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Allylic C−H Amination for the Preparation of *syn*-1,3-Amino Alcohol Motifs

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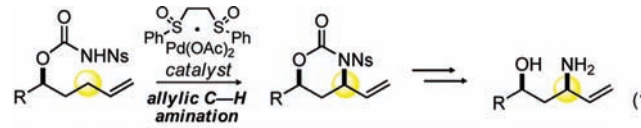
Abstract: A highly selective and general Pd/sulfoxide-catalyzed allylic C−H amination reaction *en route* to *syn*-1,3-amino alcohol motifs is reported. Key to achieving this reactivity under mild conditions is the use of electron-deficient *N*-nosyl carbamate nucleophiles that are thought to promote functionalization by furnishing higher concentrations of anionic species *in situ*. The reaction is shown to be orthogonal to classical C−C bond-forming/-reduction sequences as well as nitrene-based C−H amination methods.

Introduction

A diverse range of natural products and pharmaceuticals include *syn*-1,3-amino alcohols as dominant motifs. Important advances have been made in asymmetric C−C and C−N bond-forming reactions to generate β-amino ketones and β-hydroxy imines.[1,2] Complementary methods that furnish 1,3-amino alcohols with minimal oxidation-state manipulations would provide strategic advantages in streamlining their syntheses. Although metal nitrene systems for aliphatic C−H aminations provide direct routes for accessing *syn*-1,3-amino alcohols,[3] analogous allylic C−H aminations face challenges in chemoselectivity and/or reactivity, particularly with terminal olefins.[3b,c,4] Such reactions would be highly valuable in synthetic planning due to the latent functionality preserved in the unsaturated moiety (*vide infra*). We have recently discovered Pd(II)/sulfoxide catalyst systems that effect predictably selective allylic C−H esterifications,[5] alkylations,[6] and aminations,[7,8] and demonstrated their strategic use in streamlining complex molecule synthesis.[9] Notably, our group recently reported an intramolecular allylic C−H amination reaction of homoallylic *N*-tosyl carbamates to generate 5-membered vinyl oxazolidinones *en route* to *syn*-1,2-amino alcohol motifs.[7] We now report that the use of a more electron-deficient *N*-nosyl carbamate nucleophile enables a mild Pd(II)/sulfoxide-catalyzed allylic C−H amination reaction with extraordinary chemoselectivities that furnishes vinyl *syn*-1,3-amino alcohol precursors from terminal olefins.



•R groups may contain a wide variety of functional groups including: carbonyls, internal olefins, benzylic C—H's and ethereal C—H's

Results and Discussion

Design Principles. Mechanistic studies indicated that intramolecular allylic C−H amination to form 5-membered vinyl oxazolidinones proceeds *via* Pd(II)/sulfoxide-mediated hetero-

(1) (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (b) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964. (c) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 11276. (d) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777. (e) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734. (f) Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4079.

(2) For some recent examples of asymmetric conjugate addition reactions with nitrogen nucleophiles to furnish β-amino ketones see: (a) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959. (b) Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134. (c) Sibi, M. P.; Prabagaran, N.; Ghorpade, S. G.; Jasperse, C. P. *J. Am. Chem. Soc.* **2003**, *125*, 11796. (d) Yamigawa, N.; Qin, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13419. (e) Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328.

(3) (a) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935. (b) Fiori, K. W.; Fleming, J. J.; Du Bois, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 4349. A sulfamate product analogous to **4** was generated *via* a chemoselective Rh-nitrene-based reaction in 43% yield: (c) Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 9220. (d) Milczek, E.; Boudet, N.; Blakey, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6825. (e) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465.

(4) Interestingly, high chemoselectivities and reactivities have been reported for intermolecular Rh-nitrene allylic aminations of internal olefins: Liang, C.; Collet, F.; Robert-Peillard, F.; Müller, P.; Dodd, R. H.; Dauban, P. *J. Am. Chem. Soc.* **2008**, *130*, 343.

(5) Linear allylic C−H acetoxylation: (a) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. Branched allylic C−H esterification: (b) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970. Oxidative C−H macrolactonization. (c) Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 9032. For a linear allylic acetoxylation reaction using DMA solvent see: (d) Mistudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 481.

(6) Linear allylic C−H alkylation: (a) Young, A. J.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 14090. (b) For a system that also uses Pd(II)/bis-sulfoxide catalysis see: Lin, S.; Song, C.-X.; Cai, G.-X.; Wang, W.-H.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 12901.

(7) Intramolecular allylic C−H amination to furnish 1,2-amino alcohol motifs: Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274.

(8) Intermolecular allylic C−H amination to furnish linear (*E*)-allylic amines using *N*-(methoxycarbonyl)-*p*-toluenesulfonamide nucleophile: (a) Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 3316. (b) Reed, S. A.; Mazzotti, A. R.; White, M. C. *J. Am. Chem. Soc.* **2009**. In press, doi: /10.1021/ja903939k. For a similar system using DMA solvent see: (c) Liu, G.; Yin, G.; Wu, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4733.

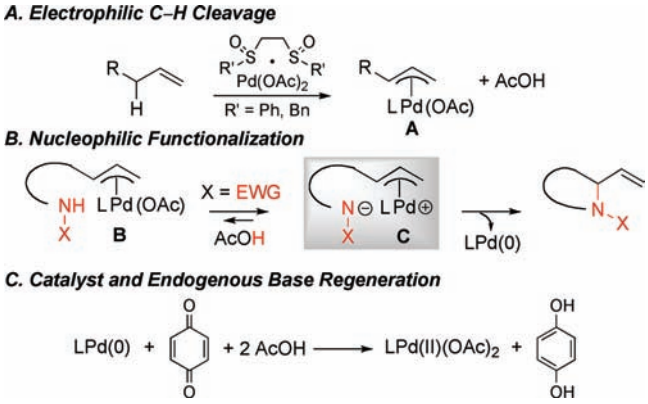


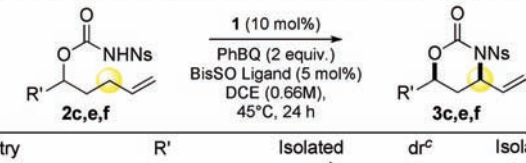
Figure 1. Design principles for intramolecular C−H amination.

lytic allylic C−H cleavage to generate a π-allyl Pd(OAc) intermediate **A** (Figure 1A).[7] Intramolecular functionalization with the acidic *N*-tosyl carbamate pro-nucleophile **B** is effectively promoted by palladium carboxylate counterion acting as a base (Figure 1B). This catalytic source of weak base is regenerated during oxidation of Pd(0) with quinone (Figure 1C). However, attempts to promote allylic C−H amination to form a 6-membered oxazinanone with this nucleophile under identical conditions gave poor yields and conversions even after 72 h (Table 1, entry 1, 75% recovered starting material).[10,11] Given the higher kinetic barrier for 6- versus 5-membered ring formation, we reasoned that functionalization was likely the problematic step. Decreasing the electron density of the nitrogen is known to assist electrophilic metal catalysis by preventing nucleophile complexation to the metal.[12] We hypothesized that even in cases like ours where metal/nucleophile interactions are not likely to be problematic,[7,8] switching to a more *electron-poor* amine might promote catalysis by increasing the equilibrium concentration of the active anionic species **C** *in situ* without prohibitively decreasing its nucleophilicity (Figure 1B).[13]

Reaction Optimization. Consistent with the hypothesis that increasing the pro-nucleophile's acidity will lead to an improvement in reactivity, examination of a series of 4-substituted *N*-arylsulfonyl carbamates revealed a positive correlation between pro-nucleophile acidity and product yields.[14] By simply changing from an *N*-tosyl carbamate to an *N*-(4-chlorophenylsulfonyl) carbamate, a doubling in yield was achieved in one-third the reaction time [Table 1, entry 2, 15% (72 h) → 38% (24 h)]. Switching to the more acidic *N*-(4-nitrophenylsulfonyl) carbamate group afforded a dramatic positive impact on the reaction rate (72 h → 24 h) and yield (15% → 67%) of 6-membered ring formation (entry 3).[15] Interestingly, evaluation of the even more acidic *N*-(2-nitrophenylsulfonyl) carbamate group afforded no further improvement, suggesting that decreasing the electron density of a nitrogen pro-nucleophile to increase anion concentration must be balanced with decreasing its nucleophilicity (entry 4). Additional reaction exploration showed that a switch in the solvent from THF to DCE and the inclusion of additives known to promote Pd(0) oxidation (e.g., O_2[16a] and *p*-nitrobenzoic acid[16b,c]) furnished the *syn*-oxazinanone in good yield and diastereoselectivity (entry 5).

Table 1. Allylic C−H Amination Reaction Optimization

Entry	R		Time	Isolated Yield[b]	dr[c]
1	*p*-Tol	**(2a)**	72 h	15%	5.1:1
2	*p*-ClPh	**(2b)**	24 h	38%	3.7:1
3	*p*-NO_2Ph (Ns)	**(2c)**	24 h	67%	4.4:1
4	*o*-NO_2Ph	**(2d)**	24 h	63%	2.6:1



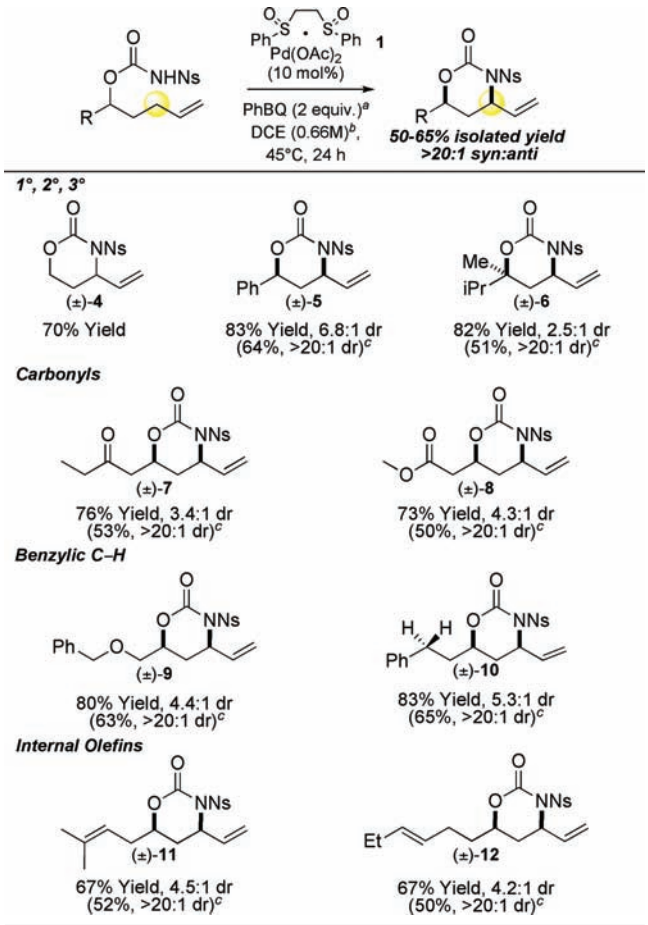
Entry	R'		Isolated Yield[b]	dr[c]	Isolated Syn[e]
5[d]	*i*Propyl	**(2c)**	80%	6.0:1	65%
6[d]	Ethyl	**(2e)**	87%	4.3:1	67%
7[d]	*t*Butyl	**(2f)**	84%	6.3:1	68%

[a] BisSO ligand = 1,2-bis(phenylsulfinyl)ethane. [b] Average of two runs. [c] Determined by GC analysis (R = *p*-Tol) or ^{1}H NMR (R = *p*-ClPh, *p*-NO_2Ph, *o*-NO_2Ph) of crude reaction mixture. [d] Reaction run using 10 mol % *p*-nitrobenzoic acid and oxygenated DCE. [e] Isolated yield of major *syn* product, >20:1 *syn:anti*.

Interestingly, reactivity and selectivity in this system are not strongly impacted by steric bulk adjacent to the carbamate (Table 1, entries 5−7). This is in stark contrast to the allylic C−H amination system furnishing *syn*-1,2-amino alcohol motifs, where one bulky substituent adjacent to the carbamate (generally a branching element) was deemed important for achieving good diastereoselectivity; a bulky quaternary alkyl substituted carbamate, albeit proceeding with excellent diastereoselectivity, suffered from poor reactivity (*vide infra*).[7]

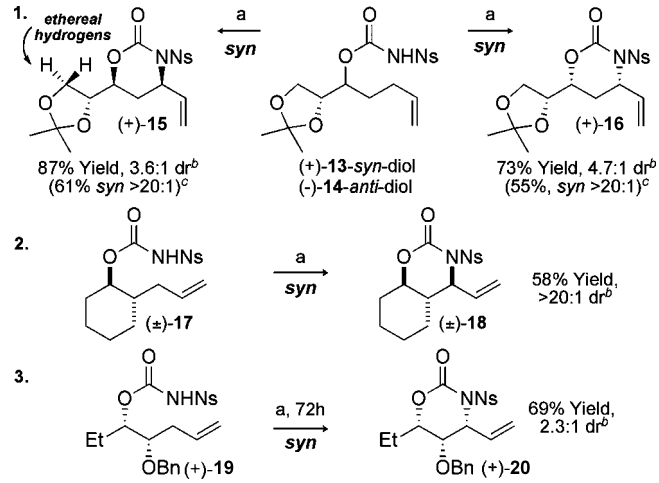
(9) (a) Fraunhoffer, K. F.; Bachovchin, D. A.; White, M. C. *Org. Lett.* **2005**, *7*, 223. (b) Covell, D. J.; Vermeulen, N. A.; Labenz, N. A.; White, M. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 8217.
(10) Carbamate and *N*-tosyl carbamate substrates have been observed to exclusively form 5-membered ring oxazolidinone products in nitrene-based systems: (a) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598. (b) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198.
(11) The inclusion of catalytic amine base, recently discovered to promote intermolecular allylic C−H aminations with *N*-tosyl carbamate nucleophiles (ref 8b), gave a minor increase in yield for substrate **2a** (15% → 37%); however, the diastereoselectivity was significantly diminished (5.1:1 → 1.8:1 *syn:anti*).
(12) This effect has explicitly been demonstrated in the oxidative amination of olefins *via* electrophilic Pd(II) catalysis: (a) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444. (b) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584.
(13) Pd(0)-mediated allylic substitution of cyclic carbonates to carbamates proceeds *via* anionic nitrogen nucleophiles: Bando, T.; Harayama, H.; Fukazawa, Y.; Shiro, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1994**, *59*, 1465.
(14) Relative pK_a values were based upon benzoic acid analogues: (a) Tao, L.; Han, J.; Tao, F-.M. *J. Phys. Chem. A* **2008**, *112*, 775. (b) Maran, F.; Celadon, D.; Severin, M. G.; Vianello, E. *J. Am. Chem. Soc.* **1991**, *113*, 9320.
(15) Heating the reaction with *N*-tosyl carbamate substrates to 65 °C also promoted reactivity; however, the yields were lower, and inconsistent results were observed.
(16) (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. Carboxylic acids have been shown to increase reactivity in oxidative Heck reactions mediated by Pd(II)/bis-sulfoxide, possibly *via* acid-promoted quinone reoxidation of the metal: (b) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076. (c) Delcamp, J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 11270.

Table 2. Allylic C−H Amination Reaction Scope



[a] Additives: *p*-nitrobenzoic acid (10 mol %), BisSO ligand (5 mol %). [b] Reaction run in oxygenated DCE. [c] Isolated yield of major *syn* product, >20:1 *syn*:*anti*.

Scheme 1. Origin of Diastereoselectivity



[a] **1** (10 mol %), 1,2-bis(phenylsulfinyl)ethane (5 mol %), *p*-nitrobenzoic acid (10 mol %), phenyl benzoquinone (2 equiv), oxygenated DCE (0.66 M), 45 °C, 24 h. [b] dr of crude reaction. [c] Isolated yield of major *syn* product.

Reaction Scope. Significantly, use of this more electron-deficient nitrogen nucleophile proved to be a general solution for the formation of a wide range of 6-membered oxazinanones (Table 2). Substrates derived from secondary alcohols having prochiral allylic C−H bonds show good to excellent levels of diastereoselectivity favoring the *syn*-1,3-isomer (**5**, **7**−**12**). The observed stereochemical outcome is consistent with functionalization proceeding *via* a chairlike transition state.[13] No conformational biasing element is required for effecting cyclization as evidenced by efficient generation of oxazinanone **4** (70%) derived from a primary alcohol precursor.[3c] Even a substrate originating from a sterically hindered tertiary alcohol generated *syn*-1,3-oxazinanone **6** in good yield.

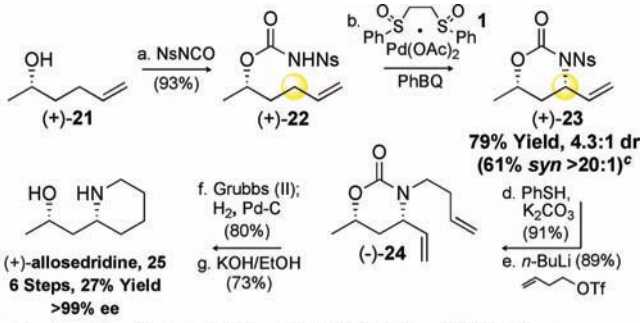
This method is orthogonal to all other current state-of-the-art methods for generating this synthetically important motif. The complementary nature of this method to C−C and C−N bond-forming/-reduction sequences is highlighted by the synthesis of oxazinanones **7** and **8** having reduction-sensitive proximal ketone and ester functionalities. In contrast to nitrene-based systems, perfect chemoselectivity is seen for allylic C−H amination over benzylic and ethereal C−H amination (**9**, **10**; (+)-**15** and (+)-**16**, Scheme 1).[3] Strikingly, this allylic C−H amination method shows unprecedented chemoselectivity for C−H amination of terminal over internal olefins (**11** and **12**). In all cases, *syn*-oxazinanone products of greater than 20:1 diastereomeric ratio can be obtained in good yields after standard column chromatography (see parenthetical yields in Table 2).

Predictable diastereomeric outcomes are crucial for C−H functionalization methods to find use at late stages of complex molecule synthesis. Gratifyingly, for substrates containing multiple stereogenic centers, the diastereomeric outcome of this reaction is controlled by the stereocenter containing the carbamate (Scheme 1). In substrates containing homoallylic (**17**, **19**) or trishomoallylic (**13**, **14**) stereogenic centers the reaction is consistently *syn*-selective relative to the *N*-nosyl carbamate.

Streamlining Synthesis. We have previously demonstrated the ability of predictably selective C−H amination reactions to streamline the synthesis of nitrogen containing molecules by "skipping" oxygenated intermediates that are burdensome to carry through synthetic sequences.[7,8] The ability of this allylic C−H amination reaction to efficiently access optically enriched *syn*-1,3-amino alcohols is highlighted in the synthesis of (+)-allosedridine **25**, a member of the sedum alkaloids that have shown promising memory enhancing properties (Scheme 2).[17] Starting from commercially available enantioenriched bis-homoallylic alcohol (+)-**21**, the nitrogen is introduced at the correct oxidation state *via* C−H amination in only two steps. Major diastereomer (+)-**23** was easily isolated using standard flash column chromatography in 61% yield with >20:1 diastereomeric purity and with no erosion in enantiomeric excess (>99% *ee*). Notably, the *N*-nosyl group can be easily deprotected using mild $PhSH/K_2CO_3$ conditions to afford the free oxazinanone in 91% yield.[18] Alkylation furnished (−)-**24** whose terminal olefin moieties could be used to forge the piperdine core *via* Grubbs ring-closing metathesis (RCM).[19] Hydrogenation, followed by basic hydrolysis completed the total synthesis of (+)-allosedridine **25** in six steps and 27% overall yield. By avoiding multiple functional group manipulations and exploiting the terminal

(17) Meth-Cohn, O.; Yu, C.-Y.; Lestage, P.; Lebrun, M.-C.; Cagniard, D.-H.; Renard, P. Eur. Pat. 1050531, 2000.
(18) Fukuyama, T.; Jow, C.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.
(19) (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. For specific reaction conditions see: (b) Anada, M.; Tanaka, M.; Washio, T.; Yamawaki, M.; Abe, T.; Hashimoto, S. *Org. Lett.* **2007**, *9*, 4559.

Scheme 2. Total Synthesis of (+)-Allosedridine[a]



• Previous Syntheses: 10 Steps (15.8%, >98% ee)[20a] & 8 Steps (2.7%, 85% ee)[20b]

[a] Reagents and conditions: (a) NsNCO (1.1 equiv), THF, rt (93%); (b) standard conditions; (c) isolated yield of major *syn* product; (d) PhSH (1.2 equiv), K_2CO_3 (3 equiv), DMF, 0 °C, 4 h (91%); (e) *n*-BuLi (1.0 equiv), THF, −78 °C; but-3-enyl trifluoromethanesulfonate (1.2 equiv), −78 °C to 0 °C, 2 h (89%); (f) Grubbs (II) (8 mol %), toluene, 65 °C, 3 h; H_2, Pd−C, MeOH, rt, 2 h (80%); (g) KOH/EtOH (1.7 M), 45 °C, 2 h (73%).

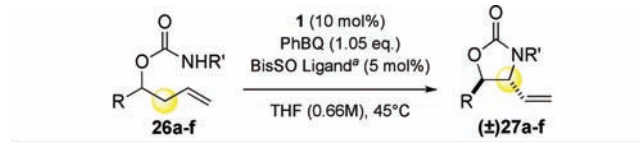
olefin functionality, an allylic C−H amination route affords the shortest and highest-yielding synthesis of (+)-**25** to date.[20]

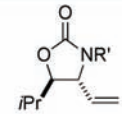
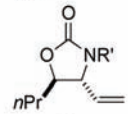
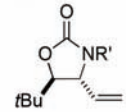
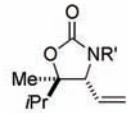
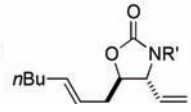
***syn*-1,2-Amino Alcohol Synthesis.** Significantly, the discovery that *N*-nosylcarbamate nucleophiles lead to improved reactivity for intramolecular allylic C−H aminations could be used to increase the efficiency of our previously reported reaction for generating 1,2-amino alcohol motifs. Homoallylic *N*-nosyl carbamates **26b** and **26d** underwent Pd(II)/sulfoxide **1**-catalyzed intramolecular allylic C−H amination to furnish *anti*-oxazolidinones **27b** and **27d** in comparable yields and diastereoselectivities and a 3-fold decrease in reaction times (72 h → 24 h) to those reported with the analogous *N*-tosyl carbamate substrates (Table 3, entries 1, 2). In contrast to the 1,3-amino alcohol system, however, reactivity with sterically congested substrates such as *tert*-butyl **26f** and tertiary alcohol-derived carbamate **26g** remained low (entries 3, 4). These results demonstrate a distinct steric limitation for this chemistry in furnishing 5-membered oxazolidinone rings that is not observed in generating 6-membered oxazinanone rings. Gratifyingly, the allylic C−H amination reaction for generating 1,2-amino alcohol motifs also proceeds with outstanding chemoselectivity. This is illustrated in the preferential C−H amination of terminal over internal olefins in the doubly homoallylic *N*-nosyl carbamate substrate **26h** (entry 5). Interestingly, *syn*-oxazolidinone **27h** is obtained in both good yields and diastereoselectivities despite the lack of an adjacent branching element previously deemed to be crucial for obtaining synthetically useful diastereomeric outcomes with this system.

Conclusion

We report herein the discovery that an electron-deficient *N*-nosyl carbamate nucleophile furnishes a general Pd(II)-sulfoxide-catalyzed allylic C−H amination reaction to generate 6-membered *syn*-oxazinanones under mild reaction conditions. The extraordinary chemoselectivity of this method is underscored by its demonstrated ability to selectively aminate allylic C−H bonds of terminal olefins preferentially to internal olefins. This feature, as well as its orthogonality to nitrene-based C−H aminations and C−C bond-forming/-reduction sequences, makes it a powerful reaction for 1,3-amino alcohol synthesis. This allylic C−H amination reaction is enabled by electronically tuning the pro-nucleophile in order to increase the equilibrium concentration of active anionic species under conditions that employ catalytic amounts of a weak base. The general strategy of decreasing the pK_a of a pro-nucleophile to promote functionalization has led to a significant rate increase for the previously reported allylic C−H amination reaction for 1,2-amino alcohol synthesis and has the potential for application to other electrophilic metal-catalyzed reactions.

Table 3. 1,2-Amination Rate Increase Using *N*-Nosyl Carbamates



Entry	Product	R'		Time	Isolated Yield[b]	dr[c]
1		Tosyl	(27a)	72 h	76%	6.0:1
		Nosyl	(27b)	24 h	78%	5.0:1
2		Tosyl	(27c)	72 h	86%	1.6:1
		Nosyl	(27d)	24 h	79%	1.7:1
3		Tosyl	(27e)	72 h	8%	18:1
		Nosyl	(27f)	72 h	20%	>20:1
4		Nosyl	(27g)	72 h	<1%	--
5		Nosyl	(27h)	24 h	68%	5.4:1

[a] BisSO ligand = 1,2-bis(phenylsulfinyl)ethane. [b] Average of two runs. [c] Determined by GC analysis (R′ = *p*-Tol) or ^{1}H NMR analysis (R′ = *p*-NO_2Ph) of crude reaction mixture.

Experimental Procedures

General Experimental Procedures. In a one-dram vial was added the corresponding carbamate starting material (1 equiv), phenyl benzoquinone (2 equiv), *p*-nitrobenzoic acid (0.10 equiv), 1,2-bis(phenylsulfinyl)ethane (0.05 equiv), $Pd(OAc)_2$/ 1,2-bis(phenylsulfinyl)ethane catalyst **1** (0.10 equiv, Strem Chemicals or Aldrich Chemical Co.), and a Teflon stir bar. In a separate flask, O_2 gas was simultaneously bubbled through 1,2-dichloroethane for 30 min. The oxygenated 1,2-dichloroethane (0.66 M) was then added to the previous one-dram vial, O_2 gas was blown over the vial for 5 s, and the vial was sealed with a Teflon-lined cap. The reaction vial was then vortexed until the solution appeared homogeneous and stirred in a 45 °C oil bath for 24 h. The solution was allowed to cool to room temperature and then transferred using a minimum amount of dichloromethane to a 250-mL separatory funnel. The solution was diluted with 15 mL of diethyl ether and rinsed with 1× 15 mL of aqueous sodium bisulfite (sat.), 1× 15 mL of water, 1× 15 mL of 5% aqueous

(20) For previous asymmetric syntheses see: (a) Takahata, H.; Kubota, M.; Ikota, N. *J. Org. Chem.* **1999**, *64*, 8594. (b) Passarella, D.; Barilli, A.; Belinghieri, F.; Fassi, P.; Riva, S.; Sacchetti, A.; Silvani, A.; Danieli, B. *Tetrahedron: Asymmetry* **2005**, *16*, 2225.

K_2CO_3/H_2O, and 1× 15 mL of water. The organic layer was collected and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography. **In general, the major *syn*-diastereomer can be isolated by flash chromatography (25−35% gradient EtOAc/hexanes) directly from the crude reaction mixture.**

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Supporting Information Available: Experimental procedures, full characterization, and additional experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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