Published in final edited form as:

J Am Chem Soc. 2009 April 1; 131(12): 4190–4191. doi:10.1021/ja809697p.

Asymmetric Synthesis of Diamine Derivatives via Sequential Palladium and Rhodium Catalysis

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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 labs has 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 amination was viewed as a particularly attractive means for preparing allylic hydroxylamine-derived sulfamate esters in enantioenriched form.³ Diastereoselective oxidative cyclization of these materials under Rh 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 for streamlining chemical synthesis is highlighted below.

Initial studies on the Pd-catalyzed amination using chiral ligand **L**₁, Pd₂dba₃•CHCl₃, cyclohexenol-derived carbonate **1**, and sulfamate nucleophile **2** (Mbs = *p*-MeOC₆H₄SO₂–) afforded the 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 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 **L**₂ improved 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 MbsNHOSO₂NH₂ 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 (DYKAT) were accomplished with both the 5- and 6-membered ring allylic carbonates (Table 2, entries 1–3). Entry 3 highlights the reaction of C₂-symmetric conduritol B tetracarboxylate, which afforded the mono-substituted product exclusively in 96% ee.⁵ A related reaction involving the asymmetric desymmetrization of a meso-dibenzoate also furnished the mono-substituted product (Table 1, entry 4). Finally, acyclic substrates, which include both the allyl carbonate and butadiene mono-epoxide, were found to couple efficiently with **2** (Table 1, entries 5 and 6). Using the latter starting material, 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

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

allylic alkylation. By way of analogy to reactions with (*S,S*)-**L**₁ and other amine surrogates, the stereochemical configuration of the products shown in Table 2 has 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 regioselectivity to yield the 7-membered ring heterocycles (Figure 2).^{9,10} Both cyclic and acyclic olefins underwent oxidative cyclization using 2 mol % Rh₂(esp)₂.¹¹ In general, substrate-controlled diastereoselectivity was quite high. The unusual aziridine products were readily isolated by chromatography, and reacted smoothly and at ambient temperatures in the presence of nucleophiles such as N₃[−]. Remarkably, ring opening to give the 7-membered heterocycle occurred even when the carbon undergoing attack was tetrasubstituted. Use of azide in the two examples shown in Figure 2 made possible the synthesis of differentially masked, stereodefined 1,2,3-triamines.

Cleavage of the N–O bond in either cyclic or acyclic 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** (3 steps from (±)-conduritol).¹²

The sequential application of two efficient and selective transformations, Pd-catalyzed allylic amination and Rh-catalyzed alkene aziridination, makes possible the rapid assembly of complex polyamine structures. Conjoining these two methods reveals opportunities to identify alternative nitrogen-based nucleophiles that will 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work has been supported by the National Institutes of Health and the National Science Foundation. S.M. gratefully acknowledges Stanford University for a graduate fellowship. D.E.O acknowledges Eli Lilly for a graduate fellowship. Palladium salts were generously supplied by Johnson-Matthey.

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- (8). Several examples of Rh-catalyzed aziridination of hydroxylamine-derived sulfamate esters are highlighted in reference 2. See supporting information for an additional example of a diastereoselective aziridination using a substrate derived from entry 6, Table 2.
- (9). We have observed that ring opening to give the 6-membered ring heterocycle is competitive in several cases. The 6-membered ring intermediate appears to decompose through a fragmentation reaction, the details of which are currently under investigation.
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Figure 1.

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

Figure 2.
Aziridine formation and subsequent ring opening.

Figure 3.

Reductive N–O cleavage affords novel amine derivatives. Product **5** purified by HPLC using H₂O/CH₃CN/CF₃CO₂H.

Table 1

Optimization of Pd-catalyzed allylic amination.

Entry ^a	X mol %	Solvent	Ligand	% Yield	% ee ^b
1	1.0 %	THF	L ₁	76	86
2 ^c	1.0 %	THF	L ₁	63	88
3 ^d	1.0 %	THF	L ₁	60	87
4	5.0 %	THF	L ₁	94	84
5	1.0 %	Dioxane	L ₁	71	82
6	1.0 %	CH ₂ Cl ₂	L ₁	18	87
7	2.5 %	DME	L ₁	54	88
8 ^e	2.5 %	THF	L ₂	56	-92
9 ^e	2.5 %	DME	L ₂	40	-93
10 ^{e,f}	2.5 %	DME	L ₂	66	-91

^aReactions conducted on a 0.25 mmol scale using 1.1 equiv carbonate and 1.0 equiv nucleophile at 0.1 M.

^bDetermined by chiral HPLC.

^cReaction performed using 20 mol % PhCO₂H.

^dReaction performed using 20 mol % Cs₂CO₃.

^eReaction performed at 0.23 M.

^fReaction performed at 50 °C.

Table 2

Pd-catalyzed asymmetric allylic amination.

Entry ^a	Electrophile	Product	% Yield	% ee
1			95	90
2			56	-92 ^b
3			98	96
4			97	95
5			98	95 ^c
6			66	94

^aReactions were performed in THF using 2.5 mol % Pd₂(dba)₃•CHCl₃, 7.5 mol % (*S,S*)-**L1**, at 0.2 M; yields based on limiting amounts of nucleophile **2**.

^bReaction conducted using (*R,R*)-**L2**.

^cReaction conducted in dioxane.