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Authors: Ilan Marek and Longyang Dian

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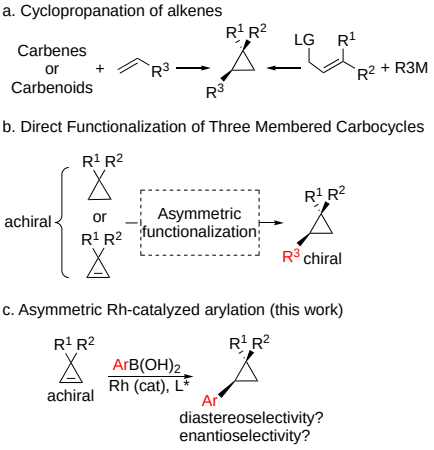
Rh-Catalyzed Arylation of Cyclopropenes Based on Asymmetric Direct Functionalization of Three-Membered Carbocycles

Longyang Dian, Ilan Marek*

Abstract: A large variety of highly diastereo- and enantiomerically enriched arylcyclopropanes is obtained through the asymmetric Rh-catalyzed arylation reaction of achiral non-functionalized cyclopropene derivatives with commercially available aryl boronic acids and (*R,S*)-Josiphos.

The most classical methods to prepare chiral cyclopropanes rely either on the asymmetric addition of carbenes and carbenoids to alkenes or on the Michael initiated ring closure reactions (Scheme 1**a**).[1] These powerful strategies have been extensively used in the literature to access large varieties of functionalized cyclopropanes with excellent diastereo- and enantioselectivities.[2] However, one intrinsic consequence of this strategy is that for every cyclopropane, a different alkene or carbene precursor is needed limiting the rapid structural diversification usually required for biological studies. An alternative strategy would consist in the preparation of a unique achiral precursor that would be transformed through a single set of reactions into a multitude of products with very high diastereo- and enantiomeric ratios. In this context, the strategy of *Asymmetric Direct Functionalization of Three-Membered Carbocycles* should provide an efficient and straightforward approach to a wide range of diversely enantiomerically enriched functionalized polysubstituted cyclopropanes (Scheme 1**b**). To realize this goal, two possible scenarios could be envisaged: i) the direct functionalization of an achiral cyclopropyl ring or ii) the direct functionalization of an achiral cyclopropenyl ring (Scheme 1**b**). In the former case, the field has been dominated by diversity oriented enantioselective C-H functionalization processes and metalation[3] whereas in the latter case, the Rh-catalyzed hydrostannation,[4] hydroboration,[5] hydroformylation,[6] hydroacylation,[7] the copper-catalyzed hydronitronylation,[8] hydroboration,[9] the carbocupration,[10] carbozincation,[11] carbomagnesiation,[12] the iron[13] and palladium[14] - catalyzed carbozincation, the Ln-catalyzed hydroamination[15] and addition of 2-methyl azaarenes[16] as well as the NHC-metal free enantioselective hydroacylation reactions[17] have been reported for the preparation of variously functionalized cyclopropanes with high diastereo- and enantioselectivities from symmetrical cyclopropenes. In this context, we have contributed in the development of diastereo- and enantioselective 1,2-bisfunctionalization of achiral cyclopropene derivatives through the copper-catalyzed asymmetric ethylzincation,[18] the copper-catalyzed asymmetric carbomagnesiation[19] as well as the copper-catalyzed vinylmetalation reactions[20] with excellent diastereo- and enantioselectivities. However, one important class of nucleophiles that failed to provide high enantioselectivity in all previously reported strategies is the enantioselective addition of aryl groups. For instance, all our attempts to perform the asymmetric copper-catalyzed arylmagnesiation or arylzincation of cyclopropenes led to very disappointing enantioselectivities.[18,19] The only asymmetric direct functionalization of three-membered carbocycles approach leading to arylated cyclopropanes from achiral cyclopropenes consisted in the two-steps diastereo- and enantioselective Cu-catalyzed hydroboration followed by a subsequent Pd-catalyzed Suzuki-Miyaura cross-coupling reaction reported by Tortosa[9] and others.[5,21] Interested to find an alternative and step-economical solution to this problem, we wondered if we could develop a direct highly diastereo- and enantioselective metal-catalyzed arylation of cyclopropenes. Herein, we report our results on the diastereo- and enantioselective Rh-catalyzed asymmetric arylation reactions of cyclopropene derivatives with commercially available aryl boronic acids and chiral ligand (Scheme 1**c**).



Scheme 1. Asymmetric Direct Functionalization of Three-Membered Carbocycles as a new approach to diastereo- and enantiomerically enriched cyclopropanes

We began exploring the diastereoselectivity and enantioselectivity of the rhodium-catalyzed arylation reaction of cyclopropene **1a** by varying the catalyst, chiral ligands, solvents and additives as summarized in Table 1 (for full details and optimization see the Supporting Information). After screening different catalysts, we were pleased to observe that the desired arylated product **2a** could be obtained with moderate diastereo- and enantioselectivity (dr 82:18, er 71:29) by the use of [Rh(acac)(cod)] as catalyst in toluene with (*R*)-BINAP as chiral ligand (Table 1, entry 1). Based on this primary result, subsequent

[a] Dr. Longyang Dian, Prof. Dr. Ilan Marek
The Mallat Family Laboratory of Organic Chemistry, Schulich Faculty of Chemistry, Technion-Israel Institute of Technology, Haifa, 3200009 (Israel)
E-mail: chilanm@technion.ac.il

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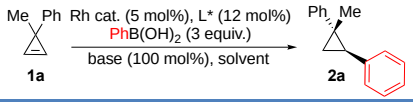
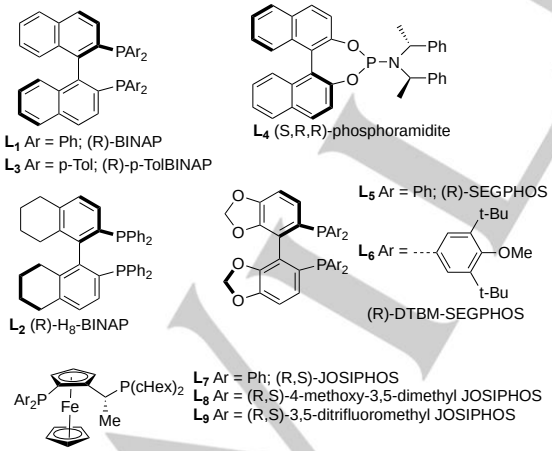
screening underlines the crucial role of the solvent in the selectivity of the reaction (Table 1, entries 2-6).

Table 1 Optimization of the Rh-catalyzed asymmetric arylation of cyclopropene **1a**.[a]

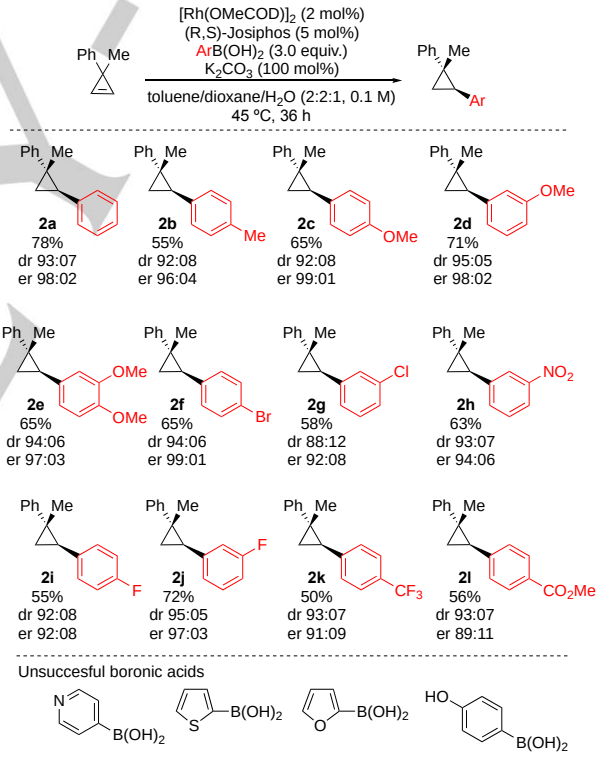


Entry	Rh	L	Solvent	dr[b]	er[c]
1	Rh(acac)(cod)	L_1	toluene	82:18	71:29
2	$[Rh(OMe)(cod)]_2$	L_1	toluene	83:17	78:27
3	$[Rh(OMe)(cod)]_2$	L_1	THF	76:24	66:34
4	$[Rh(OMe)(cod)]_2$	L_1	dioxane	64:36	73:27
5[d]	$[Rh(OMe)(cod)]_2$	L_1	H_2O	/	/
6	$[Rh(OMe)(cod)]_2$	L_1	toluene/dioxane/H_2O	89:11	83:17
7	$[Rh(OMe)(cod)]_2$	L_2	toluene/dioxane/H_2O	90:10	88:12
8	$[Rh(OMe)(cod)]_2$	L_3	toluene/dioxane/H_2O	91:09	88:12
9	$[Rh(OMe)(cod)]_2$	L_4	toluene/dioxane/H_2O	68:32	82:18
10	$[Rh(OMe)(cod)]_2$	L_5	toluene/dioxane/H_2O	90:10	88:12
11	$[Rh(OMe)(cod)]_2$	L_6	toluene/dioxane/H_2O	93:07	93:07
12	$[Rh(OMe)(cod)]_2$	L_7	toluene/dioxane/H_2O	93:07	95:05
13	$[Rh(OMe)(cod)]_2$	L_8	toluene/dioxane/H_2O	90:10	95:05
14	$[Rh(OMe)(cod)]_2$	L_9	toluene/dioxane/H_2O	86:14	73:27
15[e]	$[Rh(OMe)(cod)]_2$	L_7	toluene/dioxane/H_2O	93:07	96:04
16[f]	$[Rh(OMe)(cod)]_2$	L_7	toluene/dioxane/H_2O	93:07	98:02
17[f,g]	$[Rh(OMe)(cod)]_2$	L_7	toluene/dioxane/H_2O	93:07	98:02
18[d]	/	L_7	toluene/dioxane/H_2O	/	/
19[d]	$[Rh(OMe)(cod)]_2$	/	toluene/dioxane/H_2O	/	/
20[d]	/	/	toluene/dioxane/H_2O	/	/

[a] The reactions were run on a 0.10 mmol scale, and the reaction mixture was heated at 80 °C for 12 h; full conversion was observed by GC analysis in all cases. [b] Determined by GC or GC−MS analysis. [c] Determined by chiral GC. [d] No detection of the desired product, cyclopropene **1a** was recovered. [e] The reaction was performed at 60 °C. [f] The reaction was performed at 45 °C for 36 h. [g] 2 mol% $[Rh(OMe)(cod)]_2$, 5 mol% (*R,S*)-JOSIPHOS was used.



The best selectivity was observed when a mixture of toluene/dioxane/H_2O in a 2:2:1 ratio was used (Table 1, entry 6, dr 89:11, er 83:17). After assessment of chiral ligands (Table 1, entries 7-14; see supporting Information for a full list of chiral ligands tested), we were pleased to find that (*R,S*)-Josiphos in combination with $[Rh(OMe)(cod)]_2$ (Table 1, entry 12) gave the desired product **2a** with excellent diastereo- and enantioselectivity (dr 93:07, er 95:05). The enantioselectivity could be further improved to 98:02 when the temperature was decreased to 45 °C (Table 1, entry 16). Additional studies showed that the reaction could be performed similarly with a lower catalyst loading (2 mol% $[Rh(OMe)(cod)]_2$ with 5 mol% of (*R,S*)-Josiphos, (Table 1, entry 17). Control experiments confirmed that the combination described in entry 17 is required to achieve the expected chemical transformation with high diastereo- and enantioselectivities (Table 1, entries 18-20). Having established a straightforward and smooth access to arylated cyclopropanes through a highly diastereo- and enantioselective rhodium-catalyzed arylation reaction of cyclopropene derivatives, we then extended the scope of this transformation by performing various asymmetric Rh-catalyzed addition with commercially available aryl boronic acids on **1a** (Scheme 2). For most of the cases, excellent diastereo- and enantioselectivities were obtained for the addition of boronic acids. For instance, aryl boronic acids containing electron-donating-groups (Scheme 2, formation of **2b-e**) have nearly no influence on the diastereoselectivity and enantioselectivity of the catalytic reaction. Similarly, boronic acids containing electron-withdrawing-groups were also tested and we were pleased to observe good selectivities (Scheme 2) at the exception of **2l** where we observed an erosion of the enantioselectivity.



Scheme 2. Rh-catalyzed asymmetric arylation reaction of cyclopropene **1a**.

Even aryl boronic acid containing a NO_2 moiety in a *meta*-position gave the desired arylated product **2h** with rather high selectivities (**2h**, Scheme 2, dr 93:07, er 94:06). This approach could also be implemented to introduce fluorine substituents (**2i,j**) or the trifluoromethyl group (**2k**) on the aromatic ring with unaltered selectivities. Increasing the scale of the reaction from 0.1 to 5 mmol did not hamper yields and selectivities as **2a** was obtained with exactly the same selectivities. It should be emphasized that in all cases, the arylation is *syn*-directed towards the Me group, and a DFT mechanistic investigation is currently performed to rationalize these results.[4-14] A few functionalized heteroaromatic

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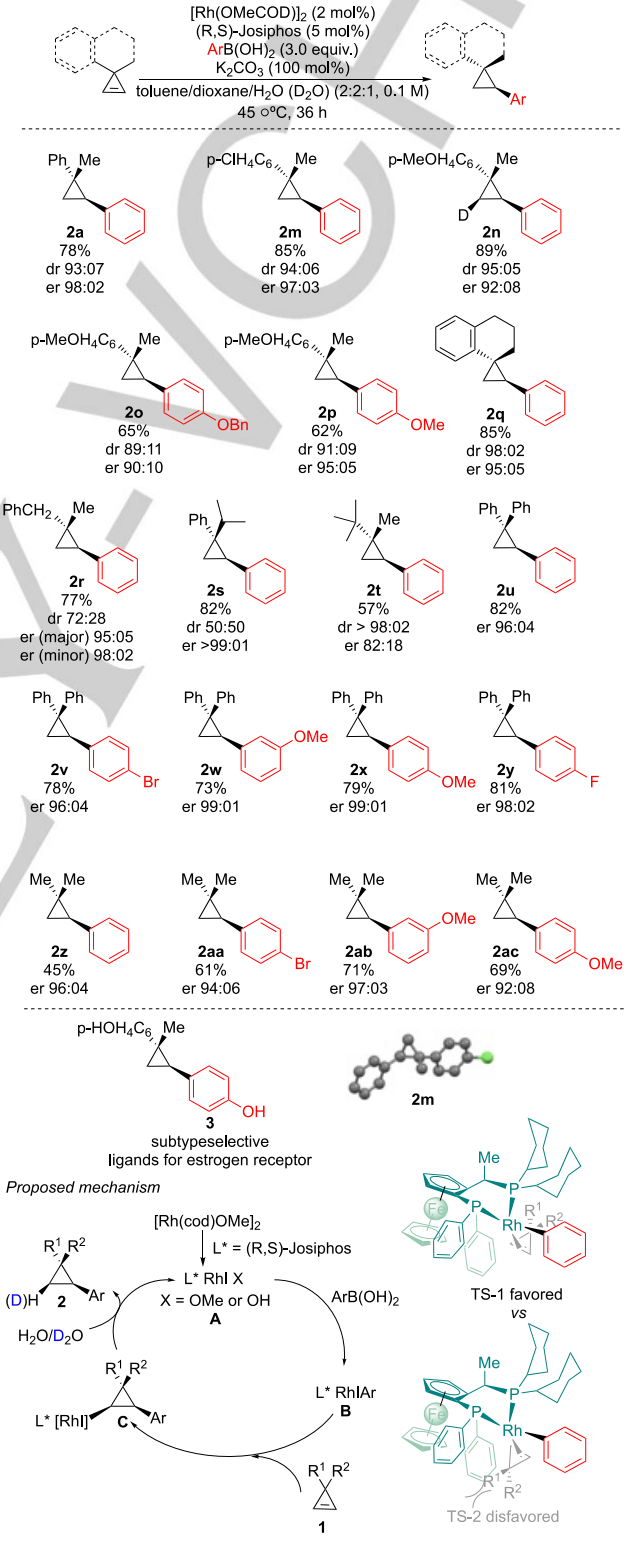
boronic acids as well aromatic boronic acid possessing an acidic hydrogen could not produce the addition product (See Scheme 2). As we have a rather broad scope for the introduction of aryl boronic acids possessing either electron donating or withdrawing substituents with good to excellent diastereo- and enantioselectivities, we were then interested to extend the scope of this reaction to various cyclopropene species (Scheme 3). Cyclopropenes containing a substituent on the aromatic group (**2m-p**) undergo the asymmetric arylation reaction with similar selectivities. The absolute configuration of the cyclopropane product was determined by X-Ray crystallographic analysis of compound **2m** (see the Supporting Information)[22] and assigned by analogy for all other products. When the solvent mixture was changed to toluene/dioxane/D_2O, the 1,2,3-polysubstituted cyclopropane **2n** was obtained with a *syn*-diastereoselectivity between the aryl group of the boronic acid and the deuterium confirming the *syn*-addition of the aryl-rhodium species across the double bond of the three-membered ring (Scheme 3).[23] When the two substituents phenyl and alkyl on the cyclopropene are fused in a cyclic structure, the aryl addition proceeds with similar diastereo- and enantioselectivity (**2q**). In contrast, when the phenyl group of the cyclopropene was changed to a benzyl moiety, the diastereoselectivity of the reaction decreased (**2r**, dr 72:28) but still with an excellent enantioselectivity (er for the major isomer is 95:05 and 98:02 for the minor isomer). Similarly, when the methyl group on the cyclopropene ring was changed to a bulkier substituent such as a secondary alkyl group, the reaction is no more diastereoselective but still proceeds with an outstanding enantioselectivity (**2s**, dr 50:50, er >99:01 for both diastereoisomers). The diastereoselectivity can be restored when a very bulky substituent is present but at the expense of the enantioselectivity of the reaction (**2t**, dr 98:02, er 82:18). Other interesting class of cyclopropenyl substrates have been envisaged such as the one who have identical substituents on the C_2 of the cyclopropenyl ring. For instance, the addition of various aryl boronic acids to cyclopropene possessing two phenyl substituents lead invariably in good to excellent enantioselectivity (Scheme 3, **2u-y**). Finally, the volatile dimethylcyclopropene was also tested in the asymmetric rhodium-catalyzed arylation reaction and we were pleased to observe that the desired arylated dimethylcyclopropane **2z-ac** could be isolated with high enantioselectivity in all cases. One potential application of the current methodology consists in the synthesis of a selective estrogen receptor modulator **3**,[24] that could be easily achieved in good diastereoselectivity and enantioselectivity by deprotection of **2o** into **3**. The proposed reaction mechanism probably involves the generation of an organorhodium species **B** by transmetalation between $ArB(OH)_2$ and the chiral rhodium complex **A**. Then the organorhodium species **B** stereoselectively adds to the cyclopropene **1** to afford the species **C**, which is in-situ hydrolyzed by H_2O (or D_2O) to deliver the final arylated cyclopropane **2** and regenerate the chiral rhodium species **A.** The stereoinduction of the asymmetric Rh-catalyzed arylation process is more difficult to rationalize but one could consider than from the two possible transition states, less steric interactions are present in TS-1 that in TS-2.[25]

In conclusion, the *asymmetric direct functionalization of three-membered carbocycles* represents a very efficient, step-economy approach, to chiral cyclopropanes with very high diastereo- and enantioselectivities. This robust and flexible asymmetric Rh-catalyzed arylation of non-functionalized achiral substrates with a large variety of aryl boronic acids in the presence of 5 mol% of commercially available (*R,S*)-Josiphos easily transforms carbocycle with a C_2-symmetry into numerous chiral arylcyclopropanes possessing a quaternary carbon stereocenter with excellent selectivities.



Scheme 3. Asymmetric Rh-catalyzed arylation of different substituted cyclopropenes.

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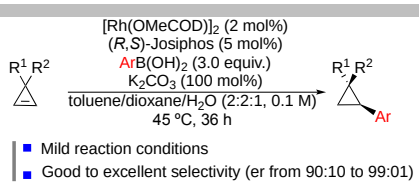
Layout 1:

COMMUNICATION

The asymmetric Rh-catalyzed arylation of simple achiral non-functionalized cyclopropene provides a large variety of arylated cyclopropanes with high diastereo- and enantioselectivity.



- Mild reaction conditions
- Good to excellent selectivity (er from 90:10 to 99:01)

*Longyang Dian, Ilan Marek**

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Rh-Catalyzed Arylation of Cyclopropenes Based on Asymmetric Direct Functionalization of Three-Membered Carbocycles