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Rhodium-Catalyzed Asymmetric Addition of Arylboronic Acids to β-Nitroolefins: Formal Synthesis of (*S*)-SKF 38393

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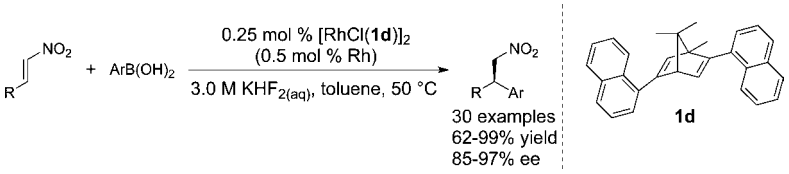
ABSTRACT



An efficient enantioselective addition of an array of arylboronic acids to various β-nitrostyrenes catalyzed by a novel and reactive rhodium−diene catalyst (S/C up to 1000) was developed, providing β,β-diarylnitroethanes in good to high yields (62−99%) with excellent enantioselectivities (85−97% ee). The method was extended to 2-heteroarylnitroolefins and 2-alkylnitroolefins similarly providing the desired products with high enantioselectivities and yields. The usefulness of this method was demonstrated in the formal synthesis of the enantiomer of the dopamine receptor agonist and antagonist, SKF 38393.

4-Aryltetrahydroisoquinolines[1] and 1-aryl-2,3,4,5-tetrahydro-1*H*-3-benzazepines[2] are synthetic targets of considerable interest owing to their biological and pharmacological activities. Cherylline is a type of 4-aryl-substituted tetrahydroisoquinoline that affects the central nervous system (Figure 1),[1a] while SCH 23390 and SCH 39166 are typical examples of potent benzazepine D_1/D_5 antagonists.[2f] Common to both of these types of alkaloids is the β,β-diarylethylamine moiety. The enantioselective conjugate addition of aryl nucleophiles to β-nitrostyrenes followed by the reduction of nitro groups appears to be the most straightforward method for accessing such chiral β,β-diarylethylamines.

While organocatalytic Friedel−Crafts-type conjugate addition reactions efficiently provide the corresponding adducts, good selectivity is achieved only using certain substrates.[3] In pioneering work in the field of transition-metal-catalyzed asymmetric conjugate addition reactions,[4] Hayashi et al. reported a rhodium−BINAP[5] catalyst for

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the asymmetric 1,4-addition of arylboronic acids to various electron-deficient olefins.[6,7] Recently, enthusiasm for the use of stable and optically active diene ligands as chiral modifiers in the field of rhodium-catalyzed asymmetric transformations has surged owing to the high catalytic activity and enantioselectivity that they impart on the catalyst.[8] In the only example of catalysis of this reaction using a rhodium complex of a chiral diene ligand, Lin et al. described the high-yielding and enantioselective arylation of a variety of β-nitrostyrenes.[9] Like Lin's C_2-symmetric chiral bicyclo[3.3.0]diene ligands, chiral sulfoxide–phosphine[10a,b] and sulfoxide–olefin ligands[10c] have proven effective ligands in the conjugate addition of arylboronic acids to β-nitrostyrenes.[10]

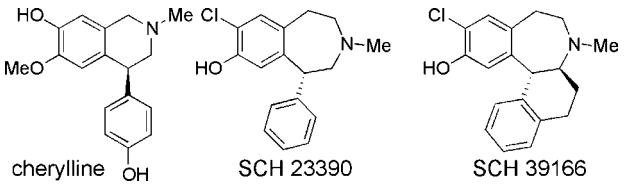

Figure 1. Biologically active compounds.

During recent development of rhodium-catalyzed asymmetric transformations for the synthesis of biologically active compounds, we discovered and developed a novel family of stable chiral C_1-symmetric 2,5-diarylbicyclo-[2.2.1]dienes **1**, derived from (−)-bornyl acetate, that were found to be effective in asymmetric arylation of α,β-unsaturated carbonyl compounds.[11] Both acyclic and cyclic substrates were effective reaction partners with excellent stereocontrol, reactivity, and efficiency (TON up to 2000) when arylboronic acids were used as nucleophiles. In light of the importance of chiral β,β-diarylnitroethanes as building blocks, we herein report improvements upon the single previously reported study[9] of Rh–diene ligand catalyzed asymmetric arylation of nitroolefins using our own novel ligands that allow significantly reduced catalyst loadings and reaction temperature while exhibiting comparable reactivity. This asymmetric arylation of β-nitrostyrenes was epitomized by catalysis at 50 °C using only 0.25 mol % of a rhodium dimer complex of chiral diene **1d** (0.5 mol % of Rh), yielding enantioenriched β,β-diarylnitroethanes with up to 97% ee.

Initially, a model conjugate addition reaction of phenylboronic acid (**3a**) to β-arylnitroalkene **2a** was investigated in the presence of 3 mol % of Rh-**1a** catalyst that was prepared in situ (Table 1). When our previously determined optimized reaction conditions for asymmetric 1,4-addition reactions to carbonyl compounds were used herein to effect this transformation, none of the desired product was observed (entries 1 and 2).[11,12] The use of KHF_2 as an additive,[9] however, successfully promoted the conjugate addition, giving the adduct **4aa** in 67% chemical yield and moderate asymmetric induction (50% ee) (entry 3). Pleasingly, while the previous report using a Rh–bicyclo-[3.3.0]diene complex required 100 °C, our Rh–diene complex was effective at only 50 °C indicating improved kinetics. While the role of KHF_2 remains unknown, the corresponding potassium organotrifluoroborate, formed in situ from the reaction of the organoboronic acid and KHF_2, was speculated to be the active nucleophilic species in the catalytic cycle;[9] however, only a trace amount of product **4aa** was obtained when potassium phenyltrifluoroborate was used as a nucleophile (entry 4).[13,14] Subsequently, the use of our novel 2,5-diarylsubstituted ligands **1b–h** was examined in conjuction with KHF_2 as an additive (entries 5–11). Ligand **1d**, with 1-naphthyl substituents, was the most stereoselective among those tested. The addition reaction, catalyzed by 3 mol % of Rh-**1d**, generated in situ from 1.5 mol % of $[RhCl(C_2H_4)_2]_2$ and 3.6 mol % of chiral diene **1d**, was completed at 50 °C within 1.5 h in toluene to yield compound **4aa** in 85% yield with 92% ee (entry 7). Solvent screening using ligand **1d** and KHF_2 as an additive showed that while xylenes and THF gave comparable results (entries 12 and 13, respectively),

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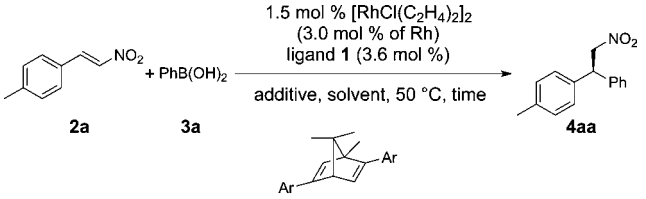
Table 1. Asymmetric Conjugate Addition of $PhB(OH)_2$ to β-Nitroalkene **2a** Catalyzed by Rh-**1**[a]



1a: Ar = Ph **1e**: Ar = 2-Naphthyl
1b: Ar = 4-Me-C_6H_4 **1f**: Ar = 4-F-C_6H_4
1c: Ar = 4-Ph-C_6H_4 **1g**: Ar = 4-Cl-C_6H_4
1d: Ar = 1-Naphthyl **1h**: Ar = 4-NO_2-C_6H_4

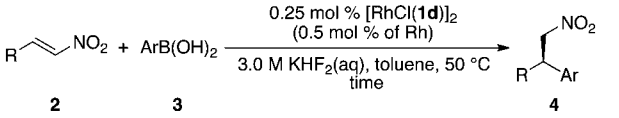
entry	ligand	time (h)	additive	solvent	yield[b] (%)	ee[c] (%)
1	**1a**	23	KOH[d]	toluene	n.r.	n.d.
2	**1a**	23	Et_3N[e]	toluene	n.r.	n.d.
3	**1a**	23	KHF_2[f]	toluene	67	50
4[g]	**1a**	23	KOH[d]	toluene	trace	n.d.
5	**1b**	23	KHF_2[f]	toluene	85	54
6	**1c**	23	KHF_2[f]	toluene	56	55
7	**1d**	1.5	KHF_2[f]	toluene	85	92
8	**1e**	23	KHF_2[f]	toluene	79	60
9	**1f**	23	KHF_2[f]	toluene	90	45
10	**1g**	23	KHF_2[f]	toluene	95	52
11	**1h**	23	KHF_2[f]	toluene	98	44
12	**1d**	8	KHF_2[f]	xylenes	90	90
13	**1d**	8	KHF_2[f]	THF	87	88
14	**1d**	8	KHF_2[f]	dioxane	71	83
15	**1d**	8	KHF_2[f]	glyme	66	90
16	**1d**	8	KHF_2[f]	diglyme	43	87
17	**1d**	8	KHF_2[f]	CH_2Cl_2	>99	80
18[h,i]	**1d**	1.5	KHF_2[f]	toluene	>99	92
19[h,j]	**1d**	2.5	KHF_2[f]	toluene	94	92
20[h,k]	**1d**	4	KHF_2[f]	toluene	99	92
21[h,l]	**1d**	23	KHF_2[f]	toluene	97	91

[a] The reaction was conducted on a 0.2 mmol scale in the presence of $[RhCl(C_2H_4)_2]_2$ (3.0 μmol) with ligand **1** (7.2 μmol) under an Ar atmosphere at 50 °C; n.r. means no reaction; n.d. means not determined. [b] Isolated yield. [c] Determined by chiral HPLC; see the Supporting Information. [d] 1.5 M $KOH_{(aq)}$ (0.13 mL) was added. K_2CO_3, NaOH, CsOH, *i*-Pr_2NH, and K_3PO_4 were found to be ineffective. [e] 0.48 mmol of Et_3N was added. [f] 3.0 M $KHF_{2(aq)}$ (0.2 mL) was added. [g] Potassium phenyltrifluoroborate was used instead of $PhB(OH)_2$. [h] Preformed $[RhCl(\mathbf{1d})]_2$ was used. [i] 1.5 mol % of $[RhCl(\mathbf{1d})]_2$ (3.0 mol % Rh). [j] 0.5 mol % of $[RhCl(\mathbf{1d})]_2$ (1.0 mol % Rh). [k] 0.25 mol % of $[RhCl(\mathbf{1d})]_2$ (0.5 mol % Rh). [l] 0.05 mol % of $[RhCl(\mathbf{1d})]_2$ (0.1 mol % Rh).

ethereal solvents (entry 14–16) provided reduced yields and lower enantioselectivities, apart from glyme (entry 15), that gave comparable ee.[15] While dichloromethane (entry 17) gave excellent conversion, the selectivity was only moderate. An improved chemical yield was obtained without sacrificing the high ee when the reaction was carried out in the presence of 1.5 mol % of preprepared $[RhCl(\mathbf{1d})]_2$ (3 mol % of Rh) (entry 18). Optimization of the catalytic loading revealed that even in the presence of 0.5 and 0.25 mol % of $[RhCl(\mathbf{1d})]_2$, the reaction proceeded smoothly to give compound **4aa** in 94–99% chemical yields and 92% ee (entries 19–20). This contrasts that reported previously,[9] where 1.5 mol % of the corresponding bicyclo[3.3.0]diene Rh dimer complexes were required for similar substrates. This suggests that bicyclo[2.2.1]-diene ligands provide more reactive Rh catalysts than the bicyclo[3.3.0]diene ligands that rely on 50 °C higher reaction temperature while using more catalyst. Notably, with 0.05 mol % of $[RhCl(\mathbf{1d})]_2$ (0.1 mol % of Rh; a S/C ratio of 1000) the asymmetric reaction provided the desired product without the loss of high catalytic activity or enantioselectivity, but a longer reaction time

(15) In this study, only an amount of adduct **4aa** was isolated from reactions in alcohol solvents, which is at odds with our previous studies that alcohol solvents were good reaction media; see ref 11.

Table 2. Asymmetric Conjugate Addition to Substituted β-Nitrostyrenes **2** Catalyzed by $[RhCl(\mathbf{1d})]_2$[a]



2a: R = 4-Me-C_6H_4 **2d**: R = 2-MeO-C_6H_4 **2g**: R = 2-Thienyl
2b: R = C_6H_5 **2e**: R = 3,4-$(MeO)_2$-C_6H_3 **2h**: R = Isopropyl
2c: R = 4-Cl-C_6H_4 **2f** : R = 2-Furyl **2i**: R = Cyclohexyl

entry	2	Ar	time (h)	yield[b] (%)	ee[c] (%)
1	**2a**	C_6H_5 (**3a**)	4	99 (*S*-**4aa**)	92
2[d]	**2a**	4-ClC_6H_4 (**3b**)	6.5	94 (*R*-**4ab**)	93
3	**2a**	3-$NO_2C_6H_4$ (**3c**)	23	81 (*R*-**4ac**)	94
4	**2a**	4-$NO_2C_6H_4$ (**3d**)	21	96 (*R*-**4ad**)	94
5	**2a**	4-CNC_6H_4 (**3e**)	72	83 (*R*-**4ae**)	94
6	**2a**	4-$CF_3C_6H_4$ (**3f**)	5	90 (*R*-**4af**)	93
7	**2a**	4-FC_6H_4 (**3g**)	6	82 (*R*-**4ag**)	95
8	**2a**	3-ClC_6H_4 (**3h**)	6	68 (*R*-**4ah**)	91
9[e]	**2a**	3-$CF_3C_6H_4$ (**3i**)	18	67 (*R*-**4ai**)	93
10	**2a**	4-^{t}BuC_6H_4 (**3j**)	24	99 (*R*-**4aj**)	89
11[e]	**2a**	3-$MeOC_6H_4$ (**3k**)	18	90 (*R*-**4ak**)	91
12	**2a**	4-$MeOC_6H_4$ (**3l**)	6	77 (*R*-**4al**)	97
13	**2a**	4-PhC_6H_4 (**3m**)	6	71 (*R*-**4am**)	95
14	**2a**	1-naphthyl (**3n**)	5	90 (*R*-**4an**)	96
15	**2a**	2-naphthyl (**3o**)	8	70 (*R*-**4ao**)	91
16[f]	**2b**	4-MeC_6H_4 (**3p**)	24	85 (*R*-**4aa**)	90
17[g]	**2b**	4-ClC_6H_4 (**3b**)	51	94 (*R*-**4bb**)	93
18[f]	**2c**	4-MeC_6H_4 (**3p**)	24	81 (*S*-**4ab**)	89
19	**2d**	4-MeC_6H_4 (**3p**)	48	93 (*S*-**4dp**)	91
20[e]	**2e**	C_6H_5 (**3a**)	18	71 (*S*-**4ea**)	95
21	**2f**	4-MeC_6H_4 (**3p**)	72	89 (*R*-**4fp**)	89
22	**2f**	4-$MeOC_6H_4$ (**3l**)	6	62 (*R*-**4fl**)	90
23	**2f**	4-CNC_6H_4 (**3e**)	20	92 (*R*-**4fe**)	92
24	**2g**	4-MeC_6H_4 (**3p**)	48	99 (*R*-**4gp**)	91
25[h]	**2g**	4-$MeOC_6H_4$ (**3l**)	18	70 (*R*-**4gl**)	91
26[i]	**2g**	4-CNC_6H_4 (**3e**)	59	94 (*R*-**4ge**)	92
27[e]	**2h**	C_6H_5 (**3a**)	9	81 (*R*-**4ha**)	95
28[e]	**2h**	4-$MeOC_6H_4$ (**3l**)	18	86 (*R*-**4hl**)	91
29[e]	**2i**	C_6H_5 (**3a**)	11	93 (*R*-**4ia**)	89
30[e]	**2i**	4-$MeOC_6H_4$ (**3l**)	18	82 (*R*-**4il**)	85

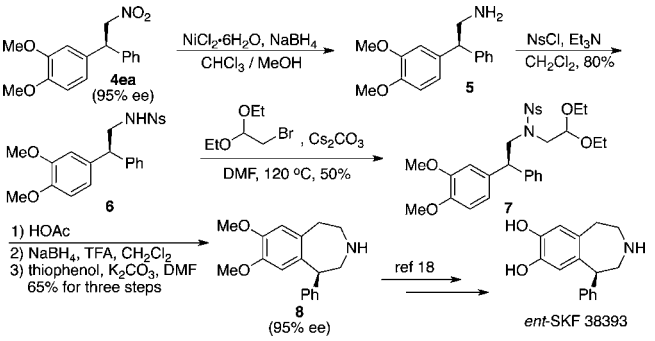
[a] The reaction was conducted on a 0.2 mmol scale, in the presence of $[RhCl(\mathbf{1d})]_2$ (0.5 μmol, 0.5 mol % Rh), under an Ar atmosphere at 50 °C. [b] Isolated yield. [c] Determined by chiral HPLC; see the Supporting Information. [d] 0.75 equiv of 4-Cl-phenylboronic acid was added after 4.5 h. [e] 1.5 equiv of arylboronic acid was added after 6 h. [f] 1.5 equiv of arylboronic acid was added after 16 h. [g] 1.5 equiv of 4-Cl-phenylboronic acid was added after 48 h. [h] 0.75 equiv of 4-MeO-phenylboronic acid was added after 6 h. [i] 0.75 equiv of 4-CN-phenylboronic acid was added after 23 h.

(23 h) was required (entry 21). Low Rh loadings could be benficial in pharmaceutical drug substance manufacture where only ppm concentrations of residual Rh are allowed by regulatory agencies. This further supports our observation that the bicyclo[2.2.1]diene ligands provide more active (lower reaction temperature and catalyst loading) Rh catalysts in conjugate additions to β-nitroolefins.

With the reaction conditions specified in Table 1, entry 20, as a starting point, we next investigated the asymmetric addition of a range of arylboronic acids to a variety of nitro-based Michael acceptors (Table 2). Under the optimal conditions, the enantioselective conjugated addition of arylboronic acids, substituted with electron-withdrawing (entries 2−9) or electron-donating groups (entries 10−13), to 4-methyl-β-nitrostyrene (**2a**) furnished products in good yields with high enantio-induction (89−97% ee). The absolute configuration of the stereogenic center was determined to be *R* by X-ray crystallographic analysis of compound **4al**.[16] The utilization of both 1-naphthyl- and 2-naphthylboronic acids (**3n** and **3o**) had a negligible effect on the outcome of the reaction, providing compounds **4an** and **4ao** in comparable yield with a similar level of enantioselectivity, respectively (entries 14 and 15). Subsequently, the enantioselective addition of various arylboronic acids to β-nitroalkenes **2b**−**i** was studied to elucidate this asymmetric transformation further. Excellent enantioselectivities were also observed from the reactions of β-nitrostyrenes regardless of whether the substituents were electron-withdrawing or electron-donating (**2b**−**e**) (89−95% ee) (entries 16−20). Notably, 2-(2-nitrovinyl)-furan (**2f**) and 2-(2-nitrovinyl)-thiophene (**2g**) were good reaction partners, yielding addition products with a comparably high stereoselectivity (89−92% ee) (entries 21−26). In addition to β-nitrostyrenes, β-nitroolefins with alkyl substituents were tested as acceptors in this asymmetric transformation. The conjugate addition of phenylboronic acid (**3a**) and 4-methoxyphenylboronic acid (**3l**) to (*E*)-3-methyl-1-nitrobut-1-ene (**2h**) and (*E*)-(2-nitrovinyl)cyclohexane (**2i**) proceeded in a highly enantiocontrolled manner (85−95% ee) to generate the corresponding adducts in excellent yields (81−93%), respectively (entries 27−30).

By way of demonstration, chiral compound **4ea**, as synthesized using the catalytic asymmetric method reported herein, was utilized in the formal synthesis of *ent*-SKF 38393,[17] the enantiomer of a dopamine receptor agonist and antagonist (Scheme 1).[2a] The reduction of compound **4ea** with nickel boride produced primary amine **5**,[18] which was converted into sulfonamide **6**. Compound **6** underwent *N*-alkylation with 2-bromo-1,1-diethoxyethane under basic conditions to give acetal **7** in good yield. A three-step manipulation that involved the acid-mediated Jackson-type cyclization[19a,b] of acetal **7**, reduction,[19c] and the removal of Ns-group furnished compound **8**, a precursor of *ent*-SKF-38393, in 63% yield with 95% ee.

Scheme 1. Synthesis of *ent*-SKF 38393



In conclusion, a highly efficient (S/C, substrate/catalyst, up to 1000) and enantioselective rhodium-catalyzed addition reaction of arylboronic acids to β-nitroalkenes utilizing a novel family of bicyclo[2.2.1]diene ligands was realized. Generally, the asymmetric addition reactions, conducted at only 50 °C in the presence of 0.25 mol % of [RhCl(**1d**)]$_2$, of various arylboronic acids with β-nitroolefins yielded enantioenriched β,β-disubstituted nitroethanes in good to excellent yields (up to 99%) with excellent enantioselectivity (up to 97%). High catalytic activity and enantioselectivity can also be observed in the reactions of 2-heteroarylnitroolefins and 2-alkylnitroolefins using our Rh−**1d** complex. In comparison to the use of bicyclo[3.3.0]diene ligands in the asymmetric arylation reaction of some β-nitroolefins and nucleophiles,[9] our system allows lower catalyst loadings to be realized while a significantly lower temperature can be used while equal or better enantioselectivity can be obtained. This method was employed to synthesize chiral 1-phenyltetrahydro-1*H*-3-benzazepine **8** efficiently, which is the intermediate of pharmacologically interesting *ent*-SKF 38393. Further investigation and application of this methodology and the development of catalytic systems for other asymmetric synthesis are currently in progress.

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Supporting Information Available. Experimental procedures and characterization of compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(16) See the Supporting Information.

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