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Asymmetric Synthesis of Diamine Derivatives via Sequential Palladium and Rhodium Catalysis

Barry M. Trost,* Sushant Malhotra, David E. Olson, Autumn Maruniak, and J. Du Bois*

Department of Chemistry, Stanford University, Stanford, California 94305-5080

Received December 11, 2008; E-mail: bmtrost@stanford.edu; jdubois@stanford.edu

Vicinal and 1,3-diamines are important structural motifs in natural products and pharmaceuticals, with useful applications in asymmetric catalysis and supramolecular chemistry.[1] Recently, one of our laboratories disclosed a method that takes advantage of Rh-catalyzed C−H insertion to synthesize differentially substituted 1,2-diamines from hydroxylamine-derived sulfamate esters.[2] With an interest in facilitating access to optically active, polyfunctionalized diamines, we envisioned a sequential process featuring asymmetric synthesis of *N*-allyl hydroxylamine-*O*-sulfamates and catalytic intramolecular aziridination (Figure 1). Palladium-catalyzed allylic

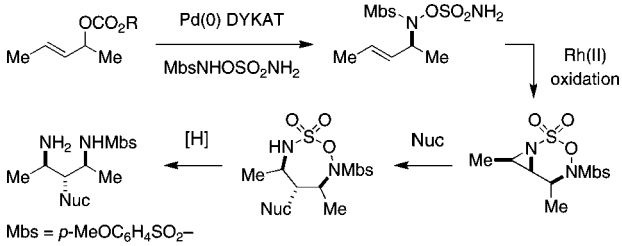


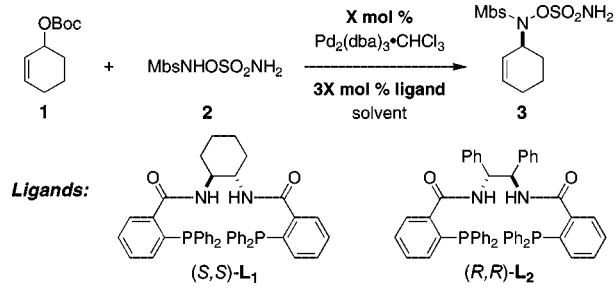
Figure 1. Asymmetric synthesis of polyfunctionalized diamines through sequential Pd- and Rh-catalyzed transformations.

amination was viewed as a particularly attractive means of preparing allylic hydroxylamine-derived sulfamate esters in enantioenriched form.[3] Diastereoselective oxidative cyclization of these materials under rhodium catalysis would then afford aziridine products. Accordingly, the successive application of these selective transition-metal-catalyzed processes makes available complex polyamine architectures from readily available, racemic starting materials. The power of these combined tactics to streamline chemical synthesis is highlighted below.

Initial studies of the Pd-catalyzed amination using chiral ligand $\mathbf{L_1}$, $Pd_2(dba)_3{\cdot}CHCl_3$, cyclohexenol-derived carbonate **1**, and sulfamate nucleophile **2** (Mbs = p-$MeOC_6H_4SO_2$−) afforded product **3** in good yield and in high enantiomeric excess (Table 1, entry 1). The catalyst loading, the addition of either acid or base, and the solvent had minimal influence on the enantioselectivity (Table 1, entries 2−6), although the use of 5 mol % catalyst resulted in a significantly higher product yield (Table 1, entry 4). Changing to ligand $\mathbf{L_2}$ improved the asymmetric induction to >90% ee (Table 1, entries 8−10).

Evaluation of the reaction scope revealed that several types of allylic derivatives participate in Pd π-allyl reactions with $MbsNHOSO_2NH_2$ as the nitrogen nucleophile (Table 2). In all cases, sulfamate products were formed with high levels of enantioinduction exclusively at the more hindered nitrogen.[4] Dynamic kinetic asymmetric transformations (DYKATs) were accomplished with both the 5- and 6-membered ring allylic carbonates (Table 2, entries 1−3). Entry 3 highlights the reaction of C_2-symmetric racemic conduritol B tetracarbonate, which afforded the monosubstituted

Table 1. Optimization of Pd-Catalyzed Allylic Amination



Entry[a]	X mol %	Solvent	Ligand	% Yield	% ee[b]
1	1.0	THF	$\mathbf{L_1}$	76	86
2[c]	1.0	THF	$\mathbf{L_1}$	63	88
3[d]	1.0	THF	$\mathbf{L_1}$	60	87
4	**5.0**	**THF**	$\mathbf{L_1}$	**94**	**84**
5	1.0	dioxane	$\mathbf{L_1}$	71	82
6	1.0	CH_2Cl_2	$\mathbf{L_1}$	18	87
7	2.5	DME	$\mathbf{L_1}$	54	88
8[e]	**2.5**	**THF**	$\mathbf{L_2}$	**56**	**−92**
9[e]	2.5	DME	$\mathbf{L_2}$	40	−93
10[e,f]	2.5	DME	$\mathbf{L_2}$	66	−91

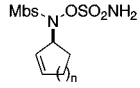
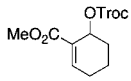
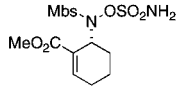
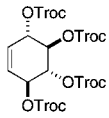
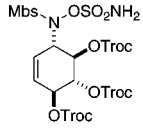
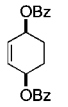
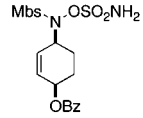
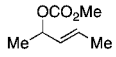
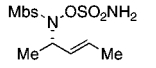
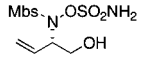
[a] Reactions were conducted on a 0.25 mmol scale using 1.1 equiv of carbonate **1** and 1.0 equiv of nucleophile **2** at 0.1 M. [b] Determined by chiral HPLC. [c] Reaction performed using 20 mol % $PhCO_2H$. [d] Reaction performed using 20 mol % Cs_2CO_3. [e] Reaction performed at 0.23 M. [f] Reaction performed at 50 °C.

product exclusively in 96% ee.[5] A related reaction involving the asymmetric desymmetrization of a meso dibenzoate also furnished the monosubstituted product (Table 1, entry 4). Finally, acyclic substrates, including both the allyl carbonate and butadiene monoepoxide, were found to couple efficiently with **2** (Table 1, entries 5 and 6). When the latter starting material was used, the DYKAT proceeded with outstanding regiocontrol and furnished a protected 1,2-amino alcohol. Oxidation of related 1,2-amino alcohols has enabled the synthesis of enantiomerically pure α-amino acids.[6] Collectively, these data establish **2** as a unique and particularly effective nitrogen nucleophile for Pd-catalyzed allylic amination. By way of analogy to reactions with (*S*,*S*)-$\mathbf{L_1}$ and other amine surrogates, the stereochemical configurations of the products shown in Table 2 have been assigned.[7]

The products of Pd-catalyzed asymmetric allylic amination can be readily transformed into differentially substituted amino aziridines upon treatment with a dinuclear Rh(II) tetracarboxylate catalyst, a hypervalent iodine oxidant, and MgO.[8] Subsequent S_N2 ring opening of the resultant aziridines occurred with modest levels of regioselectively to yield the seven-membered-ring heterocycles (Figure 2).[9,10] Both cyclic and acyclic olefins underwent oxidative cyclization using 2 mol % $Rh_2(esp)_2$.[11] In general, substrate-controlled diastereoselectivity was quite high. The unusual aziridine products were readily isolated by chromatography and reacted

10.1021/ja809697p CCC: $40.75

Table 2. Pd-Catalyzed Asymmetric Allylic Amination

Entry[a]	Electrophile	Product		% Yield	% ee
1			n = 1 n = 2	95 56	90 −92[b]
2				95	84
3				98	96
4				97	95
5				98	95[c]
6				66	94

[a] Reactions were performed in THF using 2.5 mol % $Pd_2(dba)_3 \cdot CHCl_3$ and 7.5 mol % (*S*,*S*)-$\mathbf{L_1}$ at 0.2 M; yields are based on limiting amounts of nucleophile **2**. [b] Reaction conducted using (*R*,*R*)-$\mathbf{L_2}$. [c] Reaction conducted in dioxane.

smoothly at ambient temperatures in the presence of nucleophiles such as N_3^-. Remarkably, ring opening to give the seven-membered heterocycle occurred even when the carbon undergoing attack was tetrasubstituted. Use of azide in the two examples shown in Figure 2 makes possible the synthesis of differentially masked, stereodefined 1,2,3-triamines.

Cleavage of the N−O bond in either cyclic or acylic sulfonamide products was easily effected with Zn(Cu) (Figure 3).[2] In the first example, reduction of the heterocycle and the azido group in **4** unveiled the singly protected triamino ester **5**. The availability of this material in optically active form in just four steps starting from the racemic allylic carbonate underscores the effectiveness of these combined methods. Similarly, reduction of **6** resulted in a concise enantioselective synthesis of the protected conduramine B **7** in three steps from (±)-conduritol.[12]

Sequential application of two efficient and selective transformations, Pd-catalyzed allylic amination and Rh-catalyzed alkene aziridination, makes possible the rapid assembly of complex

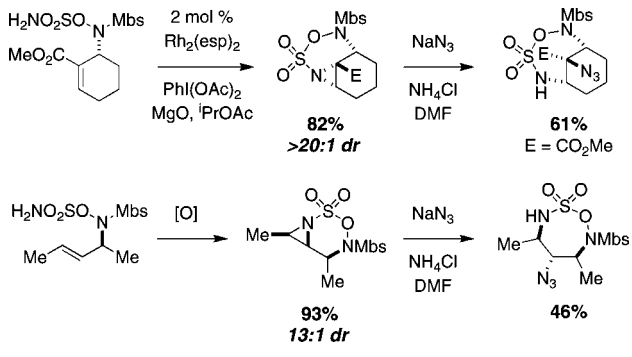


Figure 2. Aziridine formation and subsequent ring opening.

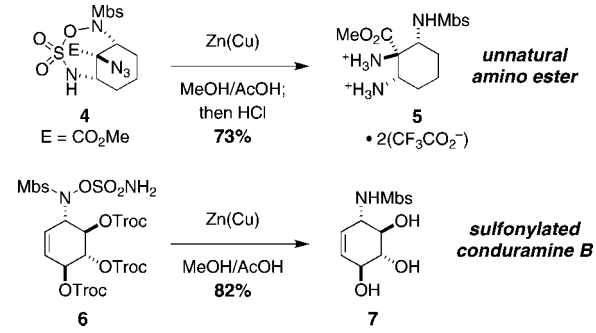


Figure 3. Reductive N−O cleavage affords novel amine derivatives. Product **5** was purified by HPLC using $H_2O/CH_3CN/CF_3CO_2H$.

polyamine structures. Conjoining these two methods reveals opportunities to identify alternative nitrogen-based nucleophiles that engage in both processes, further augmenting substrate scope and selectivity. The advancement of such technologies should diminish the effort generally needed to access structurally intricate, optically active nitrogen derivatives.

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Supporting Information Available: Experimental details and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) We assume that the allylic leaving group serves as a base to ionize the more acidic−NH proton on **2**, thus accounting for the observed regioselectivity.
(5) For DYKATs with (±)-conduritol B using oxygen and nitrogen nucleophiles, see: Trost, B. M.; Patterson, D. E.; Hembre, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 10834.
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(7) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747. Since the reaction of other nucleophiles with the substrate of Table 2, entry 2, using the *S*,*S* ligand affords the product with the *R* configuration, the product stereochemistry as depicted was assigned.
(8) Several examples of Rh-catalyzed aziridination of hydroxylamine-derived sulfamate esters are highlighted in ref 2. See the Supporting Information for an additional example of a diastereoselective aziridination using a substrate derived from Table 2, entry 6.
(9) We have observed that ring opening to give the six-membered-ring heterocycle is competitive in several cases. The six-membered-ring intermediate appears to decompose through a fragmentation reaction, the details of which are currently under investigation.
(10) Regioselective ring opening has been observed for oxathiazinane-derived aziridines. See: (a) Guthikonda, K.; Wehn, P. M.; Caliando, B. J.; Du Bois, J. *Tetrahedron* **2006**, *62*, 11331. (b) Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *J. Org. Chem.* **1999**, *64*, 5304.
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