Asymmetric Catalysis

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# Chemodivergence in Enantioselective Desymmetrization of Diazabicycles: Ring-Opening versus Reductive Arylation**

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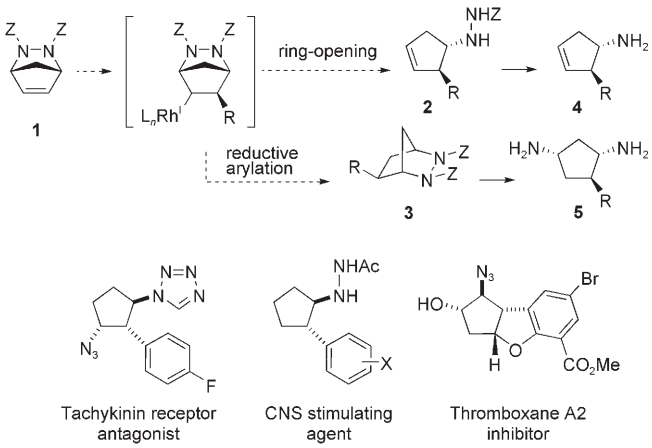
Interest in desymmetrization by asymmetric ring-opening reactions has grown significantly in recent years.[1] Although very efficient reactions have been developed for the desymmetrization of oxygenated compounds, nitrogen-containing molecules have received much less attention.[2] Given the ubiquitous nature of chiral amines in biologically active molecules and in natural products, a method to access chiral functionalized amines **4** and **5** would be useful (Scheme 1). Herein, we report a highly selective desymmetrization of diazabicycles **1** leading to ring-opened products **4** and reductive arylation products **5** after cleavage of the N–N hydrazine bond. A C–H activation/1,4-metal migration reaction pathway leading to the formation of reductive arylation products is also described.[3] To the best of our knowledge, this is the first example of an intermolecular, asymmetric rhodium-mediated hydroarylation reaction of strained alkenes with boronic acids.[4]

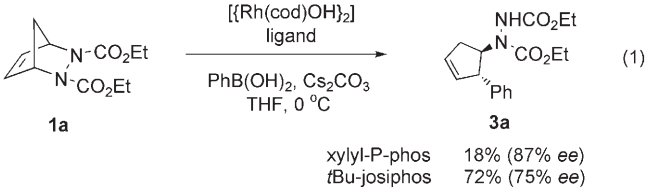



***Scheme 1.*** Desymmetrization of strained alkenes by two competing pathways involving an initial enantioselective carbometalation. Z = electron withdrawing group.

The ring-opening of diazabicycles **1** towards **2** with organometallic nucleophiles such as palladium[5] and copper[1g,6] was reported, but either the scope of the nucleophile was limited or the enantioselectivity was modest. Progress on the ring-opening of **1** with a closely related chiral Rh–bisphosphine system was recently reported by Pineschi and co-workers, but the *ee* values were variable.[7] Conversely, the racemic hydroarylation of diazabicycles using Pd was reported by Kaufmann and co-workers, but the reaction led to mixtures of **2** and **3**.[8] We found that the hydroarylation products are formed through a mechanism that is markedly different from the one proposed with Pd, thus opening up new synthetic opportunities.[9]

We focused on finding a solution to the challenging problem of enantioselective ring-opening of diazabicyclo-[2.2.1]heptanes to provide a rapid synthesis of optically active *trans*-2-arylated cyclopentyl amines **4**, which are known to be biologically active small molecules (Scheme 1).[10–12] The asymmetric ring-opening of diazabicycles **1** would complement the catalytic preparation of chiral alcohols from *meso* allylic biscarbonates.[13] Furthermore, the *trans* stereochemistry would be obtained; in contrast, the same reaction with oxa- or azabicycles always gave the *cis* ring-opened products.[14]

Bicyclic hydrazines **1** were attractive as key substrates because of their stability, ease of preparation,[15] and the utility of the ring-opened hydrazine as a known amine precursor. We opted for boronic acids as ideal nucleophiles since they are air- and moisture-tolerant. The first trials consisted of treating diazabicycle **1a** with phenylboronic acid under our previously reported conditions.[13a] Using (*S*)-xylyl-P-phos ((S)-(−)-2,2′,6,6′-tetramethoxy-4,4′-bis[di(3,5-xylyl)-phosphino]-3,3′-bipyridine)[16] as a chiral ligand yielded **3a** in 87% *ee*, albeit in low yield [Eq. (1); cod = cycloocta-1,5-diene]. The screening of ligands showed that only bidentate P,P ligands displayed useful levels of enantioselectivity. Interestingly, *t*Bu-josiphos (josiphos = (*R*)-1-[(*S*)-2-diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine) [17] shows unrivaled reactivity and enantioselectivity in Rh-catalyzed reactions with bicyclic systems.[14b] Study of various solvent systems showed THF to be a suitable solvent.

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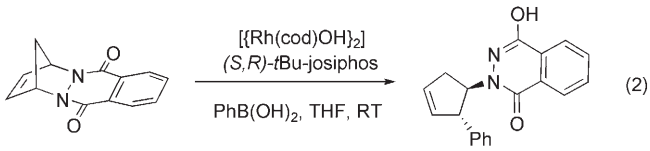
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

The stereochemical assignment is challenging in substituted five-membered ring systems because of removed rotamers. Different substituents (benzyloxy carbonyl (Cbz), *t*-butyl carbonyl (Boc), phthalyl) on the nitrogen centers were examined; notably, the phthalyl substituted substrate **1b** yielded product **3b** quantitatively and the *trans* stereochemistry was confirmed by X-ray crystallographic analysis [Eq. (2)].[18] Bis(Boc)-protected diazabicycle **1c** was selected as the substrate of choice for this study because of the ease of deprotection and practical reasons.[19]




(2)

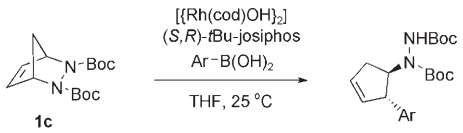
The reaction is ideally suited for the addition of *ortho*-substituted, electron-rich aryl boronic acids (*ee* > 96%, Table 1, entries 1–9).[20] Steric hindrance close to the reacting center appears necessary to achieve good selectivity (Table 1, entries 10–13). Electron-rich boronic acids generally led to higher yields and lower *ee* values, whereas electron-deficient systems proved less reactive and more selective (Table 1, entries 10–13). The reaction tolerates a range of functional groups on the boronic acid substrate. A vinylboronic acid also reacted with ring-opened **1c** in high yield but with poor enantioselectivity (i.e. *trans*-styrylboronic acid gave 99% yield, 44% *ee*).

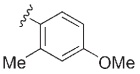
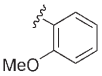
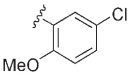
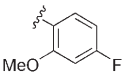
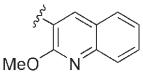
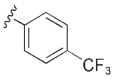
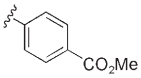
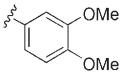
A novel enantioselective reductive arylation reaction was revealed when the boronic acids were changed to heteroaryl derivatives (Table 2). When the boronic acid bore a sufficiently activated hydrogen atom in the 2-position, the hydroarylated diazabicycles **17**–**20** were isolated. It is thought that the sigma inductive effect of neighboring heteroatoms facilitates a C–H insertion reaction (see below). 2-Fluoroboronic acid seems to lie at the inflection point of the competing reaction pathways, as both products **6** and **19** were obtained (53% and 47% yield, respectively). The trend in enantioselectivities observed for hydroarylated products **17**–**20** matches that for the ring-opened products, suggesting that both pathways are subject to the same stereodifferentiating factors.

The outcome of the reaction can be biased by changing the solvent system. For example, in preliminary studies, we found that running the reaction in a mixture of toluene/THF/water (7:2:1) rather than THF/water (50:1) gave the ring-opened product **7** as the sole product (Table 1, entry 3). In pure THF, the hydroarylated product was observed in approximately 12% yield (the remainder being unreacted **1c**).

The reductive arylation is sensitive to steric effects. When an *ortho*-hydrogen atom was flanked by a bulky group attached to the *meta* position (Table 1, entries 6 and 8), only the ring-opening reaction was observed. Notably, in all cases in which the *ortho*-hydrogen atom was accessible, the hydroarylated products were observed when THF was used as the solvent, but only in poor yield (2–15%).

***Table 1:*** Rh$^{I}$-catalyzed ring-opening of diazabicycles with substituted boronic acids.[a]



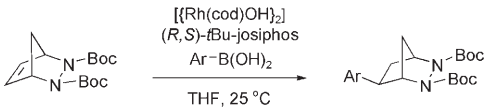

| Entry | Product | Ar | Yield [%][b] | *ee* [%][c,d] |
|---|---|---|---|---|
| 1[e] | **6** |  | 53 | 99 |
| 2 | **7** |  | 52 | 97 |
| 3[e] | **7** | | 99 | 97 |
| 4 | **8** |  | 55 | 99 |
| 5 | **9** |  | 75 | 99 |
| 6 | **10** |  | 96 | 99 |
| 7 | **11** |  | 54 | > 99 |
| 8 | **12** |  | 91 | 96 |
| 9 | **13** |  | 68 | 99 |
| 10 | **14** |  | 49 | 84 |
| 11 | **15** |  | 58 | 86 |
| 12 | **3c** |  | 85 | 68 |
| 13 | **16** |  | 80 | 50 |

[a] Reaction conditions: The {Rh}$_2$ catalyst (5 mol%) and ligand (12 mol%) were in THF/water (50:1) and under an Ar atmosphere.[20] [b] Yields of isolated products. [c] Enantiomeric excess determined by chiral HPLC. [d] Absolute configuration determined by derivatization of **3c**. [e] Reaction conducted in toluene/THF/$H_2O$ (7:2:1).

Correlation of the observed enantioselectivities of the ring opened hydrazines **6**–**16** and those of the arylated diazabicycles **17**–**20** suggest that a plausible mechanism would involve a common intermediate. As depicted in Scheme 2, the preformed active catalyst **A** undergoes a fast transmetalation to form the Ar–Rh$^{I}$ complex **B**. The alkene of diazabicycle **1** is activated by coordination to the metal center and inserts into the metal–carbon bond of **B** in the enantiodiscriminating step to give the key carbometalated intermediate **C**. Ring-opening of **C** can occur through *anti*-β-nitrogen elimination of the hydrazide leaving group to give the *trans*-cyclopentene **2**. Carborhodation of the alkene occuring on the more accessible *exo* face of the diazabicycle accounts for the *trans* diastereoselectivity observed in the ring-opened products **2**. Alternatively, if the *ortho*-hydrogen

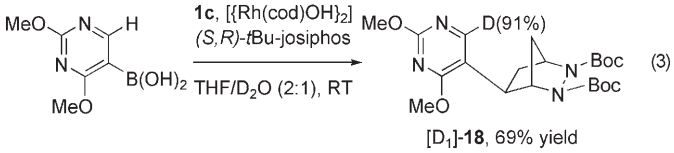
  

***Table 2:*** Rh$^{I}$-catalyzed reductive arylation of diazabicycles with substituted boronic acids.[a]




| Entry | Product | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|
| 1 | **17** | 89 | 62 |
| 2 | **18** | 66 | 99 |
| 3[d] | *ent*-**19** | 47 | 98 |
| 4 | **20** | 39 | 83 |

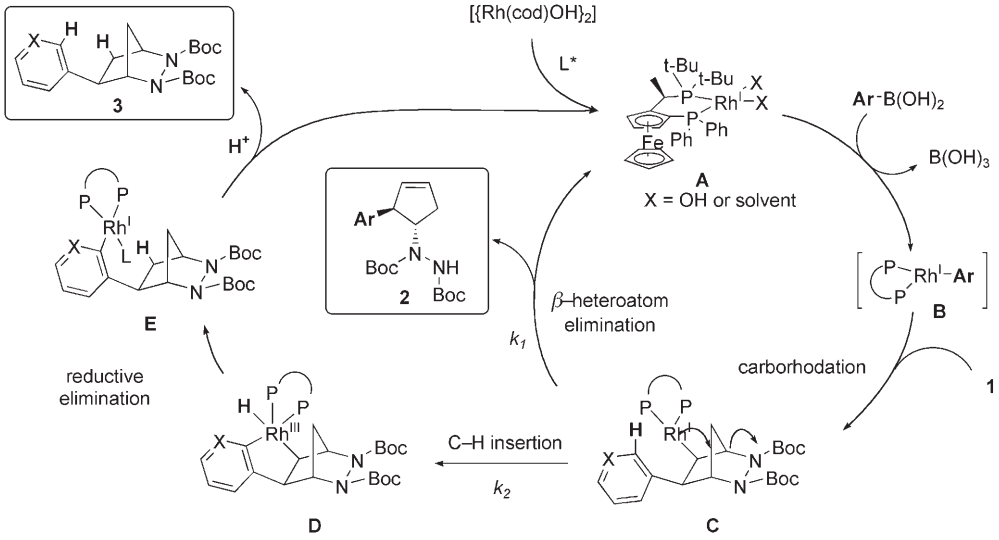
[a] Reaction conditions are as described in Table 1. [b] Yields of isolated products. [c] Enantiomeric excess determined by chiral HPLC. [d] (*S,R*)-josiphos ligand was used.




(3)

We observed exclusive deuterium incorporation on the aromatic moiety of **18** ([D$_1$]-**18**, 91% deuteration). This experiment supports a rhodium migration occuring by a C–H insertion. This oxidative pathway allows selective electrophilic functionalization at the more hindered *ortho* position of the heteroaromatic ring, a process that is not easily accomplished by other means.

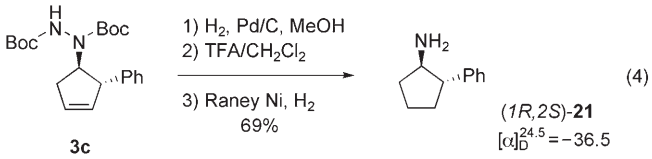
An example demonstrating the synthetic value of substituted cyclopentenes **6**–**16** is the synthesis of glycosydase inhibitor derivatives.[21] This class of compounds was reported to be accessible by stereoselective transformations of the cyclopentyl core of **3**.[22] In addition, conversion of the hydrazine moiety of the desymmetrized products **2** and **3** into the amines **4** and **5** can be accomplished by several established reduction methods.[23] It should be noted that this method provides a good way to access enantiopure building blocks bearing 1,2,4- and 1,2,5-substituted benzene rings.[24] The absolute and relative stereochemistry of the Boc-protected ring-opened products was confirmed by full reduction of **3c** and comparison of the optical rotation of **21** with literature values [Eq. (4); TFA = trifluoroacetic acid].[25] Ongoing efforts are focused on ways to influence the reaction rate constants $k_1$ and $k_2$, to alter the course of the reaction, and to obtain products **2** or **3** selectively (Scheme 2).




***Scheme 2.*** Proposed catalytic cycle for the chemodivergent Rh$^{I}$-catalyzed desymmetrization of diazabicycle **1**.

atom is sufficiently activated, the Rh$^{I}$ center of intermediate **C** can undergo an oxidative C–H insertion to give the Rh$^{III}$ complex **D**. Reductive elimination leads to the Rh–C$_{sp^2}$ complex **E**, which is thermodynamically more stable than Rh–C$_{sp^3}$ complex **C**. Subsequent proto-demetalation with boronic acid as the proton source leads to the observed reductive arylation product **3**. A working hypothesis suggests that if the C–H bond insertion rate is slow, a water molecule can fill the free coordination site in **C** and therefore prevent the formation of **D**. Thus, excess water in a less polar solvent system may favor the ring-opened products **2** (Table 1, entry 3).

To test whether the arylated bicycles **3** arise from simple protonation of the carbometalated intermediate **C**, the reaction was conducted in the presence of $D_2O$ [Eq. (3)].




(4)

In summary, the enantioselective Rh$^{I}$-catalyzed ring-opening of diazabicycles provides a rapid synthesis of chiral arylcyclopentenamine precursors and complements our related approach to chiral cyclopentenols. It is ideally suited for the addition of aryl boronic acids bearing *ortho* substituents and provides a good method to access interesting enantiopure building blocks.[24] Furthermore, we identified a

useful C–H activation pathway that leads to hydroarylated diazabicycles enantioselectively, thereby setting three stereocenters in one reaction.

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[19] Compund **1c** is a free-flowing powder, making for easy handling. Its preparation on scale is also the most convenient one, involving simple filtration of the reaction mixture to obtain analytically pure material.

[20] See the Supporting Information for full experimental details. Strictly anhydrous conditions are not appropriate for this reaction and we thank the referee for this finding.

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