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Rhodium-Catalyzed Enantioselective Conjugate Addition of Arylboronic Acids to Dihydronitronaphthalenes

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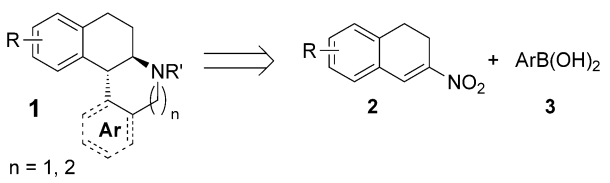
Abstract: A highly enantioselective (up to 91% *ee*) rhodium-catalyzed asymmetric addition of arylboronic acids has been achieved leading to the challenging dihydro-3-nitronaphthalenes using one equivalent of phosphoramidite ligand to rhodium catalyst. A concise formal asymmetric synthesis of the dopamine D1 agonist, dihydrexidine was accomplished using the method.

Keywords: asymmetric catalysis; conjugate addition; dihydrexidine; dihydro-3-nitronaphthalenes; rhodium

The rhodium-catalyzed asymmetric conjugate addition of organoboronic acids to electron-deficient olefins, pioneered by Miyaura and Hayashi, is one of the most efficient methods for enantioselective C–C bond formation.[1] High levels of enantioselectivity have been achieved using a variety of mono- and bidentate chiral ligands and the reaction is also applicable to a wide range of substrates.[2] In contrast, studies on nitroalkenes are still limited.[3,4] The first Rh-catalyzed asymmetric addition of organoboronic acids to cyclic aliphatic nitroalkenes was reported by Hayashi's group with excellent enantioselectivity.[3] Recently impressive results were achieved for nitrostyrenes too.[4a,b]

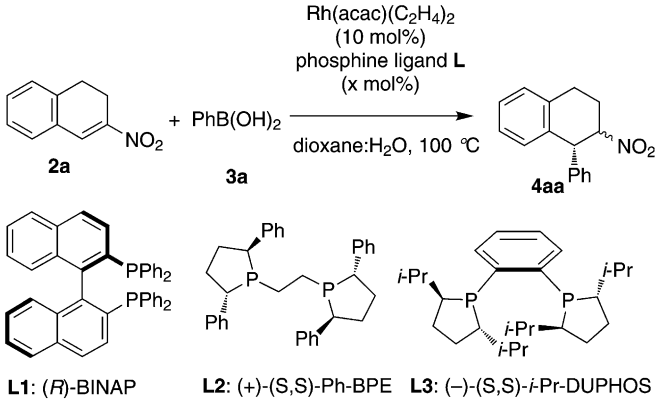
Annulated arene heterocycles and carbocycles such as hexahydrobenzophenanthrenes and their homologues **1** constitute important structural subunits of various natural products and pharmaceuticals.[5,6] Enantioselective 1,4-conjugate addition of arylboronic acids to dihydro-3-nitronaphthalenes **2** followed by reduction of the nitro group and cyclization could provide an efficient and concise protocol for the synthesis of such compounds (Scheme 1). However, despite its great synthetic importance the Rh-catalyzed asymmetric addition of arylboronic acids to dihydro-3-nitronaphthalenes **2** is still a challenge and known to be unsuccessful.[7] Our interest[8] towards the efficient asymmetric synthesis of biologically important hexahydrobenzophenanthrenes and related compounds led us to investigate the unprecedented chemistry. Herein we report the Rh-catalyzed asymmetric addition of arylboronic acids to dihydro-3-nitronaphthalenes with high enantioselectivity (*ee* upto 91%) and its application towards the asymmetric synthesis of the dopamine D1 agonist, (+)-dihydrexidine. The use of 1.1 equivalents of monodentate phosphoramidite ligand to rhodium-catalyst is also effective for the catalysis.

Initial trials on the reaction of dihydronitronaphthalene **2a** with $PhB(OH)_2$ **3a** in the presence of $Rh(acac)(C_2H_4)_2$/(*S*)-BINAP **L1** as catalyst under the standard conditions failed. A number of bidentate phosphine ligands was tested under the same reaction conditions (see the Supporting Information); most of them did not show any reaction. Only (+)-(*S*,*S*)-Ph-



Scheme 1. A straightforward construction of hexahydrobenzophenanthrene by catalytic enantioselective conjugate addition of $ArB(OH)_2$ **3** to dihydronitronaphthalenes **2**.

Table 1. Initial trial using bidentate and achiral monodentate ligands.



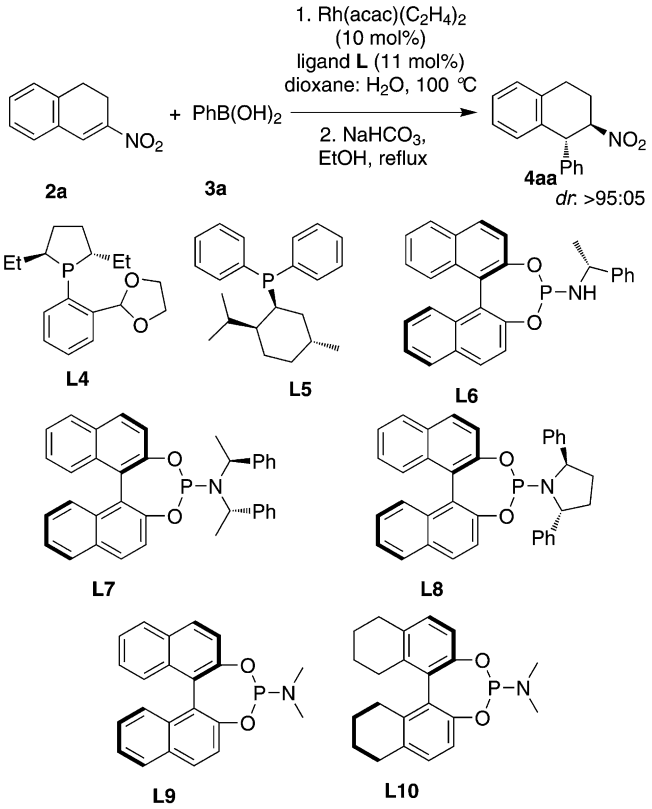
Entry	Ligand	Mol%	Conv. [%][a]	Yield [%][b]
1	**L**	22	NR	–
2	**L2**	22	10	–
3	**L3**	22	20	15
4	Ar_3P	22	NR	–
5	Me_3P	22	NR	–
6	$(n\text{-}Bu)_3P$	22	<10%	–
7	$(cy\text{-}Hex)_3P$	22	100%	75
8	$(cy\text{-}Hex)_3P$	11	100%	72

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] Isolated yields of the addition product **4aa**. Ar = Ph, *p*-Tol, *o*-Tol.

BPE **L2** and (−)-(*S*,*S*)-*i*-Pr-DUPHOS **L3** gave the desired phenyl addition product **4aa** with 10–20% conversion (Table 1; entries 2 and 3), but there was no reaction with (+)-(*S*,*S*)-Me-BPE and (−)-(*S*,*S*)-Me-DUPHOS. This result prompted us to realize that the approach of bidentate chelated cyclic aryl-rhodium (Ar-Rh) to the structurally rigid dihydronitronaphthalene **2a** might be inhibited and the sterically hindered Ph-BPE **L2** and *i*-Pr-DUPHOS **L3** might be acting as monodentate ligands providing the reaction. So we began our investigation on the above reaction with monodentate achiral phosphine ligands (Table 1). There was also no reaction with triarylphosphines Ar_3P (Ar = Ph, *p*-Tol, *o*-Tol) ligands (entry 4). In contrast, we were pleased to find that $Rh(acac)(C_2H_4)_2$/$(cy\text{-}Hex)_3P$ catalyst showed very good efficiency with 100% conversion (entry 7). Interestingly, the reaction was found to be successful even with only 1.1 equivalents of $(cy\text{-}Hex)_3P$ to $Rh(acac)(C_2H_4)_2$ (entry 8) and it was a cleaner reaction too.[9] Lowering the catalyst loading to 5 mol% and 2 mol% in the reaction gave incomplete conversion.

Preliminary findings revealed that the phosphine ligands should be single point-binding and have to be electron-rich. Now the $PhB(OH)_2$ addition to dihydronitonaphthalene **2a** was directed towards the asymmetric reaction with chiral monodentate phosphine ligands (using 1.1 equivalents to rhodium catalyst) like rajphos **L4**, (*S*)-(+)-neomenthyl-(diphenyl)phosphine **L5** and phosphoramidites[4c–e,10] **L6–L10** (Table 2). Rajphos **L4** gave very poor conversion (entry 1) whereas, the neomenthyl-(diphenyl)phosphine **L5** showed smooth addition of $PhB(OH)_2$ to dihydronitronaphthalene **2a** with 100% conversion and high yield, but no *ee* (entry 2). Among the phophoramidite ligands, phosphoramidite **L6**

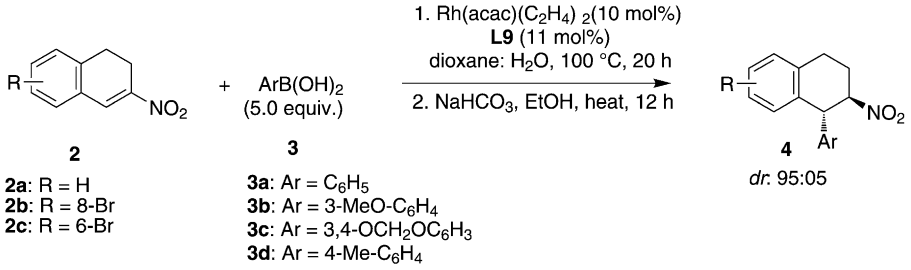
Table 2. Screening of chiral monodentate ligands for the asymmetric conjugate addition to dihydronitronaphthalene **2a**.



Entry	Ligand	Conv. [%][a]	Yield [%][b]	*ee* [%][c]
1	**L4**	NR	–	–
2	**L5**	100	84	0
3	**L6**	NR	–	–
4	**L7**	NR	–	–
5	**L8**	<5%	–	–
6	**L9**	63	56	86
7	**L10**	55	50	86
8[d]	**L9**	60	55	86

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] Isolated yield of the addition product **4aa**.
[c] Enantiomeric excess was determined by chiral HPLC.
[d] Reaction with 2.1 equiv. of ligand **L9** to rhodium catalyst.

Table 3. Rh(acac)$(C_2H_4)_2$/**L9**-catalyzed asymmetric conjugate addition to dihydronitronaphathalenes **2**.

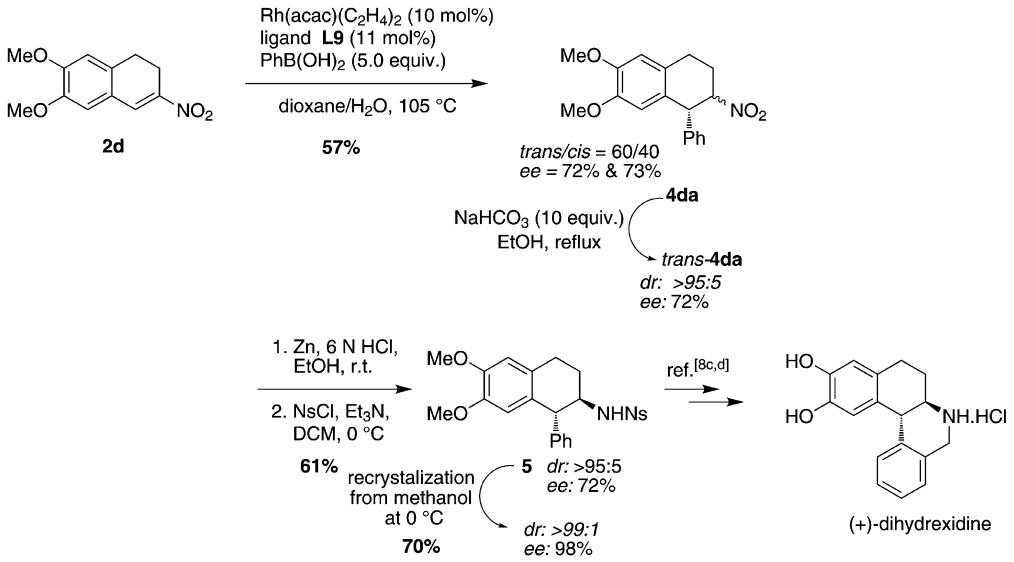


Entry	**2**	**3**	**4**	Conv. [%][a]	Yield [%][b]	*ee* of **4** [%][c]
1	**2a**	**3a**	**4aa**	63	56	86
2	**2a**	**3b**	**4ab**	56	52	87
3	**2a**	**3c**	**4ac**	42	31	81
4	**2a**	**3d**	**4ad**	55	42	80
5[d]	**2b**	**3a**	**4ba**	55	50	85
6	**2b**	**3b**	**4bb**	52	48	91
7	**2b**	**3c**	**4bc**	40	28	78
8	**2b**	**3d**	**4bd**	45	32	80
9[d]	**2c**	**3a**	**4ca**	35	30	61
10[d]	**2c**	**3b**	**4cb**	20	16	75

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture; 30–70% of the corresponding dihydro-2-nitronaphthalene **2** were recovered.
[b] Isolated yields of the respective addition product **4**.
[c] Enantiomeric excess was determined by chiral HPLC.
[d] Reactions were carried with (*S*)-phosphorimidite *ent*-**L9** and produced the other enantiomers of compound **4**.

having a free NH and sterically hindered ligands **L7** and **L8** did not show any reaction (entries 3–5). Sterically less hindered simple (*R*)-binaphthyldimethylamine phosphoramidite **L9** was found to be efficient and provided 63% conversion with high enantioselectivity (*ee* 86%) as a mixture of diastereomers (*dr*= 1:1), which on heating with $NaHCO_3$ in EtOH afforded exclusively *trans*-isomer **4aa** without any loss of *ee* (entry 6). A phosphoramidite having the partially saturated binaphthyl unit **L10** showed similar results with slightly lower conversion (entry 7). These results might further support the lesser steric demands of the arylboronic acid addition to dihydronitronaphthalene as presumed. Interestingly, reactions of dihydronitronaphthalene **2a** and $PhB(OH)_2$ **3a** in the presence of rhodium/**L9** using 2.1 equiv. (entry 8) and 1.1 equiv. (entry 6) ligand to rhodium afforded the same result. The active catalyst for the both cases might, therefore, be the same. The addition of $PhB(OH)_2$ **3a** with dihydronitronaphthalene **2a** was also tested with other rhodium catalysts such as $[RhCl(C_2H_4)_2]_2$/**L9** in the presence of additive either KOH or KHF_2 or K_3PO_4 and it provided similar results only in toluene/H_2O, but no reaction in dioxane/H_2O. The catalytic asymmetric addition of arylboronic acids to dihydro-3-nitronaphthalenes with high enantioselectivity and use of one equivalent of ligand to rhodium represents a very good achievement.

This method could produce a number of non-racemic *trans*-1-aryl-2-nitrotetralins **4**, if a different combination of dihydronitronaphthalenes **2** and arylbornic acids **3** are reacted and subjected to subsequent epimerization[3] with $NaHCO_3$ in EtOH. So this rhodium-catalyzed asymmetric method was generalized with other arylboronic acids and dihydro-3-nitronaphthalenes under the developed conditions using only 1.1 equiv. of ligand **L9** to rhodium (Table 3). In particular, bromo-substituted dihydro-3-nitronaphthalenes were tested, where the bromo functionality might provide a further avenue for structural elaboration by different kinds of coupling reactions and subsequent reactions. Under the developed conditions, we were pleased to find that most of the reactions provided clean addition products with high enantioselectivity of both diastereomers (*dr* varies from 1:1 to 2:1; see the Supporting Information). Reactions of four arylboronic acids with unsubstituted dihydronitronaphthalene **2a** afforded all the desired products with high enantioselectivity (*ee* up to 87%), but with incomplete conversion (entries 1–4). 8-Bromodihydro-3-nitronaphthalene **2b** showed a similar reactivity as **2a** with higher enantioselectivity (*ee* up to 91%; entries 5–8). In contrast, 6-bromodihydronitronaphthalene **2c** was found to be less reactive and showed lower enantioselectivity (*ee* up to 75%; entries 9–12). The diastereomeric mixture of compound **4** on refluxing with $NaHCO_3$ in EtOH afforded exclusively the *trans*-



Scheme 2. Catalytic asymmetric formal synthesis of the dopamine D1 agonist, (+)-dihydrexidine.

isomer **4** ($dr > 95:5$) without any loss of enantioselectivity.[3] This method is an unprecedented asymmetric addition of arylboronic acids to dihydro-3-nitronaphthanlenes with very good to excellent enantioselectivity, although with incomplete conversion.

Chiral *trans*-2-amino-1-aryltetralins are the key precursors to many biologically active natural products, and pharmaceuticals.[5,6,8,11] These *trans*-aminotetralins could easily be obtained from 1-aryl-2-nitrotetralins **4**. Consequently, the synthetic utility of this methodology was further demonstrated by the transformation of dihydro-3-nitronaphthalene **2d** to (+)-dihydrixdine,[8c,d,11b–d] a dopamine D1 agonist (Scheme 2). To this end, **2d** was reacted with $PhB(OH)_2$ **3a** in the presence of $Rh(acac)(C_2H_4)_2$-**L9** as a catalyst under optimized conditions. It provided a diastereomeric mixture ($dr = 1.5:1$) of 2-nitro-1-phenyltetralin **4da** in 57% yield with 72% and 73% *ee*, respectively. Epimerization[3] of the *cis*-isomer to *trans*-one, by heating of the diastereomeric mixture **4da** with $NaHCO_3$ in EtOH, provided *trans*-2-nitro-1-phenyltetralin *trans*-**4da** in high diastereoselectivity ($dr > 95:05$) without any loss of enantioselectivity (*ee* 72%). Zn/HCl-mediated reduction of the *trans*-**4da** produced *trans*-2-amino-1-phenyltetralin and subsequent nosyl protection with NsCl and Et_3N in DCM provided *N*-nosyl-aminotetralin **5** as a pale yellow solid with 61% yield over two steps. Recrystalization of the compound **5** from methanol at 0 °C crystallized out the minor enantiomer and enhanced the *ee* of the mother liquor to 98% with 72% recovery yield.[8c,d] The optical rotation of **5** {$[\alpha]_D^{25}$: −60 (*c* 1.0, $CHCl_3$)} matches very well with literature[8c] data {$[\alpha]_D^{25}$: −64.2 (*c* 1.0, $CHCl_3$)}, thus confirming the absolute stereochemistry as 1*R*,2*R*. By analogy, the absolute stereochemistry of the *trans*-isomer of all compounds **4** was assumed. Again (1*R*,2*R*)-*trans*-*N*-nosyl-1-amino-2-phenyltetralin **5** is a known[8c,d] advanced precursor for the synthesis dopamine D1 agonist, dihydrexidine, thus completing the formal synthesis.

In summary, we have developed the first rhodium-phosphoramidite **L9**-catalyzed asymmetric conjugate addition of arylboronic acids to challenging dihydro-3-nitronaphthalenes. The reaction is found to be effective only with monodentate ligand. Use of one equivalent of ligand to rhodium provided the same result as two equivalents ligand. Under optimal conditions (using one equivalent ligand to rhodium), the addition reaction proceeds well with a range of substrates and provided high enantioselectivity for both of the diastereomers that could easily be epimerized exclusively to the *trans*-isomer without any loss of *ee*. The usefulness of the method was demonstrated by a catalytic enantioselective formal synthesis of the dopamine D1 agonist, dihydrexidine. Further investigation on efficiency, mechanism and applications are underway in the laboratory.

Experimental Section

General Procedure for the Asymmetric Conjugate Addition Reaction

To a mixture of $Rh(acac)(C_2H_4)_2$ (0.001 g, 0.042 mmol, 10 mol%), ligand **L9** (0.017 g, 0.047 mmol, 11 mol%) and 3-methoxyphenylboronic acid **3b** (0.325 g, 2.14 mmol, 5.0 equiv.) was added 1,4-dioxane (3 mL) and, the mixture was stirred at room temperature for 3 min. 1,2 Dihydronitronaphthalene **2a** (0.075 g, 0.42 mmol, 1.0 equiv.) and water (0.3 mL) were then added to it and the whole mixture was stirred at 100–105 °C for 20 h. The reaction mixture was cooled to room temperature, followed by the addition of an

aqueous solution of sodium bicarbonate (5 mL). It was then extracted with ethyl acetate (3×25 mL). The combined organic extract was washed with brine, dried over sodium sulphate and evaporated under vacuum. The residue was purified by flash column chromatography using ethyl acetate and hexanes to obtain compound **4ab** (yield: 0.06 g; 52%) as a mixture of diastereomers (dr=2:1) along with the starting 1,2-dihydronitronaphthalene **2a** (recovery: 0.03 g; 40%).

The mixture was then refluxed with sodium bicarbonate (10 equiv.) and 4.0 mL of ethanol for 12 h. It was evaporated to dryness, passed through a filter column using 100–200 silica gel and ethyl acetate-hexanes as an eluent and provided *trans*-1-aryl-2-nitrotralin **4ab** as a single diastereomer; yield: 100% (dr>95:05). (In some cases addition product **4** and unreacted dihydronaphthalene **3** were found to have the same R_f. Preparative HPLC was adopted to purify the desired addition product).

Acknowledgements

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