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Catalytic Intermolecular Linear Allylic C−H Amination via Heterobimetallic Catalysis

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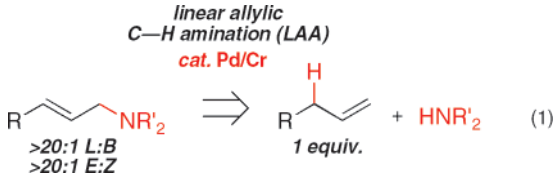
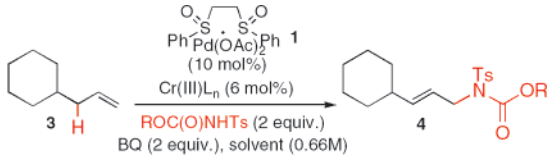
Nitrogen functionality is prevalent in synthetic and natural small molecules with significant biological activities.[1] Current state-of-the-art methods for installing nitrogen into complex organic frameworks generally proceed through oxygen.[2] While these methods feature high selectivities and predictable reactivities, they lengthen synthetic sequences by requiring unproductive chemical manipulations to install and maintain oxygen functionality. Reactions that selectively convert C−H directly to C−N stand to significantly streamline synthetic sequences by providing obvious disconnections that avoid handling oxidized materials.[3] While significant advances have been made in developing preparatively useful intramolecular C−H aminations,[4a,5] catalytic intermolecular C−H aminations are scarce and often require excess substrate.[6,7] We report herein the first general, catalytic, intermolecular allylic C−H amination reaction. This reaction directly converts a wide range of α-olefins to linear (*E*)-allylic amines with good yields and outstanding regio- and stereoselectivities (>20:1) using limiting amounts of the starting olefin. Critical for achieving this catalytic reactivity is a heterobimetallic system composed of Pd/bis-sulfoxide and Cr(salen) catalysts.



In addition to reactivity and regioselectivity challenges, intermolecular *allylic* C−H aminations face an additional chemoselectivity issue of competing reactivity with the olefin.[6d] In palladium-mediated processes, addition of nitrogen nucleophiles to the olefin (aminopalladation) is the dominant reaction pathway.[8] We recently reported that bis-sulfoxide/$Pd(OAc)_2$ catalyst **1** promotes intramolecular allylic C−H amination of α-olefins with a weak, tethered *N*-tosyl carbamate nucleophile.[4a] We hypothesized that a catalytic, intermolecular allylic C−H amination would be feasible if we could identify conditions that promote functionalization without interfering with the electrophilic C−H cleavage step. Known activation approaches for Pd(0)-mediated allylic substitutions, such as adding stoichiometric base to activate the nucleophile or strongly σ-donating ligands to activate the π-allylPd electrophile, may attenuate the electrophilicity of the Pd(II) species required for C−H cleavage.[2b,9,4b] Herein we disclose that a heterobimetallic Pd(II)−Cr(III) catalytic system promotes intermolecular linear allylic C−H amination (LAA). We provide evidence that the Pd(II)/bis-sulfoxide catalyst promotes allylic C−H cleavage and that the Cr(III)(salen) catalyst together with benzoquinone (BQ) promotes amination of the π-allylPd intermediate. This represents a rare example of heterobimetallic catalysis in which two different transition metals present in catalytic amounts are required to effect product formation.[10]

Table 1. Development of the Intermolecular LAA Reaction



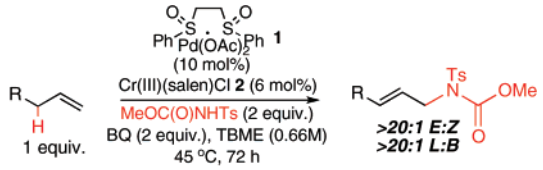
entry	$Pd(II)L_n$	R	$Cr(III)L_n$	isolated yield[a]	L:B[b]	E:Z[b]
1[c]	**1**	Me	----	----	----	----
2[c]	----	Me	(salen)Cr(III)Cl **2**	----	----	----
3[c]	**1**	Me	**2**	43%	>100:1	65:1
4[c]	$Pd(OAc)_2$	Me	**2**	17%	----	----
5[c]	**1**	Me	$CrCl_3 \cdot 3THF$	----	----	----
6[c]	**1**	Me	(TPP)Cr(III)Cl	25%	>100:1	71:1
7[d]	**1**	Me	(salen)Cr(III)Cl **2**[e]	53%	>100:1	57:1
8[d]	**1**	Me	(salen)Al(III)Cl	21%	>100:1	76:1
9[d]	**1**	Me	(salen)Co(III)OAc	17%	>100:1	91:1
10[d]	**1**	Me	(salen)Mn(III)Cl	44%	>100:1	78:1
11[d]	**1**	Bn	**2**	65%	>20:1[f]	>20:1[f]
12[d]	**1**	*t*-Bu	**2**	40%	>20:1[f]	>20:1[f]
13[d]	**1**	Fm	**2**	40%	>20:1[f]	>20:1[f]

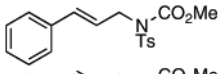
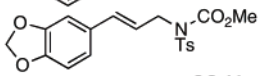
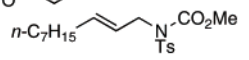
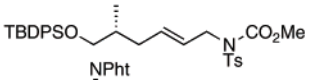
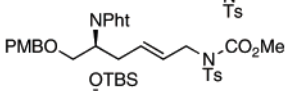
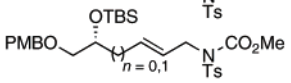
[a]Average of 2 runs at 0.3 mmol. [b] Determined by GC analysis of the crude reaction mixture (unless otherwise stated). [c] THF (0.66M). [d] TBME (0.66M). [e]Other metal complexes gave 2% or less GC yield: Ni(II)(TPP), Fe(III)(TPP)Cl, Ru(II)(TPP), Cu(II)(TPP), Co(II)(*p*-MeO-TPP) Fe(III)PthCl, Mn(III)PthCl, Si(IV)$PthCl_2$ (TPP = tetraphenylporphyrin, Pth = phthalocyanine). [f]Determined by ^1H NMR analysis of the crude reaction mixture.

Our study began by examining the reaction of allyl cyclohexane with *N*-(methoxycarbonyl)-*p*-toluenesulfonamide under our previously reported intramolecular amination conditions (Table 1, entry 1). Although we observed no reactivity, we were encouraged by stoichiometric studies that showed **1** maintained its ability to promote C−H cleavage to form a π-allylPd intermediate in the presence of an excess (2 equiv) of free nitrogen nucleophile (*vide infra*). Independent studies performed in our labs indicated that Cr(III)(salen) complexes increase the rate of π-allylPd functionalization with acetate, suggesting that this catalyst may promote π-allyl functionalization.[11] We found that the addition of 6 mol % commercial (salen)Cr(III)Cl complex **2**[12,13] with 10 mol % commercial bis-sulfoxide/$Pd(OAc)_2$ **1** gave linear (*E*)-allylic amine **4** in encouraging yield (43% based on olefin **3**) and with remarkable regio- and stereoselectivities (>100:1 L/B, 65:1 *E*/*Z*, entry 3). It is significant to note that this is the first time that linear regioselectivity has been observed in an allylic C−H oxidation process with bis-sulfoxide/$Pd(OAc)_2$ catalyst **1**.[14] Chromium catalyst **2** gave no reactivity in the absence of Pd catalyst **1**, clearly showing that a dual metal-catalyst system is required for reactivity (entry 2). We next examined the role of ligands in this reaction. In the absence of bis-sulfoxide ligand, $Pd(OAc)_2$ furnished only 17% of the aminated product (entry 4). Free chromium (III) salts shut down reactivity (entry 5), whereas chromium (III) in a porphyrin

10.1021/ja710206u CCC: $40.75

Table 2. Scope of the Intermolecular LAA Reaction



entry	allylic amine product	isolated yield[a]
1		**5** 58%
2		**6** 72%
3		**7** 59%[b]
4		(+)-**8** 57%
5		(+)-**9** 65%
6		*n* = 0 (+)-**10** 52%
7		*n* = 1 (+)-**11** 65%

[a] Average of two runs at 0.3 mmol. Products were isolated as one regio- and olefin isomer (^{1}H NMR). [b] Mixture of 7:1 L/B and 17:1 *E*/*Z* (^{1}H NMR).

framework also gave allylic aminated product, albeit in diminished yields (entry 6). Under optimized reaction parameters (TBME, entry 7), a variety of salen porphyrin, and phthalocyanine metal complexes were evaluated (entries 7−10). Notably, (salen)Mn(III)Cl was the only other complex found to catalyze the reaction with significant product yields (entry 10). Examination of other O-protected *N*-tosylcarbamate nucleophiles indicated that benzyl- was comparable under these conditions (entry 11) whereas *tert*-butyl- and 9-fluorenylmethyl-*N*-tosylcarbamates presently give diminished yields (entries 12 and 13, respectively).

The utility of the linear allylic C−H amination reaction as a means of selectively incorporating nitrogen during complex molecule synthesis was probed by investigating its scope with respect to the α-olefin substrate (Table 2 and Figure 1). A wide range of polar groups that can serve as functional handles for further elaboration (e.g., silyl and benzyl ethers, Weinreb amides, benzyloxycarbonyl (Cbz)- and phthalimide(Pht)-protected amines) may be present on the substrate. Aromatic substrates undergo allylic C−H amination with good yields and outstanding selectivities. For example, safrole derived allylic amine **6**, a direct precursor for a

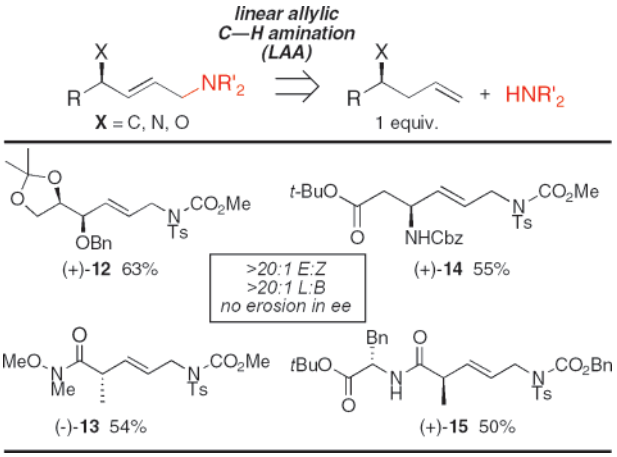
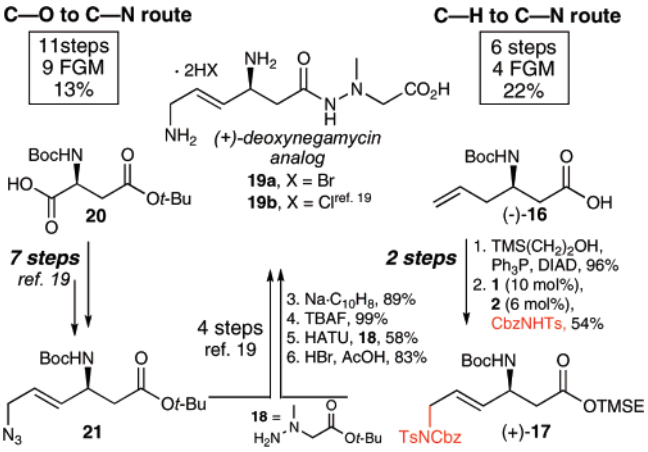


Figure 1. Streamlined synthesis of chiral 1,4-difunctionalized allylic amines.

Scheme 1

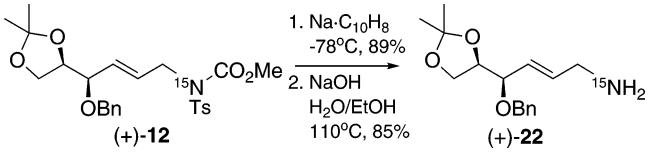


known SSAO inhibitor, was generated in 72% yield as a single isomer (Table 2, entry 2).[15] Although unsubstituted hydrocarbon substrates, such as 1-decene, show a decrease in regioselectivity (L/B, 7:1; entry 3), incorporation of a branching carbon, oxygen, or nitrogen moiety in the remote bis-homoallylic position restores high levels of selectivity (L/B > 20:1, entries 4−6).

Asymmetric allylations of aldehydes,[16a,b] imines,[16c] and enolates[16d,e] provide rapid access to stereodefined homoallylic oxygen, nitrogen, and carbon substituted α-olefins. These substrates undergo linear allylic C−H amination in good yields, excellent selectivities, and no erosion in enantiomeric purity (Figure 1). Thus, this reaction provides a highly simplifying transform for chiral 1,4-difunctionalized allylic amines that can be further elaborated to motifs common in natural products and medicinally valuable compounds. For example, tripeptide isostere (+)-**15** was readily synthesized in optically pure form via an asymmetric allylation/allylic C−H amination sequence.[17] Densely functionalized amino alcohol (+)-**12** is an intermediate toward glycamines.[18]

On the basis of our previous work,[4] we anticipated incorporation of nitrogen using selective C−H to C−N bond-forming reactions would significantly streamline the synthesis of nitrogen-containing compounds. In this vein, we compared the route to a rigidified analogue of the antibiotic deoxynegamycin (+)-**19** enabled by the linear allylic C−H amination to a previous state-of-the-art route based on allylic C−O substitution (Scheme 1).[19] Starting with commercial *β*-homoallylglycine (−)-**16**, nitrogen was incorporated in only two steps at the correct oxidation state using the linear allylic amination. In contrast, beginning with aspartic acid derivative **20**, incorporation of nitrogen via an allylic oxygenate intermediate proceeded in seven steps and required further oxidation-state manipulation of nitrogen. Overall, the C−H to C−N bond-forming route to optically pure deoxynegamycin analogue (+)-**19a** proceeded with five fewer steps, five fewer functional group manipulations (FGMs), and higher overall yield than the alternative C−O to C−N bond-forming route.

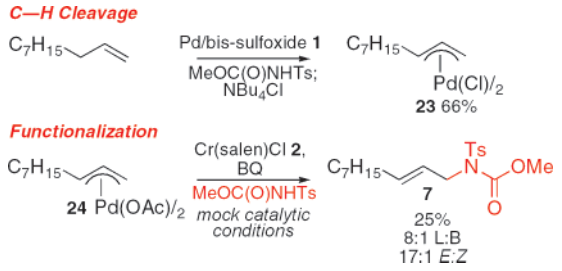
Scheme 2



Linear allylic C−H amination also provides a direct route to valuable ^{15}N-labeled compounds by using ^{15}*N*-(methoxycarbonyl)-*p*-toluenesulfonamide (readily available in two steps from $^{15}NH_4$-

Cl, 99.7% enriched). Installation of labeled nitrogen functionality late in a route minimizes loss of this valuable material that would otherwise be incurred by early-stage incorporation. As with all of the tosyl-protected amine compounds, detosylation can be effected under mild, reductive conditions without affecting the carbamate moiety. Detosylation of ^{15}N-labeled (+)-**12** followed by cleavage of the methoxy carbamate with NaOH afforded isotopically enriched free amine product (+)-**22** (99.7% enriched, Scheme 2).

Scheme 3. Stoichiometric Studies To Evaluate the Role of (salen)CrCl **2**



Stoichiometric studies were performed to evaluate the roles of Pd(II)/bis-sulfoxide catalyst **1** and Cr(III)(salen) catalyst **2** in the intermolecular allylic C−H amination reaction. When a stoichiometric mixture of 1-decene, catalyst **1**, and 2 equiv of *N*-(methoxycarbonyl)-*p*-toluenesulfonamide nucleophile were heated for 4 h, a π-allylPd complex was trapped as the corresponding chloride dimer **23**, which was isolated in 66% yield (Scheme 3). We next evaluated the effect of chromium catalyst **2** on synthetic π-allylPd complex **24** under mock catalytic conditions. We found that the combination of Cr catalyst **2** with BQ was uniquely effective at promoting formation of aminated product **7** in 25% yield with regio- and stereoselectivities similar to those observed under standard catalytic conditions (Scheme 3; Table 2, entry 3).[20] Consistent with **2**/BQ working together to promote functionalization, sterically hindered quinones such as 2,6-dimethyl quinone result in significantly diminished yields (10%, see Supporting Information, [SI]) under otherwise standard catalytic conditions. These results suggest that Pd catalyst **1** mediates allylic C−H cleavage, while Cr catalyst **2** and BQ promote functionalization. The exact mechanism by which **2**/BQ promote functionalization is currently under investigation.[21]

In summary, we report the first general and highly selective, catalytic intermolecular allylic C−H amination reaction. The excellent levels of regio- and stereoselectivity as well as the outstanding functional group compatibility make this reaction immediately applicable to complex molecule synthesis. Mechanistic studies support a heterobimetallic Pd(II)−Cr(III) catalytic system in which each metal effects different product-forming steps in the catalytic cycle. Given the excellent selectivities and broad scope of the linear allylic C−H amination, we anticipate that it, and other reactions like it, will significantly enable the streamlining of small molecule synthesis.

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Supporting Information Available: Detailed experimental procedures, full characterization, ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Allylic acetates were the other major product observed (see SI). This is consistent with the catalytic reaction where allylic acetates are the major byproduct. When allylic acetates are exposed to the reaction conditions, only trace (~6%) allylic carbamate is formed with different regio- and stereoselectivities than those observed under catalytic conditions (SI).
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