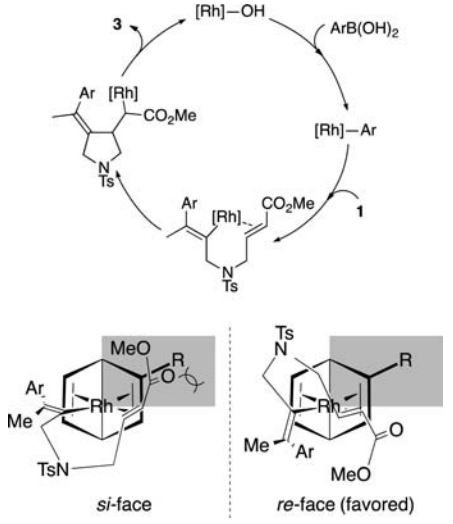
In all the prepared *N*-heterocyclic compounds, the tosylamide link was used because of the ease of preparation of the starting material compared to other protecting nitrogen groups, but it could easily be removed using mild conditions. Indeed, treatment of **3aa** of 99% ee (obtained by recrystallization of a 92% ee sample in methanol) with magnesium in anhydrous methanol under ultrasonic conditions[12] afforded deprotected pyrrolidine **6aa** in 97% yield and unchanged enantioselectivity (Scheme 3).[13]

Scheme 3. Deprotection of the Ts group



The overall mechanism is believed to involve transmetalation of the arylboron reagent to the in situ generated hydroxyrhodium(I) complex followed by the regioselective insertion of the alkyne into the arylrhodium(I) bond giving a vinylrhodium intermediate (Scheme 4). This vinylrhodium

Scheme 4. Possible Reaction Mechanism and Models for Enantioselectivity



intermediate undergoes intramolecular 1,4-addition, forming the pyrrolidine or piperidine ring and generating a rhodium-enolate intermediate. On protonation with water, the latter liberates product **3**, regenerating the active hydroxyrhodium species. The stereoselectivity observed during the carbocyclization can be rationalized by the dissymmetry created by the monosubstituted chiral diene at the rhodium center. Formation of the (*R*)-isomer is the result of preferred complexation of the enoate moiety on the *re*-face to the rhodium center to avoid steric interaction with the chiral diene substituent (Scheme 4).

In conclusion, we have developed a new, enantioselective rhodium-catalyzed cascade reaction of nitrogen-tethered alkyne-enoate with arylboronic acids, allowing access to chiral pyrrolidine and piperidines. Good yields and high enantioselectivities were generally achieved thanks to the use of an easily accessible C_1-symmetric chiral diene ligand.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, description of the compounds, and X-ray diffraction of **4ce**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) Due to the instability of **6aa** during HPLC analysis, it was converted into the Boc derivative that was analyzed by HPLC: see Supporting Information.

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