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Rhodium-Catalyzed Asymmetric Addition of Potassium Organotrifluoroborates to *N*-Sulfonyl Ketimines

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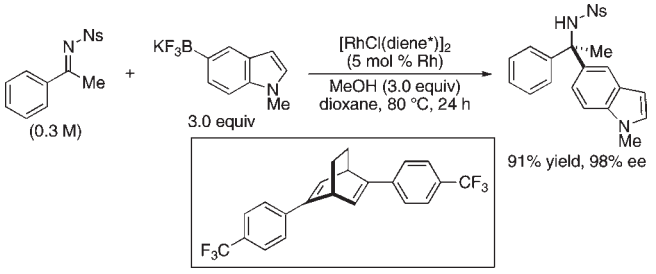
ABSTRACT



A rhodium-catalyzed asymmetric addition of readily available potassium organotrifluoroborates to both *N*-tosyl and *N*-nosyl ketimines has been developed. High enantioselectivity has been achieved by using a chiral diene ligand, and the nosyl group of the addition products can be easily removed while retaining the enantiomeric purity.

Transition-metal-catalyzed asymmetric addition of organometallic reagents to imines is one of the most powerful methods for the construction of enantioenriched chiral amines possessing an α-carbon stereocenter.[1] Most of the existing methods in this regard employ aldimines as substrates under the catalysis of copper,[2] zirconium,[3] rhodium,[4] or palladium.[5] In contrast, asymmetric additions to ketimines have been much less explored,[6] and to the best of our knowledge, only the copper-catalyzed addition of an allylboronate[7] and the copper-[8] or zirconium-catalyzed[9] addition of dialkylzincs have been known until recently.[10] To broaden the scope of the applicable organometallic nucleophiles, we reported a rhodium-catalyzed asymmetric addition of sodium tetraarylborates

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(5) (a) Ma, G.-N.; Zhang, T.; Shi, M. *Org. Lett.* **2009**, *11*, 875. (b) Liu, Z.; Shi, M. *Tetrahedron* **2010**, *66*, 2619.

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(8) Lauzon, C.; Charette, A. B. *Org. Lett.* **2006**, *8*, 2743.

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to *N*-tosyl ketimines in the presence of a chiral diene ligand in 2010.[11,12] Although high yield and enantioselectivity were achieved, the major drawback of this process in a synthetic point of view was the requirement to use tetraarylborates[13] to promote the reaction effectively. In addition, the use of *N*-nosyl ketimines resulted in moderate yields under this catalytic system. To overcome these problems, herein we describe that readily available potassium organotrifluoroborates[14,15] can now be employed as the nucleophile for the rhodium-catalyzed asymmetric addition to both *N*-tosyl and *N*-nosyl ketimines.

As we have previously reported,[11] a reaction of *N*-tosyl imine of 4′-chloroacetophenone (**1a**; 0.2 M initial concentration) with sodium tetraphenylborate (2.0 equiv) smoothly proceeds in the presence of [RhCl((*R*,*R*)-**L1**)]$_2$[16] (5 mol % Rh) and MeOH (2.0 equiv) in dioxane at 60 °C to give addition product (*S*)-**2a** in 83% yield with 97% ee (eq 1). Under these conditions, the use of potassium phenyltrifluoroborate in place of sodium tetraphenylborate significantly lowered the reactivity, giving **2a** only in 36% yield, although the enantioselectivity stayed high (98% ee). After some investigation of the reaction conditions, we were able to find a set of conditions that can efficiently promote this reaction. Thus, as shown in Table 1, entry 1, addition product **2a** can be obtained in 84% yield with 98% ee by reacting **1a** (0.3 M initial concentration) with potassium phenyltrifluoroborate (3.0 equiv) in the presence of [RhCl((*R*,*R*)-**L1**)]$_2$ (5 mol % Rh) and MeOH (3.0 equiv) in dioxane at 80 °C.

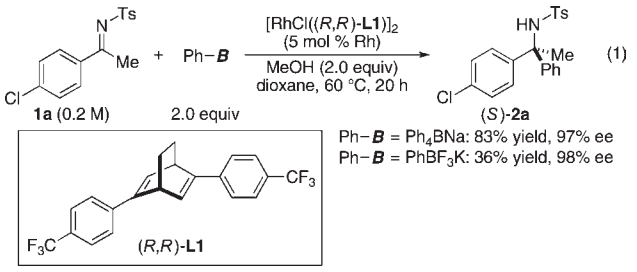
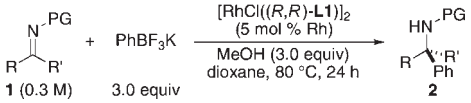
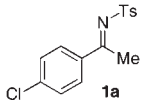
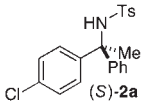
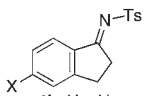
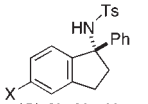
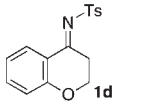
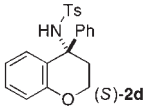
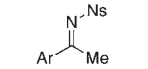
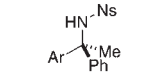


Table 1. Rhodium-Catalyzed Asymmetric Addition of Potassium Phenyltrifluoroborate to *N*-Tosyl and *N*-Nosyl Ketimines **1**



entry	substrate	product	yield (%)[a]	ee (%)[b]
1	 **1a**	 (*S*)-**2a**	84	98
2	 **1b**: X = H	 (*S*)-**2b**: X = H	97	>99.5
3	**1c**: X = Cl	(*S*)-**2c**: X = Cl	95	>99.5
4[c]	 **1d**	 (*S*)-**2d**	88	99
5	 **1e**: Ar = 4-ClC$_6$H$_4$	 (*S*)-**2e**: Ar = 4-ClC$_6$H$_4$	91	95
6[c,d]	**1f**: Ar = 4-MeC$_6$H$_4$	(*S*)-**2f**: Ar = 4-MeC$_6$H$_4$	80	95
7[c,d,e]	**1g**: Ar = 3-MeC$_6$H$_4$	(*S*)-**2g**: Ar = 3-MeC$_6$H$_4$	76	93
8[c,d]	**1h**: Ar = 2-naphthyl	(*S*)-**2h**: Ar = 2-naphthyl	77	92
9	**1i**: Ar = 2-furyl	(*S*)-**2i**: Ar = 2-furyl	71	95

[a] Isolated yield. [b] Determined by chiral HPLC with hexane/2-propanol. [c] The reaction was conducted at 90 °C. [d] The reaction was conducted for 48 h. [e] The reaction was conducted with 4.0 equiv of PhBF$_3$K and 4.0 equiv of MeOH.

Under these newly established conditions, several other *N*-tosyl ketimines **1b**−**1d** effectively undergo phenylation to give products **2** in high yields with excellent enantioselectivities (88−97% yield, ≥99% ee; entries 2−4). Furthermore, in contrast to our previous reactions using sodium tetraarylborates as the nucleophile,[11] the present catalysis is also effective for the reaction of *N*-nosyl ketimines. For example, *N*-nosyl imines of various (hetero)aryl

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(12) For reviews on chiral diene ligands, see: (a) Shintani, R.; Hayashi, T. *Aldrichimica Acta* **2009**, *42*, 31. (b) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482.

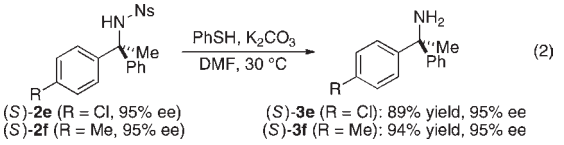
(13) For examples of the use of sodium tetraarylborates in rhodium-catalyzed addition reactions, see: (a) Ueda, M.; Miyaura, N. *J. Organomet. Chem.* **2000**, *595*, 31. (b) Miura, T.; Sasaki, T.; Nakazawa, H.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1390. (c) Ueura, K.; Miyamura, S.; Satoh, T.; Miura, M. *J. Organomet. Chem.* **2006**, *691*, 2821. (d) Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588. (e) Shintani, R.; Isobe, S.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3795. (f) Shintani, R.; Soh, Y.-T.; Hayashi, T. *Org. Lett.* **2010**, *12*, 4106. (g) Shintani, R.; Hayashi, T. *Org. Lett.* **2011**, *13*, 350. (h) Chen, J.; Chen, J.; Lang, F.; Zhang, X.; Cun, L.; Zhu, J.; Deng, J.; Liao, J. *J. Am. Chem. Soc.* **2010**, *132*, 4552.

(14) For reviews, see: (a) Molander, G. A; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240. (b) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288. (c) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623. (d) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275.

(15) For early examples of the use of potassium organotrifluoroborates in rhodium-catalyzed addition reactions, see: (a) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683. (b) Pucheault, M.; Darses, S.; Genet, J.-P. *Tetrahedron Lett.* **2002**, *43*, 6155.

(16) Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503.

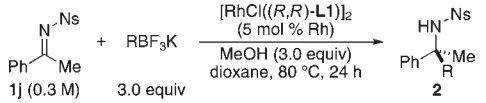
methyl ketones (**1e**−**1i**) are efficiently converted to phenylation products **2** in good to excellent yields with high ee (71−91% yield, 92−95% ee; entries 5−9). Of course, the nosyl group of the products thus obtained can be readily deprotected under mild reaction conditions while retaining the enantiomeric excesses as demonstrated in eq 2.[17]

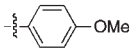
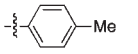
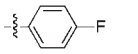
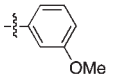
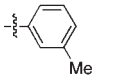
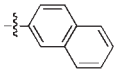
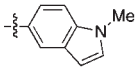
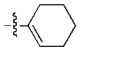


(2)

With regard to the nucleophilic component, various potassium aryltrifluoroborates including 2-naphthyl- and 5-indolylborates can be used in the reaction with *N*-nosyl imine of acetophenone (**1j**) to give the corresponding adducts **2** in high yield with ≥95% ee (Table 2, entries 1−7).[18] In addition to these aryl nucleophiles, an alkenyltrifluoroborate can also be employed to form a highly substituted allylamine derivative with high enantioselectivity (entry 8). This example also highlights the advantage of using potassium organotrifluoroborates over sodium tetraarylborates.[19]

Table 2. Rhodium-Catalyzed Asymmetric Addition of Potassium Organotrifluoroborates to *N*-Nosyl Ketimine **1j**



entry	R	product	yield (%)[a]	ee (%)[b]
1		(*R*)-**2j**	80	98
2		(*R*)-**2f**	79	98
3[c]		(*R*)-**2k**	78	96
4[c]		(*R*)-**2l**	80	95
5		(*R*)-**2g**	82	95
6[d]		(*R*)-**2h**	86	96
7		(*R*)-**2m**	91	98
8		(*S*)-**2n**	80	97

[a] Isolated yield. [b] Determined by chiral HPLC with hexane/2-propanol. [c] The reaction was conducted for 48 h at 90 °C. [d] The reaction was conducted for 48 h at 100 °C.

The stereochemical outcome in the reaction of **1a** with potassium phenyltrifluoroborate under the catalysis of Rh/(*R*,*R*)-**L1** can be rationalized as follows (Figure 1). To minimize the unfavorable steric interaction between the sulfonyl moiety on the nitrogen of **1a** and the aryl group on the olefin of (*R*,*R*)-**L1**, **1a** approaches phenylrhodium species with its *si*-face, thereby leading to the formation of **2a** with an *S* configuration.[4c,f]

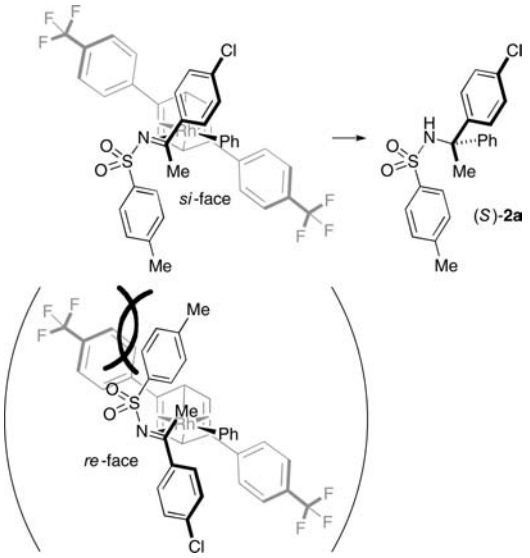


Figure 1. Proposed stereochemical pathway for the rhodium-catalyzed addition of potassium phenyltrifluoroborate to **1a**.

In summary, we have disclosed that readily available potassium organotrifluoroborates can be employed as the nucleophile for the rhodium-catalyzed asymmetric addition to both *N*-tosyl and *N*-nosyl ketimines. High enantioselectivity has been achieved by using chiral diene (*R*,*R*)-**L1** as the ligand, and the nosyl group of the addition products can be easily removed while retaining the enantiomeric purity.

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

(17) (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. (b) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353. (c) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Wiley: NJ, 2007; p 860.

(18) Potassium trifluoroborates of 4-methoxycarbonylphenyl, 3-thienyl, and 2-furyl are not suitable nucleophiles in the present catalysis.

(19) Attempts to prepare sodium tetraalkenylborates were unsuccessful (unpublished results).