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# Rhodium-Catalyzed Asymmetric Arylation of Azomethine Imines

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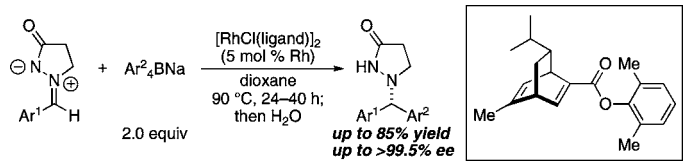
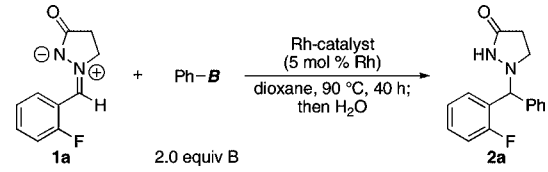
## ABSTRACT




**A rhodium-catalyzed addition of sodium tetraarylborates to azomethine imines has been described. Highly efficient asymmetric catalysis has also been achieved by employing a chiral diene ligand to give 1-(diarylmethyl)pyrazolidin-3-ones with high enantioselectivity.**

Azomethine imines are a class of 1,3-dipoles typically employed in the [3 + 2] cycloadditions with alkenes or alkynes to give five-membered nitrogen heterocycles,[1] and some effective asymmetric variants by using chiral catalysts have also been reported.[2] Among the known azomethine imines in the literature, 2-alkylidene-5-oxopyrazolidin-2-ium-1-ides (e.g., **1a** in Table 1) derived from pyrazolidin-3-ones and aldehydes have been most widely utilized primarily because of their stability and ease of handling,[3] and the cycloadducts thus obtained constitute a family of compounds with interesting biological activity.[4] Despite the high utility of these azomethine imines in cycloaddition reactions, their use as substrates for the catalytic asymmetric addition of organometallic reagents has been scarcely explored. In fact, although uncatalyzed addition of Grignard reagents to these dipoles was reported more than 30 years ago,[5] only one recent report by Shibata and co-workers addressed this issue to date, achieving asymmetric trifluoromethylation under phase transfer catalysis.[6,7] In this context,

**Table 1.** Rhodium-Catalyzed Addition of Phenylboron Reagents to Azomethine Imine **1a**: Effect of Catalyst and Nucleophile




| entry | Rh-catalyst | Ph-B | yield (%) |
|---|---|---|---|
| 1 | $[Rh(OH)(cod)]_2$ | $PhB(OH)_2$ | 0 |
| 2 | $[Rh(OH)(cod)]_2$ | $PhB(OR)_2$[a] | 0 |
| 3 | $[Rh(OH)(cod)]_2$ | $(PhBO)_3$ | 13[b] |
| 4 | $[RhCl(cod)]_2$ | $Ph_4BNa$ | 77 |
| 5 | $[RhCl(cod)]_2$ | $PhBF_3K$ | 0 |
| 6 | $[RhCl(binap)]_2$ | $Ph_4BNa$ | 0 |

[a] $(OR)_2 = OCH_2CMe_2CH_2O$. [b] Determined by $^1H$ NMR of the crude material.

(1) For a review, see: (a) Schantl, J. G. *Sci. Synth.* **2004**, *27*, 731. For recent examples, see: (b) Maiti, D. K.; Chatterjee, N.; Pandit, P.; Hota, S. K. *Chem. Commun.* **2010**, *46*, 2022. (c) Keller, M.; Sido, A. S. S.; Pale, P.; Sommer, J. *Chem.—Eur. J.* **2009**, *15*, 2810. (d) Pezdirc, L.; Cerkovnik, J.; Pirc, S.; Stanovnik, B.; Svete, J. *Tetrahedron* **2007**, *63*, 991.

(2) For a review, see: (a) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. For recent examples, see: (b) Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132*, 4076. (c) Sibi, M.; Rane, D.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2008**, *10*, 2971. (d) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 7667. (e) Suga, H.; Funyu, A.; Kakehi, A. *Org. Lett.* **2007**, *9*, 97. (f) Suárez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244.

(3) (a) Dorn, H.; Otto, A. *Chem. Ber.* **1968**, *101*, 3287. (b) Dorn, H.; Otto, A. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 214.

(4) (a) Claramunt, R. M.; Elguero, J. *Org. Prep. Proced. Int.* **1991**, *23*, 273. (b) Ternansky, R. J.; Holmes, R. A. *Drugs Future* **1990**, *15*, 149. (c) Jungheim, L. N.; Sigmund, S. K. *J. Org. Chem.* **1987**, *52*, 4007.

(5) Dorn, H.; Graubaum, H. *J. Prakt. Chem.* **1976**, *318*, 253.

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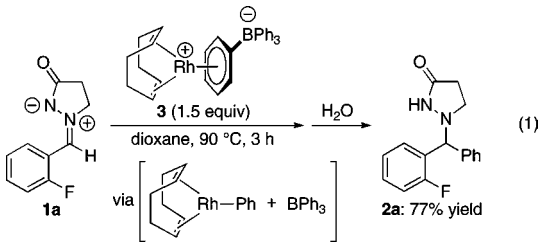
herein we describe the development of a rhodium-catalyzed asymmetric arylation of azomethine imines by the use of sodium tetraarylborates as the nucleophile in the presence of a readily available chiral diene ligand.

Initially, we conducted a reaction of azomethine imine **1a** with phenylboronic acid (2.0 equiv) in the presence of [Rh(OH)(cod)]$_2$ (5 mol % Rh) in anhydrous dioxane at 90 °C, but no addition product **2a** was observed under these conditions with partial decomposition of **1a** and full consumption of phenylboronic acid (Table 1, entry 1). The use of phenylboronic acid neopentylglycol ester instead of phenylboronic acid also resulted in no formation of **2a** (entry 2). Although the reaction did proceed by using phenylboroxine as the nucleophile, compound **2a** was obtained in only 13% yield (entry 3). In contrast, the desired phenylation smoothly took place by employing sodium tetraphenylborate[8] under the catalysis of [RhCl(cod)]$_2$, giving **2a** in 77% yield (entry 4).[9] In comparison, the use of potassium phenyltrifluoroborate[10] as the nucleophile (entry 5) or [RhCl(binap)]$_2$[11] as the catalyst (entry 6) did not promote this reaction under otherwise the same conditions as in entry 4.

As we previously proposed in the 1,4-addition to $\beta,\beta$-disubstituted $\alpha,\beta$-unsaturated ketones,[12] the uniquely high reactivity of sodium tetraphenylborate under the Rh/cod catalyst system may be attributed to the activation of substrate **1a** by Lewis acidic triphenylborane,[13] which is presumably generated upon transmetalation of a phenyl group from tetraphenylborate to rhodium. To support this hypothesis, we conducted the following two experiments. (1) A stoichiometric reaction of **1a** with Rh(cod)($\eta^6$-$C_6H_5$)BPh$_3$ (**3**), which is readily prepared from [RhCl(cod)]$_2$ and sodium tetraphenylborate,[14] smoothly proceeded to give **2a** in 77% yield after aqueous workup (eq 1). (2) In addition, a rapid and clean formation of stable 1:1 adduct of **1a** and triphenylborane was observed in THF-$d_8$ at room temperature by mixing these two components, and the structure of this adduct was confirmed by X-ray crystallographic analysis as depicted in Figure 1.




On the basis of the above consideration, a proposed catalytic cycle for the reaction of **1a** with sodium tetraphenylborate is illustrated in Scheme 1. Thus, complex **3**, initially formed by the reaction of [RhCl(cod)]$_2$ with sodium tetraphenylborate, undergoes transmetalation to give a phenylrhodium species **4** and triphenylborane. Subsequent activation of **1a** with Lewis acidic triphenylborane toward phenylation by **4** gives intermediate **5**. Ligand exchange of this intermediate with sodium tetraphenylborate then releases the phenylated product along with regeneration of complex **3** to complete the cycle.

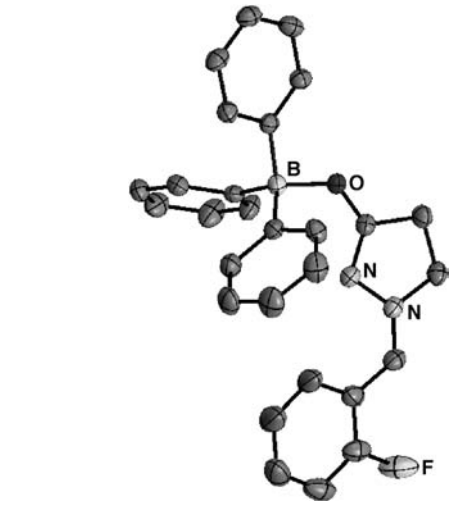
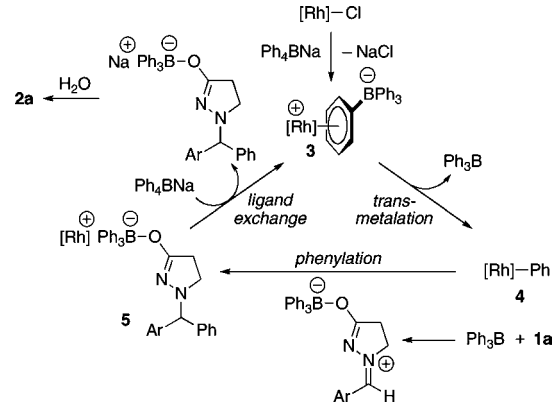



**Figure 1.** X-ray crystal structure of **1a**-BPh$_3$ adduct (hydrogen atoms are omitted for clarity).

**Scheme 1.** Proposed Catalytic Cycle for the Rhodium-Catalyzed Addition of Sodium Tetraphenylborate to **1a** ([Rh] = Rh(cod), Ar = 2-FC$_6$H$_4$)




(6) Kawai, H.; Kusuda, A.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6324.

(7) Skucas, E.; Ngai, M.-Y.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394.

(8) 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.; Isobe, S.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3795.

(9) Only a trace amount of **2a** was formed when the reaction was conducted in the presence of water or methanol (2.0 equiv).

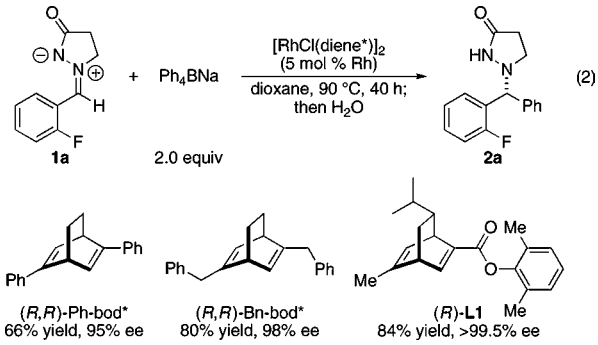
(10) (a) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683. (b) Pucheault, M.; Darses, S.; Genet, J.-P. *Tetrahedron Lett.* **2002**, *43*, 6155.

(11) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

(12) Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588.

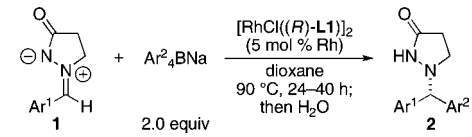
(13) (a) Tolman, C. A.; Seidel, W. C.; Druliner, J. D.; Domaille, P. J. *Organometallics* **1984**, *3*, 33. (b) Brunkan, N. M.; Brestensky, D. M.; Jones, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 3627. (c) Nakao, Y.; Yada, A.; Ebata, S.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 2428. (d) Yamashita, Y.; Gopalarathnam, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7508.

Because the present transformation is effectively catalyzed by a Rh/cod complex, we examined chiral diene ligands[15−17] to develop an asymmetric addition of sodium tetraphenylborate to azomethine imine **1a**. The use of (*R*,*R*)-Ph-bod*[18] as the ligand gave **2a** in 66% yield with 95% ee (eq 2), and higher yield and ee were achieved by changing the substituents on the olefins from phenyl to benzyl ((*R*,*R*)-Bn-bod*;[18b] 80% yield, 98% ee). Further improvements on both yield and enantioselectivity were realized by using ester-attached chiral diene (*R*)-**L1** (84% ee, >99.5% ee), which can be readily synthesized from commercially available (*R*)-α-phellandrene in a stereoselective manner.[19]




Under the conditions using [RhCl((*R*)-**L1**)]$_2$, several sterically and electronically different aryl groups are tolerated at the imine portion of substrates **1** to give the corresponding phenylation products **2** in high yield with excellent enantioselectivity (75−85% yield, ≥98% ee; Table 2, entries 1−6). With regard to the nucleophilic component, not only phenyl but also some other aryl groups can be effectively installed with similarly high enantioselectivity (50−84% yield, 96−98% ee; entries 7−10). Preparation of addition products having substituents on both of the aryl groups is also possible as shown in entry 11 (80% yield, >99.5% ee). The absolute configuration of **2c** obtained in entry 3 was determined to be *R* by X-ray crystallographic analysis after recrystallization from EtOAc/pentane (Figure 2).[20]

**Table 2.** Rhodium-Catalyzed Asymmetric Addition of Sodium Tetraarylborates to Azomethine Imines **1**: Scope




| entry | **1** ($Ar^1$) | $Ar^2$ | product | yield (%) | ee (%)[a] |
|---|---|---|---|---|---|
| 1 | **1a** (2-$FC_6H_4$) | Ph | (*R*)-**2a** | 84 | >99.5 |
| 2 | **1b** (2-$MeC_6H_4$) | Ph | (*R*)-**2b** | 75 | 99 |
| 3 | **1c** (3-$ClC_6H_4$) | Ph | (*R*)-**2c** | 82 | 98 |
| 4 | **1d** (3-$MeOC_6H_4$) | Ph | (*R*)-**2d** | 83 | >99.5 |
| 5 | **1e** (4-$MeO_2CC_6H_4$) | Ph | (*R*)-**2e** | 85 | 99 |
| 6 | **1f** (4-$MeC_6H_4$) | Ph | (*R*)-**2f** | 75 | 99 |
| 7[b] | **1g** (Ph) | 4-$MeC_6H_4$ | (*S*)-**2f** | 63 | 98 |
| 8[b] | **1g** | 4-(*i*-Pr)$C_6H_4$ | (*S*)-**2g** | 79 | 98 |
| 9[c] | **1g** | 4-$MeOC_6H_4$ | (*S*)-**2h** | 50 | 96 |
| 10[b] | **1g** | 3-$MeC_6H_4$ | (*S*)-**2i** | 84 | 98 |
| 11 | **1a** | 3-$MeC_6H_4$ | (*R*)-**2j** | 80 | >99.5 |

[a] Determined by chiral HPLC with hexane/2-propanol. [b] 8 mol % of catalyst was used. [c] 10 mol % of catalyst was used.

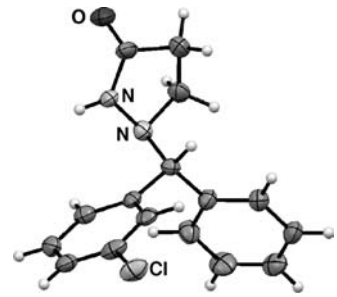



**Figure 2.** X-ray crystal structure of (*R*)-**2c** (Flack parameter = 0.00(6)).

In addition to unsubstituted pyrazolidinone-derived azomethine imines **1** described so far, 4,4-dimethyl substrate **6** also smoothly undergoes addition of sodium tetraphenylborate under the same conditions to give product **7** in 82% yield with 99% ee (eq 3). Furthermore, when a racemic mixture of 3-phenyl azomethine imine **8** (1.5 equiv) is employed, one enantiomer preferentially reacts over the other,[2f] giving phenylation product **9** in 53% yield (out of 75% ideal maximum yield) with good diastereoselectivity and excellent enantioselectivity (eq 4).[21]

(14) (a) Schrock, R. R.; Osborn, J. A. *Inorg. Chem.* **1970**, *9*, 2339. See also: (b) Oro, L. A.; Pinilla, E.; Tenajas, M. L. *J. Organomet. Chem.* **1978**, *148*, 81. (c) Aresta, M.; Quaranta, E.; Albinati, A. *Organometallics* **1993**, *12*, 2032.

(15) For reviews, 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.

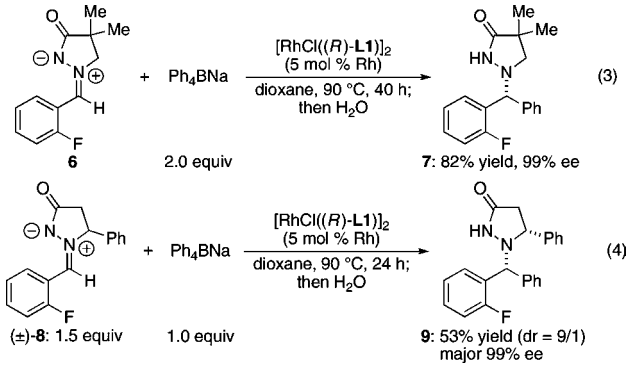
(16) For examples of asymmetric reactions using chiral diene ligands, see: (a) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628. (b) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850. (c) Läng, F.; Breher, F.; Stein, D.; Grützmacher, H. *Organometallics* **2005**, *24*, 2997. (d) Helbig, S.; Sauer, S.; Cramer, N.; Laschat, S.; Baro, A.; Frey, W. *Adv. Synth. Catal.* **2007**, *349*, 2331. (e) Noël, T.; Vandyck, K.; Van der Eycken, J. *Tetrahedron* **2007**, *63*, 12961. (f) Gendrineau, T.; Chuzel, O.; Eijsberg, H.; Genet, J.-P.; Darses, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7669. (g) Hu, X.; Zhuang, M.; Cao, Z.; Du, H. *Org. Lett.* **2009**, *11*, 4744. (h) Brown, M. K.; Corey, E. J. *Org. Lett.* **2010**, *12*, 172. (i) Luo, Y.; Carnell, A. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2750.

(17) (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (b) Otomaru, Y.; Kina, A.; Shintani, R.; Hayashi, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1673. (c) Kina, A.; Ueyama, K.; Hayashi, T. *Org. Lett.* **2005**, *7*, 5889. (d) Shintani, R.; Ichikawa, Y.; Takatsu, K.; Chen, F.-X.; Hayashi, T. *J. Org. Chem.* **2009**, *74*, 869. (e) Nishimura, T.; Kumamoto, H.; Nagaosa, M.; Hayashi, T. *Chem. Commun.* **2009**, 5713.

(18) (a) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584. (b) Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503.

(19) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Chem. Commun.* **2009**, 4815.

(20) See Supporting Information for details.




In summary, we have described the development of a rhodium-catalyzed arylation of azomethine imines by the use of sodium tetraarylborates as the nucleophile. Highly efficient asymmetric catalysis has also been realized to give chiral 1-(diarylmethyl)pyrazolidin-3-ones by employing chiral diene (*R*)-**L1** as the ligand.

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**Supporting Information Available:** Experimental procedures and compound characterization data and X-ray data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) For the determination of stereochemistry of compound **9**, see Supporting Information.