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# Dynamic Kinetic Asymmetric Allylation of Hydrazines and Hydroxylamines

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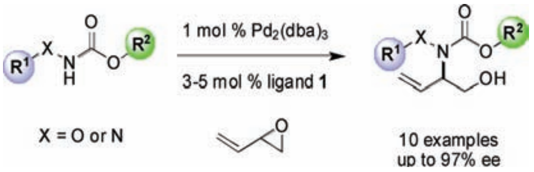
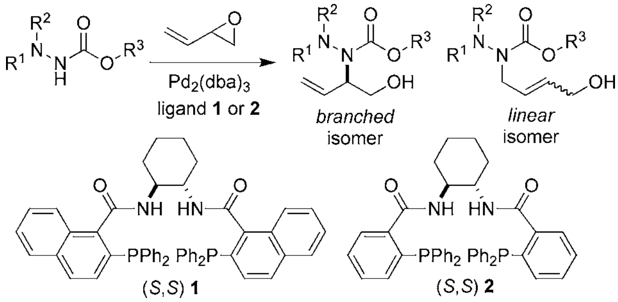
## ABSTRACT



**Hydrazines and hydroxylamines have been found to be excellent nucleophiles for the palladium-catalyzed dynamic asymmetric allylic amination of vinyl epoxide, with good yields and enantioselectivities of up to 97% ee. This method is applicable to acyclic and heterocyclic amines and was applied toward a five-step synthesis of (*R*)-piperazic acid.**

The central importance of new methods for the enantioselective synthesis of chiral amines has been demonstrated through numerous recent advances in asymmetric catalysis.[1] Despite the abundance of hydrazines and hydroxylamines in biologically active compounds, there are few general methods for their synthesis in a stereocontrolled fashion.[2] We became interested in dynamic kinetic asymmetric allylic allylation[3] as a broadly useful tool for the introduction of C−N stereogenicity. An intriguing recent report demonstrated the utility of imido carboxylates in the enantioselective amination of vinyl aziridines and epoxides.[4] We sought to demonstrate that hydrazines and hydroxylamines could display analogous reactivity, enabling access to new chiral synthons (Scheme 1).

**Scheme 1.** Asymmetric Allylation of Hydrazines



The Trost family of ligands (such as **1** and **2**) have a well-documented ability to impart enantiodiscrimination for a number of different reactions involving palladium $\pi$-allyl

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[1] For recent examples, see: (a) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D.; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918. (b) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (c) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054.

[2] (a) Fässler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3054. (b) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (c) Jin, X. L.; Sugihara, H.; Daikai, K.; Tateishi, H.; Jin, Y. Z.; Furuno, H.; Inanaga, J. *Tetrahedron* **2002**, *58*, 8321. (d) Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 16178. (e) Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120. (f) Imada, Y.; Nishida, M.; Kutsuwa, K.; Murahashi, S.-I.; Naota, T. *Org. Lett.* **2005**, *7*, 5837. (g) Miyabe, H.; Takemoto, Y. *Synlett* **2005**, 1641.

[3] (a) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1995**, *34*, 462. (b) Glorius, F.; Pfaltz, A. *Org. Lett.* **1999**, *1*, 141. (c) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968. (d) Malkov, A. V.; Spoor, P.; Vinader, V.; Kocovsky, P. *Tetrahedron Lett.* **2001**, *42*, 509. (e) Hughes, D. L.; Palucki, M.; Yasuda, N.; Reamer, R. A.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 2762. (f) Lueseem, B. J.; Gais, H.-J. *J. Org. Chem.* **2004**, *69*, 4041.

[4] Trost, B. M.; Fandrick, D. R.; Brodmann, T.; Stiles, D. T. *Angew. Chem., Int. Ed.* **2007**, *46*, 6123.

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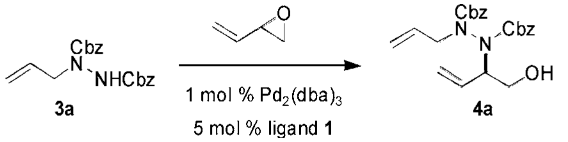
intermediates.[5] Our initial efforts focused on the application of these ligands to the dynamic asymmetric allylic amination of hydrazine **3a** with vinyl epoxide (Table 1). Using 1 mol % of $Pd_2(dba)_3$ and 5 mol % of **1** in degassed acetonitrile at 0 °C, we obtained the desired chiral alcohol in 89% ee (entry 1, Table 1) and full conversion with respect to the hydrazine. A notable observation was formation of the achiral (linear) product resulting from addition of the hydrazine in an $S_N2'$ sense to the vinyl terminus of the epoxide.[6] The ratio of the chiral, "branched" product to this "linear" byproduct was sensitive to the reaction conditions, so a range of solvent systems and additives were then surveyed for improved chemoselectivty and asymmetric induction.

Acid or base additives were not observed to have appreciable impact on the selectivity of the reaction and had a slightly deleterious effect on reaction rate (entries 2 and 3, Table 1, 88−89% ee). Further exploration revealed a marked halide effect on selectivity. Tetrabutylammonium and phosphonium halide additives were the most efficient, with tetrabutylammonium bromide (TBAB) being the best additive for the improvement of enantio- and chemoselectivity (entries 7−9, 90−94% ee). In particular, 1 equiv of TBAB provides the best balance of the conditions tried of conversion and

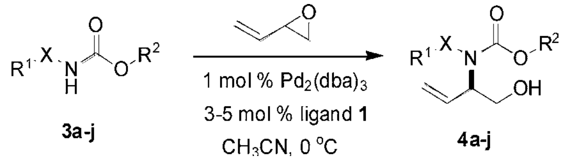
**Table 1.** Catalyst Optimization and Additive Survey for **4a**[a]

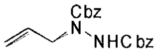
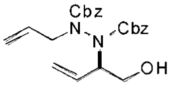
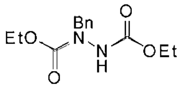
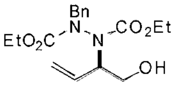
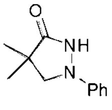
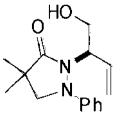
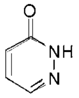
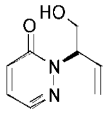
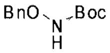
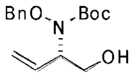
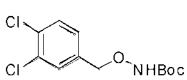
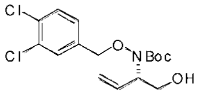
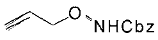
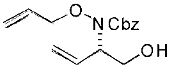
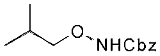
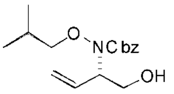
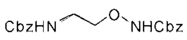
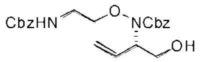
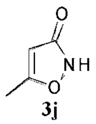
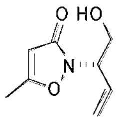


| entry | solvent | additive | conversion[b] | ee[c] | b:l[c,d] |
|---|---|---|---|---|---|
| 1 | $CH_3CN$ | none | 100 | 89 | 5:1 |
| 2 | $CH_3CN$ | $Et_3N$ (0.1 equiv) | 95 | 88 | 5:1 |
| 3 | $CH_3CN$ | AcOH (0.1 equiv) | 86 | 89 | 5:1 |
| 4 | $CH_3CN$ | LiBr (1 equiv) | 0 | – | – |
| 5 | $CH_3CN$ | $Bu_4NCl$ (1 equiv) | 100 | 95 | 7:1 |
| 6 | $CH_3CN$ | $Bu_4NI$ (1 equiv) | 100 | 91 | 6:1 |
| **7** | **$CH_3CN$** | **$Bu_4NBr$ (1 equiv)** | **100** | **94** | **11:1** |
| 8 | $CH_3CN$ | $Bu_4NBr$ (0.1 equiv) | 100 | 90 | 6:1 |
| 9 | $CH_3CN$ | $Bu_4NBr$ (2 equiv) | 79 | 94 | 11:1 |
| 10 | $CH_3CN$ | $Bu_4PBr$ (1 equiv) | 89 | 89 | 9:1 |
| 11[e] | $CH_3CN$ | $Bu_4NBr$ (1 equiv) | 86 | 81 | 1:1 |
| 12 | $CH_2Cl_2$ | $Bu_4NBr$ (1 equiv) | 100 | 88 | 10:1 |
| 13 | THF | $Bu_4NBr$ (1 equiv) | 70 | 92 | 7:1 |
| 14 | toluene | $Bu_4NBr$ (1 equiv) | 100 | 89 | 6:1 |

[a] All reactions run at 0 °C for 20 h with 1.1 equiv of vinyl epoxide, 1 mol % of $Pd_2(dba)_3$ and 5 mol % of (*S,S*)-**1** except where noted. [b] Conversion of hydrazine **3a**. [c] Determined by SFC. [d] Ratio of branched regioisomer to linear regioisomer. [e] Run with ligand **2** in place of **1**.

**Table 2.** Asymmetric Aminations of Vinyl Epoxide[a]



| entry | reactant | product | yield[b] | ee[c] |
|---|---|---|---|---|
| 1 |  **3a** |  **4a** | 79 | 94 |
| 2 |  **3b** |  **4b** | 88[d] | 83 |
| 3 |  **3c** |  **4c** | 87 | 83 |
| 4 |  **3d** |  **4d** | 91 | 87 |
| 5 |  **3e** |  **4e** | 85 | 84[e] |
| 6 |  **3f** |  **4f** | 83 | 88[e] |
| 7 |  **3g** |  **4g** | 79 | 80[e] |
| 8 |  **3h** |  **4h** | 86 | 85[e] |
| 9 |  **3i** |  **4i** | 72 | 87[e] |
| 10 |  **3j** |  **4j** | 77 | 97[e] |

[a] All reactions run at 0 °C in $CH_3CN$ with 1.1 equiv of vinyl epoxide, 1.0 equiv of $Bu_4NBr$, 1 mol % of $Pd_2(dba)_3$ and 5 mol % of (*S,S*)-**1** except where noted. [b] Isolated yield. [c] Determined by HPLC or SFC, see Supporting Information. [d] Isolated as a 76:24 mixture of branched and linear regioisomers. [e] Reaction run with 3 mol % of (*R,R*)-**1**.

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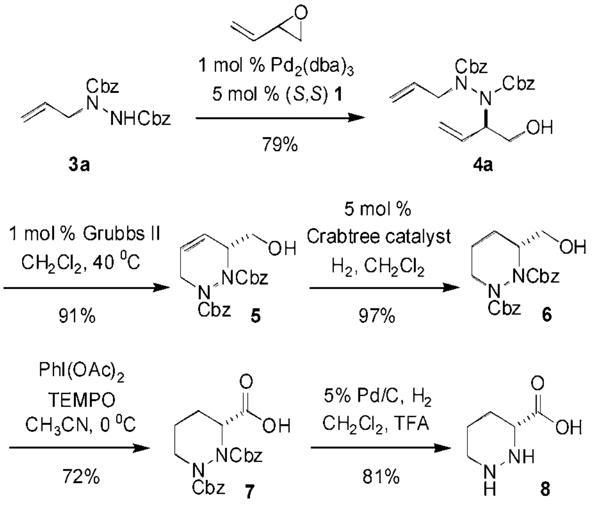
(5) (a) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355. (b) Trost, B. M. *Chem. Rev.* **1996**, *96*, 395. (c) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747.

(6) This regioselectivity has been observed previously, see: (a) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. (b) Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761. (c) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471. (d) Bartels, B. G.; Yebra, C.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, 1097.

selectivity (entry 7, 94% ee, 11:1 *b*:*l*). Using fewer equivalents of TBAB lowered the selectivity (entry 8, 90% ee), while using more than 1 equiv led to poorer conversion (entry 9). Chloride and iodide additive sources also helped selectivity, though to a slightly lesser degree (entries 5 and 6). The influence of added halide on enantiocontrol has been observed previously in palladium-mediated asymmetric allylations[3a,7] with the hypothesis that the halide increases the rate of interconversion of diastereomeric palladium $\pi$-allyl intermediates.[8] Ligand **2** exhibited diminished enantioselectivity under these conditions and 1:1 chemoselectivity (entry 11, 81% ee). The best asymmetric induction was achieved at 0 °C with $CH_3CN$ as the preferred solvent (entry 7) though other solvents such as $CH_2Cl_2$, THF, and toluene provided comparable results (entries 12−14, 88−92% ee).[9]

With highly enantioselective conditions in hand for asymmetric allylation of hydrazine **3a**, we sought to expand the scope of this reaction and to examine the use of other hydrazines as well as hydroxylamines. Both cyclic and acyclic hydrazines reacted with high yield and selectivity (entries 1−4, Table 2, 83−94% ee), including 3-pyridazinone (entry 4, 91% yield, 87% ee). To our delight, a range of aminoxy nucleophiles also performed successfully, with enantioselectivity as high as 97% ee (entries 5−10, 80−97% ee). Benzyl, allyl, and alkyl aminoxy ethers were all well tolerated (entries 5−8, 80−88% ee). In a substrate containing both aminoxy and amino carbamates, complete selectivity was observed for reactivity with the aminoxy component, consistent with relative nucleophilicity predicted from the α-effect (entry 9, 87% ee).[10] High enantioselectivity could also be seen in the case of a cyclic hydroxylamine (entry 10, 97% ee).

**Scheme 2.** Total Synthesis of (*R*)-Piperazic Acid[a]



[a] Conditions: (a) Vinyl epoxide, 1 mol % of $Pd_2(dba)_3$, 5 mol % of (*S*,*S*)-**1**, $Bu_4NBr$, $CH_3CN$, 0 °C, 79%; (b) 1 mol % of $(H_2IMes)RuCl_2(PCy_3){=}CHPh$, $CH_2Cl_2$, 40 °C, 91%; (c) 5 mol % of Crabtree's catalyst, $H_2$, $CH_2Cl_2$, 97%; (d) $PhI(OAc)_2$, TEMPO, $CH_3CN$, 0 °C, 72%; (e) 5% Pd/C, $H_2$, $CH_2Cl_2$, TFA, 81%.

For a representative application of these asymmetric vinyl epoxide resolutions, we sought to apply the chiral hydrazine **4a** toward a synthesis of piperazic acid,[11] an amino acid component of naturally occurring antibiotics (Scheme 2).[12] Our synthesis began with the dynamic kinetic resolution of vinyl epoxide with hydrazine **3a** to furnish **4a** in 94% ee. Ring-closing metathesis of **4a** then provided the tetrahydropyridazine **5**. The olefin was selectively reduced via hydrogenation using Crabtree's catalyst, after which alcohol **6** was oxidized to the corresponding acid (**7**). Hydrogenolysis of the benzyl carbamates completed the synthesis of (*R*)-piperazic acid in five steps from hydrazine **3a** in 41% overall yield.

The palladium-catalyzed enantioselective amination of vinyl epoxide by hydrazines and hydroxylamines has been demonstrated. The Trost bisphosphine ligand **1** imparts high enantiocontrol and regiochemical control, and halide additives have been found that enhance the selectivity. This method was used in a short synthesis of piperazic acid and should find further utility in the asymmetric synthesis of natural and pharmaceutical products. Efforts are currently underway to explore mechanistic considerations of the effect of halide additives.

**Acknowledgment.** The authors would like to thank Prof. Barry M. Trost (Stanford University) for helpful discussions.

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

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(7) (a) Trost, B. M.; McEachern, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 12702. (b) Trost, B. M.; Calkins, T. L.; Oertelt, C.; Zambrano, J. *Tetrahedron Lett.* **1998**, *39*, 1713.

(8) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(9) Over extended reaction time or at elevated temperatures in the presence of the Pd catalyst, **4a** has been observed to isomerize to its linear regioisomer; it is recommended to purify these reactions upon completion. See also: Weihofen, R.; Tverskoy, O.; Helmchen, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 5546.

(10) (a) Grekov, A. P.; Veselov, V., Ya *Russ. Chem. Rev.* **1978**, *47*, 631. (b) Fina, N. J.; Edwards, J. O. *Int. J. Chem. Kinet.* **1973**, *5*, 1.

(11) For isolation of piperazic acid, see: Bevan, K.; Davies, J. S.; Hassall, C. H.; Morton, R. B.; Phillips, D. A. S. *J. Chem. Soc. (C)* **1971**, 514.

(12) (a) Hale, K. J.; Cai, J.; Delisser, V.; Manariazar, S. *Tetrahedron Lett.* **1992**, *33*, 7613. (b) Aoyagi, Y.; Saitoh, Y.; Ueno, T.; Horiguchi, M.; Takeya, K. *J. Org. Chem.* **2003**, *68*, 6899. (c) Henmi, Y.; Makino, K.; Yoshitomi, Y.; Osamu, H.; Hamada, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 3477.