Asymmetric Catalysis

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Enantioselective Synthesis of α-Aryl Alkylamines by Rh-Catalyzed Addition Reactions of Arylboronic Acids to Aliphatic Imines**

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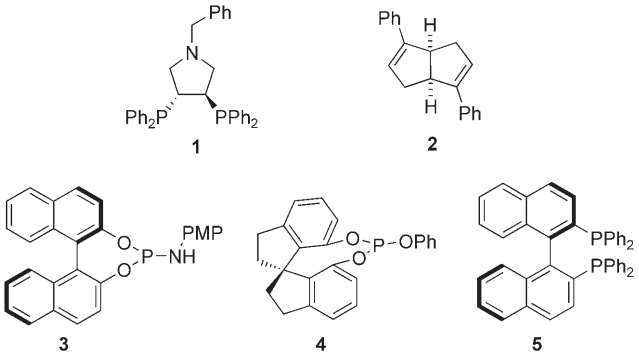
α-Aryl alkylamines are prevalent in biologically active natural products and drugs.[1] In addition, they are of significant use for the synthesis of chiral auxiliaries and optically active ligands.[2] The development of methods for the asymmetric synthesis of α-aryl alkylamines is consequently an important goal in synthetic organic chemistry.[3] One of the most attractive approaches for the synthesis of chiral amines is the enantioselective catalytic addition of organometallic reagents to imines.[4] Recently, highly enantioselective transition-metal-catalyzed additions of organozinc,[5] titanium,[6] tin,[7] and boron reagents[8] to aromatic imines have been achieved, with the addition of arylboronic acids being particularly attractive due to the large number and diversity of commercially available derivatives. Despite these considerable advances, catalytic enantioselective addition reactions of aryl boron reagents have been reported only for aromatic imines, thus dramatically limiting the generality of these methods. Herein, we report the first enantioselective catalytic addition of arylboronic acids to aliphatic imines that are activated with the diphenylphosphinoyl (dpp) or the 4-toluenesulfonyl (tosyl) substituent at the nitrogen center.

Previously, we reported the enantioselective addition of arylboronic acids to aromatic *N*-dpp imines.[9] The dpp substituent was selected because it is well documented that this protecting group can readily be removed by simple acid treatment to give near-quantitative yield of the addition product.[10] The optimal reaction conditions are: dioxane as the solvent, triethylamine and powdered molecular sieves (4 Å) as the additives, [Rh(acac)(coe)$_2$] as the precatalyst, and (*R*,*R*)-deguphos (**1**) as the chiral ligand (Scheme 1; acac = acetylacetonate, coe = cyclooctene, (*R*,*R*)-deguphos = (*R*,*R*)-l-benzyl-3,4-bis-(diphenylphosphino)pyrrolidine). Slow addition of the arylboronic acid over 10 h minimized protodeborylation. Unfortunately, addition of arylboronic acid **8** to aliphatic imine **6a** gave **9a** in low yield with extensive imine self-condensation (Table 1, entry 1). In an attempt to minimize self-condensation the triethylamine additive was omitted, and to accelerate the rate of the addition reaction versus the self-condensation reaction, the catalyst loading was doubled and the imine substrate was added last (Table 1, entry 2). Under these reaction conditions the yield of **9a** was greatly improved, but with a modest 59% *ee*.



Scheme 1. The chiral ligands tested. PMP = *para*-methoxyphenyl.

Increasing the ligand to rhodium mol ratio from 1.1:1.0 to 1.4:1.0 greatly improved the enantioselectivity (86% *ee*; Table 1, entry 3). Further increases did not result in improvements to the enantioselectivity of the reaction (data not shown). Significantly, at the optimal ligand/Rh mol ratio of 1.4:1, the catalyst loading could be reduced to 5% with only a minimal loss in yield and selectivity (Table 1, entry 4). The enantioselectivity was further increased to 90% *ee* by using 5% catalyst loading as well as preincubating the ligand, precatalyst [RhCl(acac)(coe)$_2$], and arylboronic acid for 90 minutes prior to the addition of imine **6a** (Table 1, entry 5). Lowering the catalyst loading to 3% resulted in lower enantioselectivity (Table 1, entry 8). Finally the precatalyst [{RhCl(C_2H_4)$_2$}$_2$], which had also been reported as useful for additions of arylboronic acids to imines,[8e] was evaluated. It was found to maintain high enantioselectivities, however, gave lower yields either with (Table 1, entry 10) or without (Table 1, entry 9) Et_3N as an additive.

A diverse selection of ligands, previously reported to be successful for enantioselective additions of arylboronic acid to aromatic imines, were also investigated (Scheme 1). Chiral diene **2**, which was reported to give extremely high selectivities for arylboronic acid additions to aromatic *N*-tosyl imines,[8e] gave modest yields and enantioselectivities for both the reported reaction conditions (Table 1, entry 11) and our optimized conditions (Table 1, entry 12). In addition, the monodentate ligands phosphoramidite **3**[8c] (Table 1, entry 13) and phosphite **4**[8d] (Table 1, entry 14), which were also previously shown to be very effective for catalytic enantioselective additions of arylboronic acids to aromatic imines, were both found to be much less efficient in terms of conversion and selectivity. The ligand binap (**5**) gave moder-

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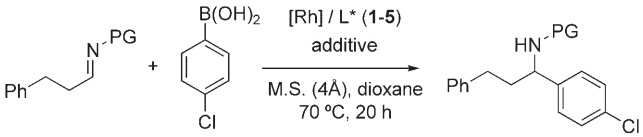
Table 1: Optimization of the reaction conditions for *N*-dpp and *N*-tosyl imines.[a]



6a: PG = $P(O)Ph_2$
7a: PG = tosyl

8a

9a: PG = $P(O)Ph_2$
10a: PG = tosyl

Entry	Imine	Rh (mol%)	Chiral ligand (mol%)	Prod.	Yield [%][b]	*ee* [%][c]
1	**6a**	$[Rh(acac)(coe)_2]$ (5)	**1** (5.5)	**9a**	17	n.d.
2	**6a**	$[Rh(acac)(coe)_2]$ (10)	**1** (11)	**9a**	74	59
3	**6a**	$[Rh(acac)(coe)_2]$ (10)	**1** (14)	**9a**	71	86
4	**6a**	$[Rh(acac)(coe)_2]$ (5)	**1** (7)	**9a**	65	84
5	**6a**	$[Rh(acac)(coe)_2]$ (5)	**1** (7)	**9a**	70	90
6[d]	**6a**	$[Rh(acac)(coe)_2]$ (5)	**1** (7)	**9a**	91	89
7[e]	**6a**	$[Rh(acac)(coe)_2]$ (5)	**1** (7)	**9a**	95	90
8	**6a**	$[Rh(acac)(coe)_2]$ (3)	**1** (3.3)	**9a**	53	81
9[f]	**6a**	$[\{RhCl(C_2H_4)_2\}_2]$ (5)	**1** (5.5)	**9a**	44	91
10[f]	**6a**	$[\{RhCl(C_2H_4)_2\}_2]$ (5)	**1** (5.5)	**9a**	46[g]	90[g]
11[f]	**6a**	$[\{RhCl(C_2H_4)_2\}_2]$ (5)	**2** (5.5)	**9a**	75	−80
12	**6a**	$[Rh(acac)(coe)_2]$ (5)	**2** (7)	**9a**	45	−60
13	**6a**	$[Rh(acac)(coe)_2]$ (5)	**3** (14)	**9a**	40	14
14	**6a**	$[Rh(acac)(coe)_2]$ (5)	**4** (15)	**9a**	35	10
15	**6a**	$[Rh(acac)(coe)_2]$ (5)	**5** (7)	**9a**	36	74
16	**7a**	$[Rh(acac)(coe)_2]$ (5)	**1** (7)	**10a**	69	92
17	**7a**	$[Rh(acac)(coe)_2]$ (3)	**1** (3.3)	**10a**	78	93
18[h]	**7a**	$[Rh(acac)(coe)_2]$ (3)	**1** (3.3)	**10a**	99	95
19[f]	**7a**	$[\{RhCl(C_2H_4)_2\}_2]$ (5)	**2** (5.5)	**10a**	79	−69
20	**7a**	$[Rh(acac)(coe)_2]$ (3)	**2** (3.3)	**10a**	55	−62
21	**7a**	$[Rh(acac)(coe)_2]$ (3)	**3** (7.5)	**10a**	85	19
22	**7a**	$[Rh(acac)(coe)_2]$ (3)	**4** (6)	**10a**	40	12
23	**7a**	$[Rh(acac)(coe)_2]$ (3)	**5** (3.3)	**10a**	75	63

[a] The reaction was carried out with 1 equivalent of imine (0.125 mmol) and 2 equivalents of boronic acid (0.25 mmol) in the presence of rhodium catalyst and the chiral ligand, as given, in dioxane (0.12 M) at 70 °C with an incubation time for the precatalyst and ligand (further experimental details are available in the Supporting Information) Abbreviations: M.S. = molecular sieves, n.d. = not detected, PG = protecting group, Ts = tosyl = 4-toluenesulfonyl. [b] Yields were determined by ^1H NMR analysis using 2,6-dimethoxytoluene as the internal standard in $CDCl_3$. [c] The *ee* values were determined by HPLC on a chiral stationary phase. [d] Reaction was performed on a 1 mmol scale with the addition of K_3PO_4 (20 mol%). [e] Reaction was performed on a 5 mmol scale with the addition of K_3PO_4 (20 mol%). [f] The reaction was carried out at 55 °C. [g] Addition of 2 equivalents of Et_3N. [h] Addition of K_3PO_4 (20 mol%).

ate conversion and reasonable selectivity (Table 1, entry 15; binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl).

Given the very high enantioselectivities reported for additions of arylboronic acid to aromatic *N*-sulfonyl imines when ligands **1**–**5** were used,[8c–d] we evaluated this set of ligands for arylation of the aliphatic *N*-tosyl imine **7a**. At 5% catalyst loading, (*R*,*R*)-deguphos gave an impressive 69% yield with 92% *ee* (Table 1, entry 16). Good yields and selectivities were maintained after dropping the catalyst loading to 3% (Table 1, entry 17). For the aliphatic *N*-tosyl imine substrate, ligands **2**–**5** again provided significantly lower selectivities (Table 1, entries 19–23).

Sakuma and Miyaura demonstrated that inorganic bases exert a remarkable accelerating effect upon the addition of arylboronic acids to α,β-unsaturated amides.[11] Consequently, we investigated the influence of inorganic bases on the reaction of imines **6a** and **7a**, and found that an optimal 20 mol% of K_3PO_4 had a pronounced effect on the efficiency of the reactions while maintaining high enantioselectivities (Table 1, entries 6, 7, and 18). Importantly, both enantioselectivity and yield remained high when the reaction was performed on a 5 mmol scale, as was demonstrated for imine **6a** (Table 1, entry 7).

The optimized reaction conditions for additions of arylboronic acids to *N*-tosyl imines (Table 1, entry 18) were next evaluated with diverse aliphatic *N*-tosyl imines **7**[12] and arylboronic acids **8** (Table 2). To our delight, the additions

Table 2: Asymmetric arylation of *N*-tosyl imines **7** with arylboronic acids **8**.[a]

7 **10**

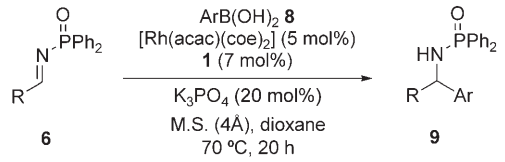
Entry	R	Ar	**10**	Yield [%][b]	*ee* [%][c]
1	$PhCH_2CH_2$	$4\text{-}ClC_6H_4$	**10a**	94	95
2	$CH_3CH_2CH_2$	$4\text{-}ClC_6H_4$	**10b**	89	93[d]
3	$(CH_3)_2CHCH_2$	$4\text{-}ClC_6H_4$	**10c**	96	91
4	$CH_2{=}CHCH_2CH_2$	$4\text{-}ClC_6H_4$	**10d**	87	98
5	cyclohexyl	$4\text{-}ClC_6H_4$	**10e**	80	96
6	cyclohexyl	$4\text{-}MeC_6H_4$	**10f**	71	96
7	cyclohexyl	$4\text{-}MeOC_6H_4$	**10g**	74	90
8	cyclohexyl	$4\text{-}CF_3C_6H_4$	**10h**	89	91
9	cyclohexyl	$3\text{-}ClC_6H_4$	**10i**	75	90
10	cyclohexyl	$3\text{-}AcC_6H_4$	**10j**	81	89
11	$PhCH_2CH_2$	$3\text{-}ClC_6H_4$	**10k**	74	93
12	$PhCH_2CH_2$	$3\text{-}AcC_6H_4$	**10l**	80	90

[a] The reaction was carried out with preincubation of the rhodium precatalyst and **1** in dioxane at 70 °C for 90 min, and heating was continued for 20 h after the addition of 1 equivalent of imine, 2 equivalents of boronic acid, and K_3PO_4 (20 mol%). [b] Yield of isolated product. [c] The *ee* values were determined by HPLC on a chiral stationary phase. [d] The absolute configuration of **10b** was determined as *R* by optical rotation after removal of the protecting group.

proved to be remarkably general. Good yields and high selectivities were maintained for *N*-tosyl imines that were β branched (Table 2, entry 3) and α branched (Table 2, entries 5–9). Moreover, excellent selectivities were observed for the addition of arylboronic acids that were electron rich (Table 2, entries 6 and 7) and electron poor (Table 2, entries 8–10). The excellent functional group compatibility of our method is highlighted by the efficiency observed for addition reactions of 3-keto-substituted arylboronic acid (Table 2, entries 10 and 12).

We further explored the scope of aliphatic *N*-dpp imines **6**.[12] A good yield and reasonable selectivity was observed for a β-branched dpp imines (Table 3, entry 3), and addition

Table 3: Asymmetric arylation of *N*-dpp imines **6** with arylboronic acids **8**.[a]



6 **9**

Entry	R	Ar	**9**	Yield [%][b]	*ee* [%][c]
1	$PhCH_2CH_2$	4-ClC_6H_4	**9a**	92[d]	90
2	$CH_3CH_2CH_2$	4-ClC_6H_4	**9b**	89	86
3	$(CH_3)_2CHCH_2$	4-ClC_6H_4	**9c**	80	81
4	$(CH_3)_2CH$	4-ClC_6H_4	**9d**	75	84
5	cyclopropyl	4-ClC_6H_4	**9e**	79	95
6	$PhCH_2CH_2$	4-MeC_6H_4	**9f**	71	91
7	$PhCH_2CH_2$	4-$MeOC_6H_4$	**9g**	68	86
8	$PhCH_2CH_2$	4-$CF_3C_6H_4$	**9h**	85	82

[a] The reaction was carried out with preincubation of the rhodium catalyst and **1** in dioxane at 70 °C for 90 min, and heating was continued for 20 h after addition of 1 equivalent of imine (0.125 mmol scale), 2 equivalents of boronic acid, and K_3PO_4 (20 mol %). [b] Yield of isolated product. [c] The *ee* values were determined by HPLC on a chiral stationary phase. [d] The reaction was performed with imine **6a** on a 5 mmol scale.

reactions to α-branched imines proceeded with only slightly reduced yields while good selectivity was maintained (Table 3, entries 4 and 5). Both electron-rich (Table 3, entries 6 and 7) and electron-poor (Table 3, entry 8) arylboronic acids added with good selectivities. Only a modest decrease in yield was observed for the electron-rich derivatives.

In conclusion, the catalytic enantioselective addition of arylboronic acids to aliphatic imines has been demonstrated for the first time. Broad substrate scope, with high yields and selectivities, was observed for addition reactions to aliphatic *N*-tosyl imines. Good substrate scope, with only slightly lower selectivities, was observed for addition reactions to *N*-dpp imines. Further optimization of the catalyst system, to provide even higher selectivity and catalytic efficiency, will be reported in due course.

Experimental Section

General procedure for the reactions described in Tables 2 and 3: A solution of $[Rh(acac)(coe)_2]$ (Table 2; 1.6 mg, 0.0037 mmol, 0.03 equiv, or Table 3; 2.6 mg, 0.0062 mmol, 0.05 equiv) and (*R*,*R*)-deguphos (Table 2; 2.2 mg, 0.0041 mmol, 0.033 equiv, or Table 3; 4.6 mg, 0.0087 mmol, 0.07 equiv) in dioxane (0.5 mL) was prepared in a glove box and then stirred for 90 min at 70 °C. Then imine **6** or **7** (0.125 mmol) in dioxane (0.5 mL), arylboronic acid (0.25 mmol), powdered molecular sieves (4 Å; 200 mg), and K_3PO_4 (5.3 mg, 0.025 mmol, 0.2 equiv) were successively added, and the resulting reaction mixture was stirred for 20 h at 70 °C. The mixture was diluted with water, extracted with CH_2Cl_2, and the solvent was then removed in vacuo. The crude material was taken up in THF (5 mL) and *N*,*N*-diethanolaminomethyl polystyrene resin (PS-DEAM; 200 mg) and shaken for 10 h. The THF solution was filtered and the resin was washed with ethyl acetate. The crude residue was purified by flash column chromatography to afford products **9** and **10**, respectively.

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