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Rhodium-catalyzed asymmetric arylative ring opening of bicyclic hydrazines

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Abstract—The development of a novel asymmetric ring opening of bi- and polycyclic hydrazines with aryl organometallic reagents is presented. The application of this reaction to the most simple bicyclic hydrazine **1a** gives a straightforward regio- and diastereoselective access to synthetically useful trans 3,4-disubstituted hydrazinocyclopentenes in an enantioenriched form.

Disubstituted cyclopentenes are versatile synthons for the construction of a variety of biologically interesting molecules, and several methodologies are suitable for their preparation.[1] In particular, 3,5-disubstituted hydrazino cyclopentenes, which are useful intermediates for the synthesis of heterocyclic components by elaboration of the hydrazine moiety,[2] can be obtained by stereoselective ring opening of symmetrical bicyclic hydrazines.[3] Symmetrical bicyclic hydrazines, are fundamental structures that have been known for a very long time and can be easily obtained from the hetero Diels–Alder reaction of cyclopentadiene with azodicarboxylates.[4] Descriptions of a palladium-catalyzed hydroarylation and a palladium-catalyzed reaction of allyl- and arylstannanes in ionic liquid to give 3,4-disubstituted hydrazinocyclopentenes are quite recent, but the ring-opened products were obtained invariably in a racemic form.[5] To the best of our knowledge, no example of asymmetric ring opening of bicyclic hydrazines with *aryl* organometallic reagents has been described so far. We recently reported a new copper-catalyzed ARO of symmetrical bicyclic hydrazines of type **1** with hard *alkyl* metals to give 3-alkyl-4-hydrazino cyclopentene derivatives (Fig. 1).[6a] Nevertheless, with our reaction protocol that make use of a copper–aminophosphine catalyst,[6b] an effective arylation of bicyclic hydrazines with aryl organometallic reagents was not feasible. In order to address this problem we turned our attention to the use of a rhodium catalysts in combination with air and moisture tolerant arylboronic acids.

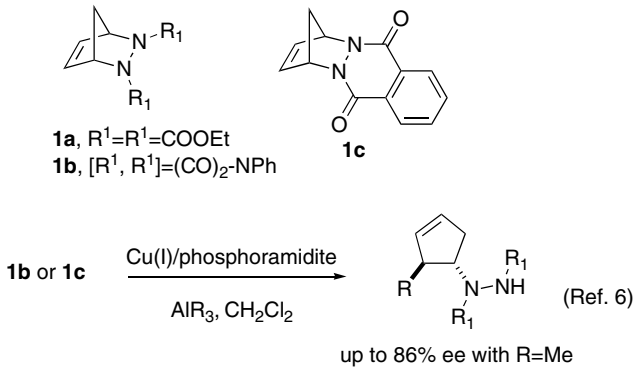

Figure 1. Bicyclic hydrazines of type **1** used as starting material for new asymmetric arylation.

The development of new asymmetric carbon–carbon bond formation by means of rhodium catalysis has attracted much attention in recent years.[7] In particular, spectacular advances have been made in the area of the asymmetric rhodium-catalyzed ring opening of 7-aza- and 7-oxanorbornene derivatives with aryl boronic acids by Lautens et al.[8]

We herein report the development of a rhodium-catalyzed asymmetric arylation of symmetrical bicyclic hydrazines with aryl organometallic reagents to give a new regioselective and diastereoselective access to arylated hydrazinocyclopentenes in an enantioenriched form.

A preliminary screening of the reaction with phenylboronic acid showed that the use of a rhodium-catalyst

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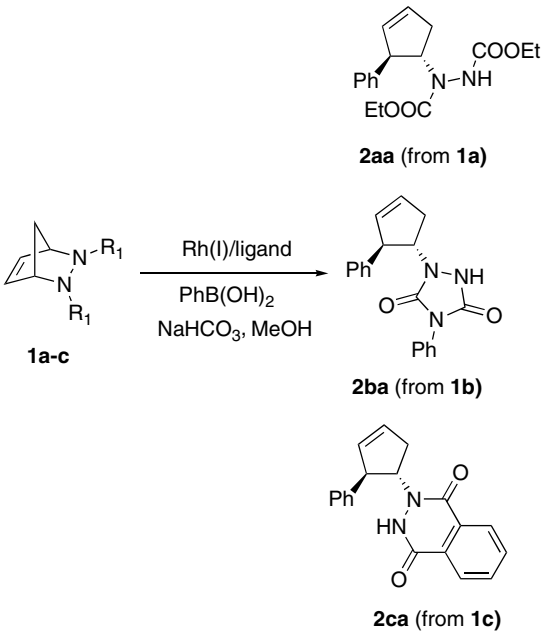
in ethereal solvents or a mixture of ethereal solvents and water (i.e., THF/H_2O or dioxane/H_2O), delayed the arylation reaction, and promoted the formation of an unidentified mixture of products.

The best results were obtained with the use of alcoholic solvents (MeOH, EtOH) and ligands containing an electron-poor phosphorus atom. For example, the use of $PhB(OH)_2$ (1.5 equiv) in MeOH in combination with $[Rh(cod)Cl]_2$ (cod = cycloocta-1,5-diene) (3 mol %), $P(OEt)_3$ (6 mol %), and $NaHCO_3$ (2.0 equiv) gave complete conversion in 1 h at 65 °C and ring-opened adduct **2aa** was isolated in a 90% yield after chromatographic purification on silica gel (Scheme 1).[9] Slightly lower yields of adducts **2ba** and **2ca** were obtained using the corresponding more rigid tri- and tetracyclic Diels–Alder adducts **1b** and **1c** (see Supplementary data).

Some representative structurally different monodentate ($\mathbf{L_1}^*$) and bidentate ($\mathbf{L_2}^*$, $\mathbf{L_3}^*$, $\mathbf{L_4}^*$ and $\mathbf{L_5}^*$) ligands (Fig. 2) were tested in order to obtain an asymmetric ring opening of bicyclic hydrazines of type **1**. Subsequently, our efforts to develop an asymmetric version of this reaction concentrated on the most simple bicyclic hydrazine **1a** for two main reasons: (a) compounds **2ba** and **2ca** have a very low solubility in common organic solvents thus complicating their HPLC analysis for the enantioselectivity determination (b) hydrazinocyclopentenes **2ba** and **2ca** are bulky and inert to any chemical transformation and/or cleavage of the hydrazine moiety, thus rendering difficult any further elaboration.

Consistently with our preliminary observations, the use of ligands containing an electron-poor phosphorus such as (*S*)-Monophos ($\mathbf{L_1}^*$),[10] and Binol-derived phosphite $\mathbf{L_2}^*$,[11] gave a fast reaction and complete conversion was reached within 2–8 h at 65 °C (Table 1, entries 1–3), while the use of chiral diphosphines of various kinds (ligands $\mathbf{L_3}^*$–$\mathbf{L_5}^*$) delayed the reactions, but gave significant levels of enantioselection (entries 4–14). In particular, an appreciable level of asymmetric induction (52% ee) was obtained with the Et–DuPHOS ligand ($\mathbf{L_4}^*$), albeit accompanied by a very low conversion rate (entry 8). An unsatisfactory reactivity was obtained with the ferrocenyl diphosphine $\mathbf{L_5}^*$ (entry 9). Probably, the better π-acceptor ability of ligands $\mathbf{L_1}^*$, $\mathbf{L_2}^*$ gives the rhodium catalyst a more electrophilic character and an increased reactivity. However, a better selectivity of the enantiotopic reaction sites of the strained double bond present in **1a** was associated with the use of rhodium complexes with electron-richer bidentate phosphines $\mathbf{L_3}^*$ and $\mathbf{L_4}^*$.



Scheme 1. Rhodium-catalyzed arylation of bicyclic hydrazines of type **1** with phenylboronic acid.

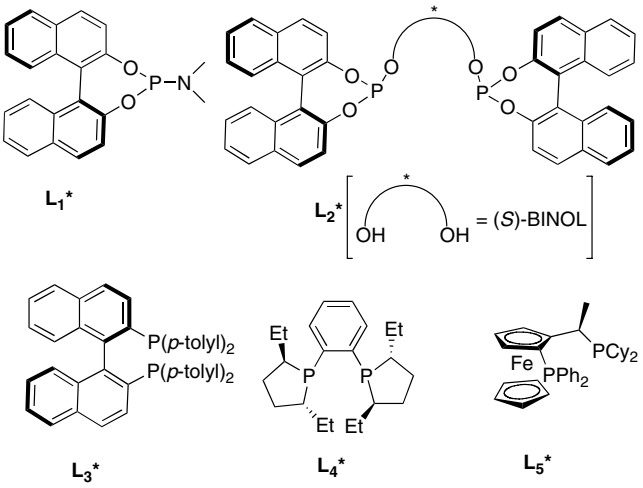


Figure 2. Chiral phosphorus-containing ligands used in this study.

Table 1. Rh(I)-catalyzed ARO of compound **1a** with phenylboronic acid[a,12]

No	Rh(I) salt	$\mathbf{L}^*$	Time (h)	Conv.[b] (%)	ee[c] (%)
1	$[Rh(cod)Cl]_2$	$\mathbf{L_1}$	2	>98	0
2	$[Rh(C_2H_4)_2Cl]_2$	$\mathbf{L_1}$	2	>98	10
3	$[Rh(C_2H_4)_2Cl]_2$	$\mathbf{L_2}$	1	>98	16
4	$[Rh(cod)Cl]_2$	$\mathbf{L_3}$	22	90	0
5	$[Rh(COD)OH]_2$	$\mathbf{L_3}$	22	88	8
6	$[Rh(C_2H_4)_2Cl]_2$	$\mathbf{L_3}$	22	82	25
7	$[Rh(C_2H_4)_2(acac)]$	$\mathbf{L_3}$	24	80	Nd
8	$[Rh(C_2H_4)_2Cl]_2$	$\mathbf{L_4}$	22	35	52
9	$[Rh(C_2H_4)_2Cl]_2$	$\mathbf{L_5}$	24	<20	Nd
10[d]	$[Rh(C_2H_4)_2Cl]_2$	$\mathbf{L_3}$	24	88	60
11[e]	$[Rh(C_2H_4)_2Cl]_2$	$\mathbf{L_3}$	24	82	6
12[f]	$[Rh(C_2H_4)_2Cl]_2$	$\mathbf{L_3}$	12	>98	52
13[g]	$[Rh(C_2H_4)_2Cl]_2$	$\mathbf{L_3}$	24	>98	42
14[h]	$[Rh(C_2H_4)_2Cl]_2$	$\mathbf{L_3}$	24	50	47

[a] All reactions were performed in accordance with the general procedure reported in Ref. 12, unless stated otherwise.
[b] Determined by ^1H NMR examination of the crude mixture.
[c] Determined by HPLC on CSPs. Absolute configuration of adduct **2aa** has not been determined.
[d] Reaction carried out with 2.0 equiv of the ethylene glycol ester of $PhB(OH)_2$.
[e] Reaction carried out without an added base.
[f] Reaction carried out with CsF.
[g] Reaction carried out with K_2CO_3.
[h] Reaction carried out with NEt_3.

Also the rhodium catalyst precursor influenced to a certain extent the enantioselectivity, with the best results obtained with $[Rh(C_2H_4)_2Cl]_2$. The air stable, hydroxorhodium(I) complex $[Rh(cod)OH]_2$, which has been conveniently used in some catalytic asymmetric arylations,[13] gave a clean reaction mixture but a poor enantioselectivity (entry 5). The use of catalysts derived from $Rh(C_2H_4)_2(acac)$, which is a rhodium salt widely used in asymmetric 1,4-additions to α,β-unsaturated compounds,[7a] gave a very low conversion and a mixture of products (entry 7). The use of $[Rh(cod)Cl]_2$ generally displayed an increased reactivity, but a lesser enantioselectivity, with respect to other rhodium complexes was observed (e.g., cf. entries 1 vs 2 and 4 vs 6). Other parameters were then varied in order to learn more about the reaction and it was interesting to find that the use of the ethylene glycol ester of phenylboronic acid gave a slightly improved enantioselectivity (entry 10). Moreover, in contrast with the previously reported rhodium-catalyzed addition of arylboronic acids to oxabenzonorbornadienes,[8,9] the presence of a base is not essential in order to effect the reaction, and it gave compound **2aa** also without an added base, albeit with a slightly lower rate (entry 11). However, it should be noted that without an added base the reaction is poorly enantioselective and furthermore, the choice of the base had a certain influence on the reaction course (entries 6, 12–14), with the best results obtained with 2.0 equiv of CsF (entry 12).

In order to explore the reaction further, we next studied the use of other potential sources of phenyl groups in the ARO of compound **1a**, and the results are reported in Table 2. For example, phenylzinc chloride prepared by metathesis from PhLi and $ZnCl_2$ is known to be an effective nucleophile for the rhodium-catalyzed asymmetric 1,4-addition to activated olefins.[14] The ring opening reactions were effected in anhydrous THF with 3 mol % of $[Rh(C_2H_4)_2Cl]_2$ and 7.5 mol % of chiral ligand. In these reaction conditions, the best results were obtained with the diphosphite ligand $\mathbf{L_2}^*$ (Table 2, entry 1), whereas other ligands tested gave an incomplete conversion and the formation of a mixture of products (see, e.g., entries 2 and 3). The attempt to generate arylzinc compounds in ethereal solvents from aryl iodides and zinc powder,[15] and by boron-to-zinc exchange procedures (from Ph_3B, $PhB(OH)_2$, and $PhBO_3 + Et_2Zn$),[16] proved not to be effective arylating agents in our reaction conditions (data not shown in Table 2).

To our delight, the use of simple Ph_3B in combination with 3 mol % of $[Rh(C_2H_4)_2Cl]_2$ and 7.5 mol % of $P(OEt)_3$ gave a high yield of the arylated hydrazino cyclopentene **2aa** (Table 2, entry 4). The addition of Ph_3B in the presence of chiral ligands gave, in some cases, moderate enantioselectivities and satisfactory isolated yields of the arylated product (entries 5 and 6). To the best of our knowledge, the use of simple triphenylborane as a mild nucleophilic phenylating agent in a ring-opening process is unprecedented.

Amongst boron-based reagents, potassium organotrifluoroborates are an attractive alternative because they are air- and moisture-stable salts and they are readily accessible by a variety of high-yielding methods.[17] However, the use of $PhBF_3K$ in combination with catalytic amounts of Rh(I)-complex with ligand $\mathbf{L_3}^*$ afforded compound **2aa** with low yield and in racemic form (entry 8).[18]

Next, the scope of arylative ARO of bicyclic hydrazine **1a** was extended with a number of aryl boronic acids and esters using $[Rh(C_2H_4)_2Cl]_2$ (3.0 mol %) and (*R*)-Tol-Binap ($\mathbf{L_3}^*$, 6.0 mol %) as the chiral catalyst; the results are summarized in Table 3. Under the optimized conditions, bicyclic hydrazine **1a** underwent asymmetric addition of *p*-iodo substituted phenylboronic acid to give a good yield of the corresponding arylated product **2ab** (54% ee) without the concomitant insertion of the rhodium catalyst onto the Ar–I bond (Table 3, entry 1). A similar enantioselectivity was also obtained with the use of *p*-methoxyphenylboronic acid (entry 2), whereas the use of *o*- and *m*-methoxyphenylboronic acids proved not to be enantioselective (entries 3 and 4). The addition of *m*-fluoro- and *p*-methylphenylboronic acids proceeded smoothly, to give the corresponding adducts **2af** and **2ag** with a high yield and an appreciable enantioselectivity (entries 5 and 6). Although the highest enantioselectivity (89%) was

Table 2. Rh(I)-catalyzed ARO of compound **1a** with other phenyl organometallic reagents[a]

No	Aryl source	L*	Solvent	Yield[b] (%)	ee[c] (%)
1	$PhLi + ZnCl_2$	$\mathbf{L_2}^*$	THF	82	46
2	$PhLi + ZnCl_2$	$\mathbf{L_3}^*$	THF	Nd	Nd
3	$PhLi + ZnCl_2$	$\mathbf{L_1}^*$	THF	8	30
4	Ph_3B	$P(OEt)_3$	MeOH	85	NA
5	Ph_3B	$\mathbf{L_1}^*$	MeOH	78	36
6	Ph_3B	$\mathbf{L_3}^*$	MeOH	72	55
7	Ph_3B	$\mathbf{L_4}^*$	MeOH	22	0
8	$PhBF_3K$	$\mathbf{L_3}^*$	MeOH	25	2

[a] All reactions were performed with 3 mol % of $[Rh(C_2H_4)_2Cl]_2$ and 7.5 mol % of ligand with 2.0 equiv of the organometallic reagent at 65 °C for 20 h (see Supplementary data).
[b] Isolated yield of compound **2aa** after chromatographic purification.
[c] See corresponding note of Table 1.

Table 3. Scope of desymmetrization reaction of **1a** with arylboronic acids[a]

No	Ar	Time (h)	Conv.[b] (%)	Yield (%)	ee[c] (%)
1	*p*-I–C_6H_4	18	>98	62 (**2ab**)	54
2	*p*-OMe–C_6H_4	18	90	65 (**2ac**)	52
3	*o*-OMe–C_6H_4[d]	48	40	35 (**2ad**)	0
4	*m*-OMe–C_6H_4[d]	18	>98	90 (**2ae**)	0
5	*m*-F–C_6H_4[d]	18	>98	88 (**2af**)	70
6	*p*-Me–C_6H_4	18	>98	90 (**2ag**)	46
7	*m*-CN–C_6H_4[d]	18	>98	65 (**2ah**)	12
8	*m*-NO_2–C_6H_4[e]	48	95	20 (**2ai**)	89

[a] All reactions were performed with 3 mol % of $[Rh(C_2H_4)_2Cl]_2$ and 6 mol % of chiral ligand $\mathbf{L_3}^*$, in MeOH at 65 °C with $ArB(OH)_2$ (2.0 equiv) and CsF (2.0 equiv), unless stated otherwise.
[b,c] See corresponding notes of Table 1.
[d] Reaction carried out with $NaHCO_3$.
[e] Reaction carried out with K_2CO_3.

reached with the use of *m*-nitrophenylboronic acid, the reaction conditions were not synthetically efficient, giving the corresponding addition product **2ai** in a modest 20% isolated yield (entry 8).

In summary, we have developed a new catalytic asymmetric arylation of bicyclic hydrazines allowing a new and practical access to chiral nonracemic arylated hydrazinocyclopentenes which can provide a useful scaffold in medicinal chemistry research. This rhodium-catalyzed reaction proceeds in good yields with excellent regio- and stereoselectivities and nicely complements the alkylative desymmetrization of bicyclic hydrazines with copper-catalysts and organoaluminum reagents recently developed by us.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.153.

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