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Rhodium-catalyzed asymmetric intramolecular hydroarylation of allenes: access to functionalized benzocycles†

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A rhodium-catalyzed regio- and enantioselective cyclization of tethered allenylbenzenes is reported. Employing a Rh^{I}/Josiphos catalytic system a diverse set of 6-membered, α-chiral benzocycles were obtained, scaffolds found in many bioactive compounds. Moreover, a gram scale reaction as well as the application of suitable transformations are demonstrated.

Hetero- and carbocycles are ubiquitous in natural products, pharmaceuticals and functional molecules.[1] In particular, benzocycles bearing an α-chiral carbon center are important structural motives in natural isolates ((−)-bruceol and (−)-Δ^9-*trans*-tetrahydrocannabinol) and pharmaceuticals (levonantradol) (Fig. 1).[2,3]

One general approach for the synthesis of α-chiral benzocycles is the intramolecular C-allylation of electron rich benzenes, in which these proceed as Friedel–Crafts-type alkylation reactions.[4] In particular, the groups of Hamada and You contributed to the development of intramolecular, catalytic asymmetric dearomatization (CADA) reactions through Pd^0- and Ir^I-catalyzed C-allylation of phenols and anilines.[5] Furthermore, You and Carreira developed different asymmetric intramolecular allylic alkylations of phenols, anilines and general electron-rich arenes using Ir^I/phosphoramidite-based catalyst systems.[6]

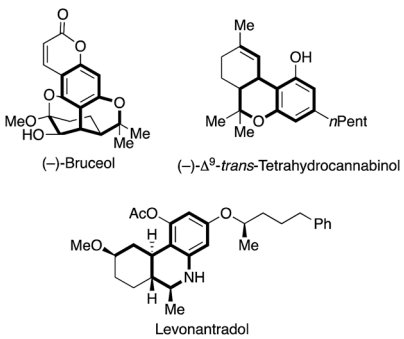
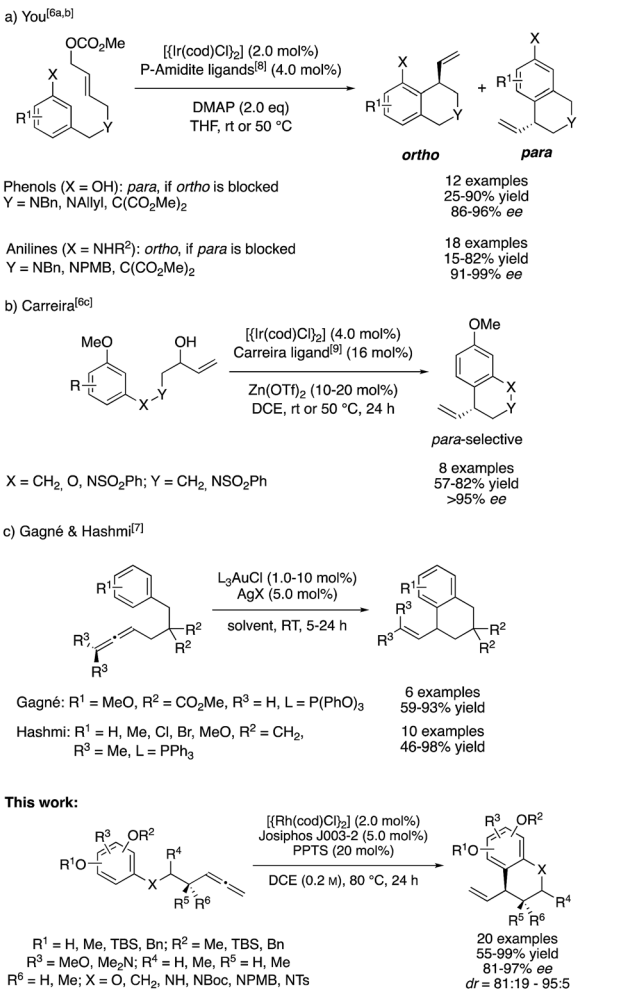


Fig. 1 Natural products and bioactive compounds possessing an α-chiral benzocyclic scaffold.



Scheme 1 Strategies for the synthesis of allylic benzocycles.

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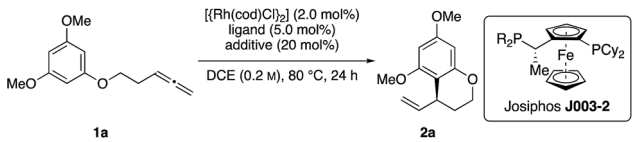
Despite their respective synthetic utility and their excellent selectivities, these methods represent allylic substitutions and thus violate the principle of atom economy by formation of stoichiometric amounts of a side product. In this context, the addition of C–H pronucleophiles to C–C multiple bonds is of great synthetic interest. Following this thought, Gagné and Hashmi developed an intramolecular, Au^{I}-catalyzed addition of benzene derivatives to terminal and internal allenes for the preparation of racemic allylic benzocycles (Scheme 1).[7a,b]

Throughout the last years, we reported on a series of Rh^{I}-catalyzed chemo-, regio- and enantioselective coupling reactions involving allenes[10] and alkynes[11] as allylic electrophile precursors with various pronucleophiles.[12] Meanwhile, we were also able to expand this methodology toward asymmetric intramolecular transformations.[13] However, the X–H pronucleophiles were always of an acidic character. On the basis of these previous studies, we wondered whether an allylic Rh^{III}-complex, which is generated in the presence of a suitable Brønstedt-acid additive,[14] can be trapped by a sufficiently nucleophilic reagent in a regio- and enantioselective fashion. In the recent past, Dong and our group confirmed this hypothesis by developing asymmetric additions of indoles to allenes and alkynes, respectively.[15] In this context, we herein report a Rh^{I}-catalyzed, asymmetric addition of tethered allenylarenes providing the desired chiral benzocycles.

Initial reactivity assays were carried out using allenylbenzene **1a** in the presence of [{Rh(cod)Cl}$_2$] (2.0 mol%), dppf (**L1**) (5.0 mol%) and TFA (20 mol%) in DCE at 80 °C (Table 1, entry 1). To our delight we obtained the allylated benzocycle **2a** in a high yield of 92%. Supporting our previously mentioned hypothesis, no conversion was observed in the absence of an acidic additive (entry 2). By screening numerous chiral bidentate ligands we were pleased to discover that Josiphos ligand **J003-2** led to a formation of the desired product in good yield (70%) and promising enantioselectivity (54% ee) (entry 3). After evaluation of different acids and pyridinium salts, we observed that PPTS provided the desired product **2a** in 73% yield and 90% ee (entry 4). In contrast, a similar yield with lower enantiomeric excess was obtained in the presence of free *p*-toluenesulfonic acid. These different results are possibly effects of different counter anions.[16] As to be expected, similar results in terms of yield and enantioselectivity were obtained using the enantiomeric Josiphos ligand **J003-1**.[17]

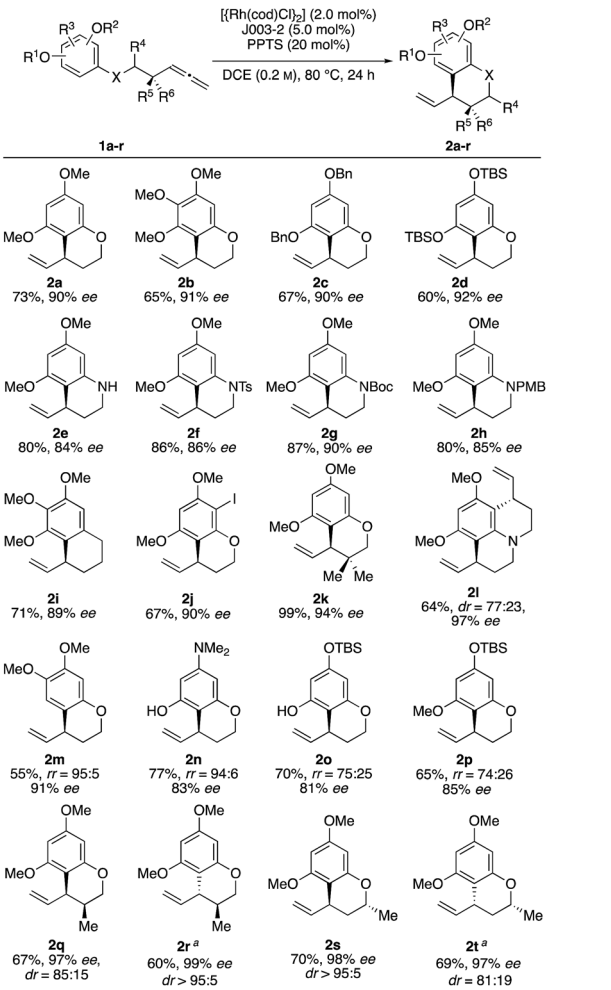
With these optimized conditions in hand, we sought to examine the reaction scope (Scheme 2). Towards this end, we subjected a variety of different benzenes to the indicated reaction conditions.[18] We were pleased to see that several symmetrical allenylarenes were successfully converted into the corresponding products **2a–2h** in good yields and high enantioselectivities. Aside from substrates that incorporate heteroatom tethers, benzocyclic product **2i** was isolated in good yield and very good enantioselectivity, as well. Notably, even an iodide-substituted benzene – prone for enabling side reactions by facile oxidative addition of the rhodium catalyst – could be implemented in the catalysis. Furthermore, the double allylated

Table 1 Rhodium-catalyzed intramolecular, enantioselective cyclization of allenylbenzenes[a]



Entry	Ligand	Additive	Solvent	Yield[b]	ee[c]
1	dppf (**L1**)[d]	TFA	DCE	92%	*rac*
2	dppf (**L1**)	—	DCE	—	—
3	**J003-2**	TFA	DCE	70%	54%
4	**J003-2**	PPTS	DCE	73%	90%
5	**J003-2**	*p*-TolSO$_3$H	DCE	80%	66%
6	**J003-1**[e]	PPTS	DCE	72%	−90%

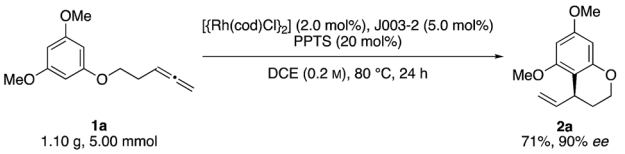
[a] Reactions were performed in 0.4 mmol scales. [b] Yield of isolated product. [c] The ee was determined by HPLC analysis using a chiral stationary phase. [d] dppf = 1,1′-bisdiphenylphosphinoferrocene. [e] **J003-1** = enantiomer of Josiphos ligand **J003-2.**



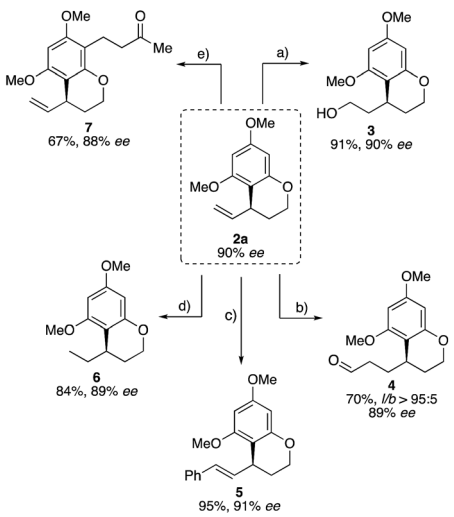
Scheme 2 Scope of intramolecular addition of arenes to allenes. Reactions were performed in 0.4 mmol scales. [a] J003-1 was used instead of J003-2.

product **2l** could be synthesized after double ring closure in 64% yield, a dr of 77 : 23 and 97% ee. Interestingly, the use of substrates **1m** and **1n** led to exclusive cyclization at the position *para* to the methoxy or amine substituent. This stands in contrast to observations by You, where product mixtures in dependence of the substituents were usually observed. Due to the presence of a TBSO-group in *meta* position, which is sterically more demanding than the hydroxy or methoxy group, the 6-membered ring was preferably closed in *para*-position for substrates **1o** and **1p**.[19]

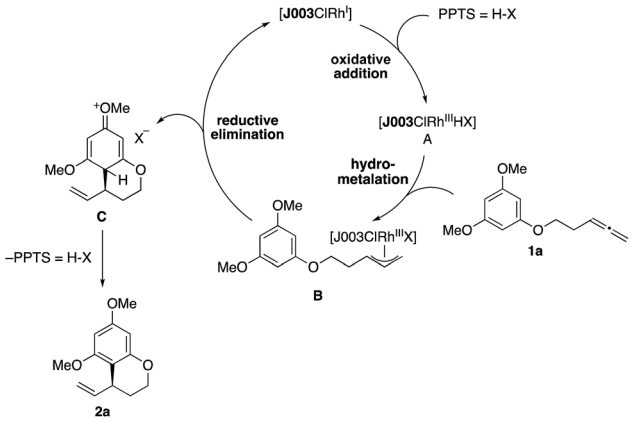
Finally, it was of interest to study catalyst control of diastereoselectivity employing substrates equipped with a stereogenic center either in α- or β-position relative to the allenyl substituent. Starting from the substrates **1qr** and **1st**, two diastereomeric products could be obtained using the two enantiomeric Josiphos ligands **J003-1** and **J003-2** respectively. As a result **2r** and **2s** were identified as the matched cases displaying very high diastereoselectivity. Conversely, **2q** and **2t** were the mismatched cases which were still formed in good diastereoselectivities. Based on the known absolute configuration of starting materials **1qr** and **1st**, the absolute configuration of the newly formed allyllic stereocenter could be determined by means of NOE NMR experiments (for details see ESI†).



Scheme 3 Gram-scale catalysis.



Scheme 4 Various functionalizations of allylated benzocycle **2a**. Reagents and conditions: (a) 9-BBN (1.05 eq.), THF (0.5 M), 0 °C – rt, 6 h; then H_2O_2 (30%, 3.00 eq.), NaOH (2.0 M, 3.00 eq.), 1 h, 91%, 90% ee; (b) [Rh(CO)$_2$acac] (0.50 mol%), 6-DPPon (5.0 mol%), CO/H_2 (1 : 1, 20 bar), toluene (0.13 M), 80 °C, 16 h, 70%, linear/branched >95 : 5, 89% ee; (c) Hoveyda–Grubbs II (10 mol%), *trans*-stilbene (10 eq.), DCE (0.2 M), 80 °C, 18 h, 95%, 91% ee; (d) Pd/C (10 wt%, 10 mol%), MeOH (0.1 M), rt, 18 h, 91%, 89% ee; (e) methyl vinyl ketone (1.3 eq.), $BF_3 \cdot Et_2O$ (30 mol%), CH_2Cl_2 (0.2 M), 0 °C – rt, 18 h, 67%, 88% ee (6-DPPon = 6-diphenylphosphinopyridin-2-(1*H*)-one).



Scheme 5 Proposed reaction mechanism.

Inspired by these synthetic possibilities, this new intramolecular allylation was applied to different functionalizations on the C–C double bond as well as the arene moiety. Preceding this, the synthetic utility of this methodology was highlighted by performing a gram-scale catalysis (Scheme 3).

To explore the synthetic utility of the obtained allylated benzocycles, we subjected **2a** to various transformations. It was possible to functionalize the vinyl group in four different reactions while fully preserving the stereo center. **2a** could be converted into the corresponding alcohol **3** in good yield by hydroboration. Hydroformylation of the terminal double bond, using our self-assembly ligand 6-diphenylphosphinopyridone (6-DPPon), furnished aldehyde **4** in good yield and excellent linear/branched selectivity (>95 : 5).[20] Hoveyda–Grubbs II catalyzed cross metathesis of **2a** with *trans*-stilbene provided the internal olefin **5** in excellent yield. Furthermore, the C–C double bond could be hydrogenated in very good yield. Finally, the nucleophilicity of the aromatic building block was to be used for regioselective Friedel–Crafts acylation or alkylation. For this purpose **2a** was reacted with methyl vinyl ketone in the presence of catalytic $BF_3 \cdot Et_2O$ yielding regioselectively the product **7** in 67% yield (Scheme 4).

On the basis of our previous studies of this catalytic system, we propose the following mechanism for this reaction (Scheme 5).[15a,18] After initial preformation from [{Rh(cod)Cl}$_2$] and Josiphos ligand **J003-2**, a rhodium^{III} hydride complex **A** is generated upon reaction with PPTS,[16] followed by hydrometallation of the allene moiety in **1a** to give the allylrhodium^{III} intermediate **B**. Subsequent nucleophilic attack of the arene releases arenium ion **C**, while simultaneously regenerating the Rh^{I}-catalyst. Rearomatization through elimination of HX then furnishes the benzocycle **2a**.

Conclusions

In summary, we have accomplished an enantioselective, intramolecular addition of electron-rich benzenes to allenes in an

atom-efficient manner by using a rhodium/Josiphos **J003** based catalyst system. The benzocycles were synthesized in good yields and high stereoselectivities, thereby tolerating a broad range of benzenes and different substituted allenes. We also demonstrated possible opportunities for derivatization of either the allylic moiety or the benzene itself. Further investigations regarding the mechanism and the expansion of this method to alkynes as well as the application of this methodology in target oriented-synthesis are being pursued in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

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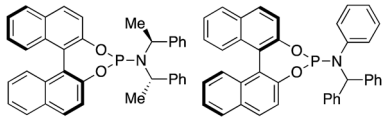
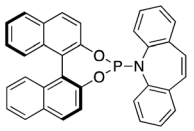
8 The following ligands were used:



Phenol-Nu$^-$ P-amidite ligand (S,S,S_a)-**L1** **Aniline-Nu**$^-$ P-amidite ligand (*R*)-**L2**

9 The following ligand was used:



Carreira ligand (*S*)-**L3**

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17 For the screening of different ligands, additives, solvents and catalyst loadings see the ESI.†

18 Unfortunately, 7- and 8-membered benzocycles could not be obtained by this methodology. 1,1-Disubstituted and internal allenes were not feasible under the given conditions as well. For an overview of tested substrates, see ESI.†

19 It was necessary for the benzene moiety to incorporate at least three donating substituents for a successful outcome of the reaction. For an overview of tested substrates, see ESI.†

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