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Rhodium-Catalyzed Enantioselective Arylation of Aliphatic Imines

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Abstract: Chiral rhodium(I)-catalyzed highly enantioselective arylation of aliphatic *N*-sulfonyl aldimines with arylboronic acids has been developed. This transformation is achieved by the use of a rhodium/bis(phosphoramidite) catalyst to give enantiomerically enriched α-branched amines (up to 99% *ee*). In addition, this system enables efficient synthesis of (+)-NPS R-568 and Cinacalcet which are calcimimetic agents.

As attractive structural elements, chiral α-branched aryl alkyl amine derivatives are present in biologically active molecules and drugs such as *NPS R-568*,[1] *Cinacalcet*,[2] and *Maraviroc*[3] (Figure 1). Several strategies have been developed to access chiral α-branched aryl alkyl amines in an enantioselective manner.[4] Among those synthetic approaches, asymmetric arylation of aliphatic aldimines with arylboronic acids is a particularly useful and powerful synthetic method. Several groups have reported successful examples of catalytic asymmetric arylation of alkyl imines to give α-branched amines with excellent levels of asymmetric induction.[5,6]

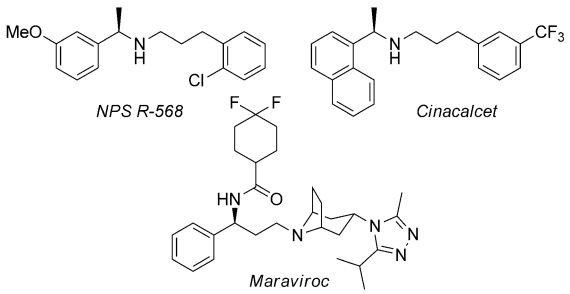

Figure 1. Examples of drugs containing chiral amine parts.

For example, in 2011, Lin and co-workers reported a rhodium/diene-catalyzed enantioselective arylation of *N*-tosyl or -nosyl aliphatic aldimines.[5c] Recently, Beisel and Manolikakes reported a convenient enantioselective arylation of aromatic and aliphatic imines that were synthesized in situ from aldehydes and sulfonamides.[5d]

We have succeeded in the development of a bis(phosphoramidite) ligand, called Me-BIPAM, that possesses a linked-binol backbone and shows a unique reactivity (Figure 2). The properties of these ligands can be adjusted by changing the linker atom, such as nitrogen, oxygen, and sulfur. BIPAM ligands with a transition-metal complex work as an effective catalyst for asymmetric 1,2-addition[7] and 1,4-addition reactions of arylboronic acids,[8] hydrogenation,[9] and C–H functionalization.[10]

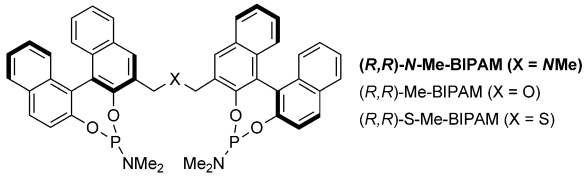

Figure 2. BIPAM ligands.

We have already reported enantioselective arylation of *N*-sulfonyl aromatic aldimines[7a] and iminoesters[7c] with aryl boron reagents in the presence of a rhodium/bis(phosphoramidite) (*N*-Me-BIPAM) catalyst. Herein, we report rhodium/*N*-Me-BIPAM-catalyzed arylation of aliphatic imines with arylboronic acids, which proceeds enantioselectively to give a variety of optically active α-branched amines. Furthermore, we show that the newly developed reaction can be used for the synthesis of *NPS R-568* and *Cinacalcet*, which are known as calcimimetic agents.[1] To the best of our knowledge, although results of excellent previous work have been reported by several groups, there is no example of application to the synthesis of such useful compounds by asymmetric arylation of aliphatic aldimines.

We began our study by examining reaction parameters, such as catalyst precursors and ligands in asymmetric arylation of aliphatic aldimine **1a** as a model substrate with phenyl boronic acid (Table 1). The use of cationic rhodium ($[Rh(nbd)_2](BF_4)$) (nbd = 2,5-norbornadiene) and *N*-Me-BIPAM proved to be particularly effective in terms of yields compared with other precursors and ligands (73%, 99% *ee*; Table 1, entry 2). Precursor screening showed that the counter anion of the cationic rhodium complex had some influence on both yield and enantioselectivity (entries 1–5). Concurrently, a neutral complex displayed somewhat low catalytic activity (entry 6). Raising the reaction temperature from 50 to 80 °C slightly increased the yield (81% yield, 98% *ee*, entry 7). We then examined the effects of linker atoms of BIPAM ligands, and only

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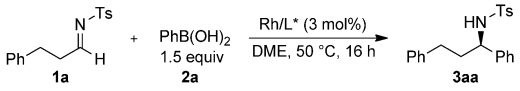
Table 1. Optimization of the reaction conditions.[a]



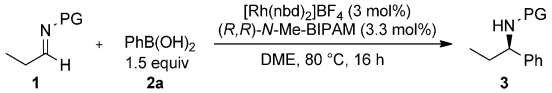
Entry	Precursor	L*	Yield [%]	ee [%]
1	$[Rh(nbd)_2](ClO_4)$	(*R,R*)-*N*-Me-BIPAM	69	98
2	**$[Rh(nbd)_2](BF_4)$**	**(*R,R*)-*N*-Me-BIPAM**	**73**	**99**
3	$[Rh(nbd)_2](PF_6)$	(*R,R*)-*N*-Me-BIPAM	71	99
4	$[Rh(nbd)_2](SbF_6)$	(*R,R*)-*N*-Me-BIPAM	71	97
5	$[Rh(nbd)_2](NTf_2)$	(*R,R*)-*N*-Me-BIPAM	66	98
6	$Rh(acac)(coe)_2$	(*R,R*)-*N*-Me-BIPAM	60	97
7[b]	**$[Rh(nbd)_2](BF_4)$**	**(*R,R*)-*N*-Me-BIPAM**	**81**	**98**
8	$[Rh(nbd)_2](BF_4)$	(*R,R*)-Me-BIPAM	48	68
9	$[Rh(nbd)_2](BF_4)$	(*R,R*)-S-Me-BIPAM	45	86
10	$[Rh(nbd)_2](BF_4)$	(*R*)-BINAP	n.r.	–
11	$[Rh(nbd)_2](BF_4)$	(*R*)-monophos	28	7

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 equiv), rhodium cat. (3 mol%), and (*R,R*)-*N*-Me-BIPAM (1.1 equiv to Rh) in DME (2 mL) was stirred for 16 h at 50 °C. [b] The reaction was conducted at 80 °C.

a moderate yield was obtained in the case of Me-BIPAM or S-Me-BIPAM (entries 8 and 9). Other typical asymmetric ligands, such as 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) or Monophos, gave the corresponding product in low yields (entries 10 and 11). Unfortunately, under our reaction conditions, aldimine **1a** decomposed to give an alcohol as a byproduct by arylation of aldehydes in all cases.

We also examined arylation of substrates bearing various protecting groups on the nitrogen atom of imine (Table 2). The

Table 2. Optimization of the protecting group of imines.[a]



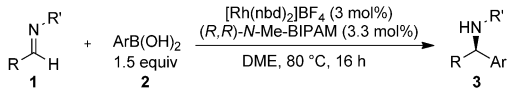
Entry	PG	Yield [%]	ee [%]
1	**Ts (1b)**	**76 (3ba)**	**96**
2	Ns (**1c**)	73 (**3ca**)	97
3	Bn (**1d**)	n.r. (**3da**)	–
4	Boc (**1e**)	n.r. (**3ea**)	–
5	OBn (**1f**)	n.r. (**3fa**)	–

[a] Reaction conditions: **1** (0.5 mmol), **2a** (1.5 equiv), rhodium cat. (3 mol%), and (*R,R*)-*N*-Me-BIPAM (1.1 equiv to Rh) in DME (2 mL) was stirred for 16 h at 80 °C.

type of protecting group of imines noticeably affected the reactivity, and no reaction occurred when *N*-Bn (**1d**), *N*-Boc (**1e**) (Boc = *tert*-butoxycarbonyl), and *N*-OBn (**1f**) aldimines were used as substrates because of the instability or low electrophilicity of imines. According to the results of the screening, *N*-sulfonyl-type aldimines, such as Ts (**1b**) and Ns (**1c**), are most effective in our developed catalytic arylation.

With the optimized reaction conditions in hand, various aldimine substrates and boronic acids were examined (Table 3).

Table 3. Substrate scope.[a]

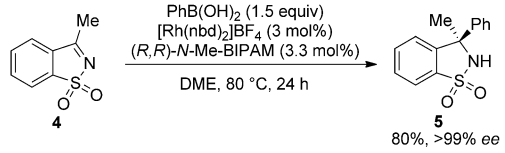


Entry	R	R′	Ar	Yield [%]	*ee* [%]
1	$PhCH_2CH_2$ (**1a**)	Ts	C_6H_5 (**2a**)	81 (**3aa**)	98
2	Et (**1b**)	Ts	C_6H_5 (**2a**)	76 (**3ba**)	96
3	Me (**1g**)	Ts	C_6H_5 (**2a**)	58 (**3ga**)	96
4	*n*-Pent (**1h**)	Ts	C_6H_5 (**2a**)	63 (**3ha**)	95
5	*i*Bu (**1i**)	Ts	C_6H_5 (**2a**)	74 (**3ia**)	97
6[b]	*i*Pr (**1j**)	Ts	C_6H_5 (**2a**)	66 (**3ja**)	94
7	*i*Pr (**1k**)	Ns	C_6H_5 (**2a**)	79 (**3ka**)	97
8	Cy (**1l**)	Ns	C_6H_5 (**2a**)	77 (**3la**)	95
9	$PhCH_2CH_2$ (**1a**)	Ts	4-$MeOC_6H_4$ (**2b**)	79 (**3ab**)	93
10	$PhCH_2CH_2$ (**1a**)	Ts	4-$PhOC_6H_4$ (**2c**)	81 (**3ac**)	89
11	$PhCH_2CH_2$ (**1a**)	Ts	4-$MeSC_6H_4$ (**2d**)	66 (**3ad**)	96
12	$PhCH_2CH_2$ (**1a**)	Ts	4-MeC_6H_4 (**2e**)	70 (**3ae**)	97
13	$PhCH_2CH_2$ (**1a**)	Ts	4-HOC_6H_4 (**2f**)	61 (**3af**)	89
14	$PhCH_2CH_2$ (**1a**)	Ts	4-PhC_6H_4 (**2g**)	74 (**3ag**)	86
15	$PhCH_2CH_2$ (**1a**)	Ts	4-ClC_6H_4 (**2h**)	56 (57[c]) (**3ah**)	69 (97[c])
16[c]	$PhCH_2CH_2$ (**1a**)	Ts	4-BrC_6H_4 (**2i**)	59 (**3ai**)	97
17[c]	$PhCH_2CH_2$ (**1a**)	Ts	4-FC_6H_4 (**2j**)	49 (**3aj**)	96
18[c]	$PhCH_2CH_2$ (**1a**)	Ts	4-$CF_3OC_6H_4$ (**2k**)	65 (**3ak**)	92
19[c]	$PhCH_2CH_2$ (**1a**)	Ts	4-$CF_3C_6H_4$ (**2l**)	47 (**3al**)	92
20	$PhCH_2CH_2$ (**1a**)	Ts	3-$MeOC_6H_4$ (**2m**)	74 (**3am**)	97
21	$PhCH_2CH_2$ (**1a**)	Ts	2-$MeOC_6H_4$ (**2n**)	59 (**3an**)	78
22	$PhCH_2CH_2$ (**1a**)	Ts	2-naphthyl (**2o**)	76 (**3ao**)	88
23	$PhCH_2CH_2$ (**1a**)	Ts	3,5-$MeOC_6H_3$ (**2p**)	70 (**3ap**)	99

[a] Reaction conditions: **1** (0.5 mmol), **2** (1.5 equiv), rhodium cat. (3 mol%), and (*R,R*)-*N*-Me-BIPAM (1.1 equiv to Rh) in DME (2 mL) was stirred for 16 h at 80 °C. [b] Reaction was conducted at 50 °C. [c] $[Rh(acac)(coe)_2]$ (3 mol%) was used instead of $[Rh(nbd)_2]BF_4$.

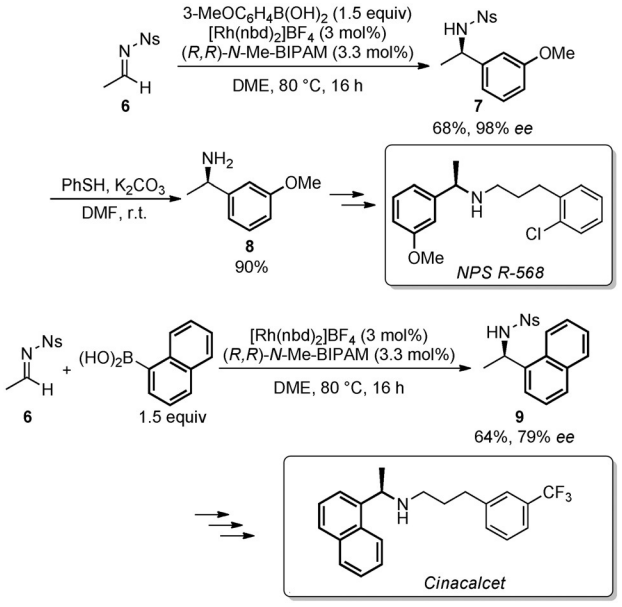
The reaction of the simplest substrate **1g** showed a high enantioselectivity to give **3ga** in 58% yield with 96% *ee*, a high enantioselectivity that has never been achieved by catalytic arylation (Table 3, entry 3). Although some catalytic systems are known to promote asymmetric arylation of alkyl aldimines, there is only one report for the arylation of **1g** with insufficient results,[5d] despite their structural potential including the *NPS R-568* and *Cinacalcet*. When the R group was changed from methyl to other primary alkyl groups, the reactions also proceeded smoothly to afford the corresponding chiral products in good yields and with high enantioselectivities (entries 4 and 5). Substrates possessing a substituent at the α-position effectively underwent arylation to give products with high enantioselectivities (entries 6–8). In the case of these imines, Ns-aldimine was more suitable than Ts-aldimine (entries 7 and 8). Next, asymmetric arylation of **1a** with various arylboronic acids was examined under optimized conditions (entries 9–23). Arylboronic acid containing an electron-donating group could be effectively added to imine **1a** with good to high enantioselectivities (entries 9–13). It is noteworthy that a non-protected hydroxyl group did not affect the reaction (entry 13). However, a strongly electron-deficient substituent, such as a Cl, Br, F, or a OCF_3 or CF_3 group reduced the reactivity of the substrate (entries 15–19). In these reactions, $[Rh(acac)(coe)_2]$ (acac = acetylacetonate; coe = cyclooctene) showed higher enantioselectivities than $[Rh(nbd)_2](BF_4)$. Arylboronic acids **2m**–**p** were also

used in this reaction, giving the corresponding amines (entries 20–23). This method was successfully applied to ketimine; saccharin-derived substrate **4** afforded the corresponding product **5** in 80% yield with >99% *ee* (Scheme 1).



Scheme 1. Asymmetric arylation of ketimine **4**.

To demonstrate the usefulness of this method, we applied it to synthetic key intermediates of *NPS R-568* and *Cinacalcet* (Scheme 2). Asymmetric arylation of Ns-aldimine **6** gave the corresponding products **7** and **9** in 68% yield with 98% *ee* and 64% yield with 79% *ee*, respectively. Then the nosyl group was removed under basic conditions to give **8** in 90% yield.



Scheme 2. Synthetic application of asymmetric arylation.

In summary, we have developed a rhodium/*N*-Me-BIPAM-catalyzed asymmetric arylation of aliphatic imines with arylboronic acids, which can serve as an efficient method for the synthesis of chiral α-branched amines. We have also shown the synthetic utility of this reaction by synthesizing drug intermediates. Further studies of this catalytic transformation with the aim of expanding the substrate scope and obtaining mechanistic insights into the enantioselection are in progress.

Experimental Section

General procedure

A flame-dried flask was charged with $[Rh(nbd)_2](BF_4)$ (0.015 mmol, 3 mol%) and (*R,R*)-*N*-Me-BIPAM (0.017 mmol, 3.3 mol%) under a nitrogen atmosphere. DME (2 mL) was added to the flask and the mixture was then stirred at room temperature for 30 min to prepare the catalyst. Arylboronic acid (0.75 mmol) and imine (0.5 mmol) were then added to this catalyst solution. After being stirred for 16 h at 80 °C, the reaction mixture was extracted with AcOEt and dried over $MgSO_4$. The mixture was purified by silica gel column chromatography (eluent: hexane/AcOEt) to afford the pure α-branched amine product.

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Keywords: asymmetric arylation · cationic rhodium · imines · phosphoramidite · α-branched amine

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