Published in final edited form as:

J Am Chem Soc. 2019 June 19; 141(24): 9468–9473. doi:10.1021/jacs.9b02690.

Synthesis of *anti*-1,3-Amino Alcohol Motifs via Pd(II)/SOX catalysis with the Capacity for Stereodivergence

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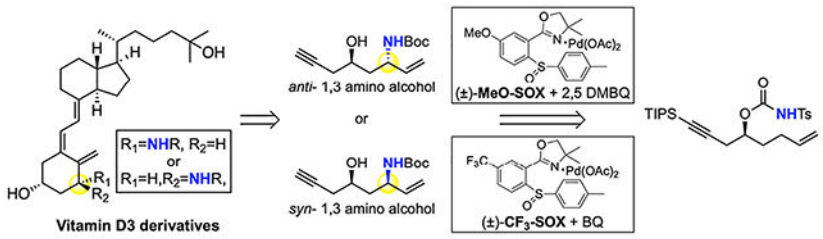
Abstract

We report the development of a Pd(II)/(±)-MeO-SOX/2,5-dimethylbenzoquinone system that enables unprecedented access to *anti*-1,3 amino alcohol motifs in good yields (33 substrates, avg. 66% isolated yield, >20:1 dr) and high selectivities (avg. 10:1 dr). Switching ligands to (±)-CF_3-SOX using a less bulky quinone oxidant, the kinetic *syn*-1,3 amino alcohol motif can be accessed in comparable yields and selectivities. Advantages of the stereodivergent nature of this reaction are seen in the synthesis of *anti*- and *syn*-1,3-amino alcohol vitamin D3 analogue intermediates in half the steps and higher overall yield to previous routes. Additionally, all eight possible stereoisomers of a chiral diamino alcohol core are generated from two amino acids. Mechanistic studies reveal that the *anti*-isomer is furnished through concurrent Pd(II)(SOX) catalyzed C—H amination and Pd(0)(SOX)-catalyzed isomerization cycles.

Graphical Abstract



1, 3 amino alcohols are prominent structures in a di-verse range of biologically active natural products and pharmaceuticals. Direct C—H aminations, including metallonitrene systems[1] and Pd(II)/bis-sulfoxide catalyzed allylic C—H amination[2], are effective for synthe-sizing *syn*-1,3 amino alcohols with reduced oxidation-state manipulations and synthetic overhead. However, these methods have not been shown to furnish *anti*-1,3 amino alcohols. Classic methods for *anti*-1,3 amino alcohol synthesis involve C—C bond coupling reactions of pre-

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The authors declare the following competing financial interest(s): The University of Illinois has filed a patent application on SOX ligands for allylic C–H functionalizations.

oxidized fragments to generate *β*-hydroxy imines[3] or *β*-amino ketones[4] followed by diastereoselective hydride reductions. Advances in transition metal catalyzed C–N cyclization of *N*-tosyl carbamates into allylic oxygenates[5] and allenes[6] still necessitate the use of pre-oxidized compounds.

Existing Pd(II)/bis-sulfoxide catalyzed intramolecular allylic C—H amination of *N*-nosyl carbamate substrates affords syn-1,3 amino alcohol precursors in preparative yields (avg. 60%) and diastereoselectivities (avg. 5.4:1 dr).[2a] These reactions proceed with a reversibly coordi-nating bis-sulfoxide ligand that relies on quinone oxidant to promote functionalization of a neutral π-allyl Pd.[7] We questioned if the Pd(II)/SOX catalysis[8,9], where functionalization proceeds via a cationic π-allylPd(SOX) intermediate[9] gives an alternative stereooutcome. Herein we demonstrate that *anti*-1,3 amino alcohol motifs can be accessed for the first time via C—H amination using Pd(II)/(±)-MeO-SOX catalysis with a 2,5-dimethylbenzoquinone oxidant (2,5-DMBQ). Using the same substrate and switching the catalyst to Pd(II)/(±)-CF_3-SOX and benzoquinone oxidant (BQ) affords the *syn*-1,3 amino alcohol motif.

We initiated examining the reactivity of a *N*-tosyl carbamate substrate. Under Pd(II)/bis-sulfoxide catalysis[2a] (Table 1, entry 1), we observed low reactivity of this less acidic nitrogen nucleophile favoring *syn*-oxazinanone. Switching to (±)-MeO-SOX ligand, reported to promote intermolecular allylic C—H aminations with comparable nucleophiles,[9] the reaction gave trace reactivity with phenylbenzoquinone (PhBQ) oxidant (entry 2). Analogous to previous reports,[9] using highly substituted 2,5 DMBQ significantly increased the reaction productivity furnishing 88% yield of aminated product. The reaction also proceeded with good diastereoselectivity (7.3:1 dr) favoring the elusive thermodynamic[5,6,10] *anti*-diastereomer (entry 3). Further exploration revealed that decreasing the equivalents of 2,5 DMBQ (2 → 1.2 equiv.) increased the yield and diastereoselectivity (entry 4). Low conversion under Pd(II)/MeO-SOX conditions with less hindered quinones appears to be due to an inhibitory effect on catalysis, perhaps by forming a η^2-π/Pd complex that competes with essential substrate binding[11]: doping in 10 mol% BQ into otherwise standard *anti*-conditions results in significantly diminished yield of oxazinanone favoring the *syn* isomer (entry 5, *vide infra*). Continued evaluation of racemic SOX ligands revealed that simple (±)-SOX ligand gave less *anti*-diastereomer (4:1, entry 6), whereas one bearing an electron-withdrawing CF_3 group ((±)-CF_3 SOX) favored the kinetic *syn*-diastereomer (1:4, entry 7). Using BQ was beneficial to the yield and diastereoselectivity (76%, 1:7 dr, entry 8). Lowering the BQ loading (2 → 1.6 equiv.) increased the yield further to 87% (entry 9), whereas further decreases were not beneficial (entry 10). Brønsted acid additive (10 % diphenyl phosphinic acid)[8a] was used to promote reactivity for both the *anti*- and *syn*-conditions with substrates that showed sluggish reactivity (vide infra, Table 2, **16**. Table 3, **29**, **33–36**, **43**). For reactive substrates, acid additive may shorten reaction times (24h → 6h) albeit with diminishments in selectivity (entry 11, 12). Pd(II)/bis-sulfoxide catalysis under otherwise identical conditions showed improvements in yield but diastereoselectivity still favoring the *syn*-oxazinanone (entry 13, 14), underscoring the significance of the SOX ligand in the observed stereodivergence.

Evaluation of a broad range of substrates under Pd(II)/(±)-MeO-SOX catalysis afforded after isolation an average of 66% yield of > 20:1 *anti*-oxazinanone (Table 2). Arylated 1, 3-amino alcohol motifs, widely represented in bioactive compounds such as CERT antagonist HPA-12[12], sedacryptine[13] and nikkomycin Z[14], afforded preparative yields and diastereoselectivities irrespective of electronic substitution (Table 2, **2**-**9**). In general, electron neutral or rich aromatic substrates furnished *anti*-products with the highest yields (**2**-**4**) whereas highly electron deficient aromatics afforded products in the highest crude diastereoselectivities (**7**, **8**). Aryl substrates bearing different substituted 1- or 2- naphthalene undergo allylic C—H amination with preparative yields and selectivities (**10**, **11**). Medicinally important, oxida-tively labile heteroaromatic moieties including indole, benzothiophene, benzofuran, dibenzothiazine, and phenyl sulfonyl morpholine are all well tolerated in Pd(II)/(±)-MeO-SOX catalysis (**12**-**16**).

Aliphatic 1,3 amino alcohol motifs are common building blocks among bioactive small molecules including lopinavir[15], ritonavir[16] and negamycin[17] (Figure 1a). A broad range of aliphatic substrates also afford *anti*-1,3-amino alcohol precursors in preparative yields and diastereoselectivities. Diastereoselectivity is not strongly impacted by the steric bulk of the alkyl substituent adja-cent to the carbamate. Alkyl substituents ranging in size from small methyl groups to larger cyclic alkanes (e.g. cyclopropanes, cyclopentane, adamantane) all underwent productive allylic C—H amination (**17**-**21**) with no correlation between steric bulk and diastereoselectivity. Aliphatic substrates derived from tertiary alcohols proceeded with good yields but poor diastereoselectivity under both the *anti*- and *syn*-conditions (see Supporting Information, Scheme S8). Common heterocycles such as Boc-protected piperidine are well-tolerated (**22**). Remote primary alcohols, both silyl protected and unpro-tected, give allylic C—H amination product with no observed alcohol oxidation (**23**, **24**), showcasing chemoselectivity not common for Pd(II) oxidation systems.[18] In contrast to metallo-nitrene based C—H aminations[1], Pd(II)/sulfoxide-catalyzed amination shows high chemoselectivity for allylic C—H bonds over benzylic, propargylic and ethereal C—H bonds (**25**-**27**). The or-thogonality of this method to existing β-hydroxy imines[3] or β-amino ketones[4] reduction and rhodium-hydride catalyzed cyclization[6] is highlighted by its tolerance of proximal alkyne and ketone functionalities (**26**, **28**). Substrates with proximal stereocenters, even acidic ones, undergo allylic C—H amination with no detected epimerization (**28**).

Several of the aromatic and aliphatic *N*-tosyl carbamate substrates were additionally evaluated under $Pd(OAc)_2$/(±)-CF_3-SOX/BQ catalysis. Gratifyingly, we observed by only altering the catalyst and oxidant, we were able to obtain the *syn*-oxazinanone products. Although the diastereoselectivities were not entirely turned over, all the substrates examined afforded after isolation an average of 62% yield of >20:1 *syn*-oxazinanone (Table 3). Significantly, although the previous Pd(II)/bis-sulfoxide catalyzed allylic C—H amination also affords *syn*-1,3 amino alcohol motifs in useful- albeit lower-yields and diastereoselectivities, installation of the more acidic *N*-nosyl carbamates requires synthesis of nosyl isocyanate (Table 1, entry 1).[2] In contrast, *N*-tosyl carbamates, synthesized in one step from commercial tosyl isocyanate and homo-allylic alcohol, afford via Pd(II)/SOX catalysis either *anti*- or *syn*-1,3 amino alcohol motifs.

The impact of stereochemistry on small molecule function underscores the benefits of stereodivergency. For example, in the discovery phase of Vitamin D3 analogue synthesis[19] for treating metabolic diseases, both *syn*- and *anti*-1,3 amino alcohol fragments towards modified A-rings were examined (Figure 2). The traditional route started from an oxygenated chiral precursor (*L*)-malic acid and proceeded via a lengthy functional group manipulations sequence. The allylic C—N bond was forged via a poorly diastereoselective intramolecular allylic carbamate rearrangement to furnish the *syn*- and *anti*-amino alcohols as a 2:1 mixture in ca. 18 steps ca. 14% yield for the *anti*-**48a** and 7 % for the *syn*-**48b** (Figure 2).[19] In contrast, starting from commercial epichlorohydrin, the hydrocarbon core of chiral homoallylic carbamate **46** for the allylic C—H amination routes proceeds in 4 steps. Nitrogen is directly and stereoselectively installed into the hydrocarbon scaffold by using either Pd(II)/(±)-MeO-SOX or Pd(II)/(±)-CF_3-SOX catalysis to afford preparative yields of the desired *anti*-**47a** or *syn*-**47b** products, respectively. Mild reductive *N*-desulfonylation[6,20], Boc protection, base-mediated oxazinanone hydrolysis, followed by acetylene desilylation affords the desired *anti*- and *syn*-1,3 amino alcohol motifs (+)-**48a**, (−)-**48b** in 9 steps and 22% and 18% overall yields, respectively. Stereochemically pure *anti*- and *syn*-1,3 amino alcohols are furnished in higher overall yields and half the steps of the traditional route, making the C—H amination route favorable.[19]

A distinctive feature of the stereodivergent allylic C—H amination is predictable and controllable diastereomeric outcome (*anti* or *syn*), even in the presence of proximal stereogenic centers. In chiral substrates, we have shown the absolute stereochemistry of the aminated site is controlled by the Pd(II)/SOX system in combination with the carbamate stereocenter (Table 2 and 3, entry **27**, **28** and **44**, **45**). We envision that this feature will enable facile access to all possible stereoisomers of amino acid derived chiral diamino alcohol cores. These chiral subunits are found in hydroxyethylene dipeptide isostere pharmaceuticals (e.g. lopinavir[15] and ritonavir[16], Figure 1a). Alkylation of the Weinreb amide derivatives of Boc protected (*L*)- and (*D*)-phenylalanine furnished homoallylic amino ketones (+)-**49** and (−)-***ent*-49** (Figure 3). Diastereoselective reduction of the ketones with $LiAl(O\textit{t}\text{-}Bu)_3H$ provided *anti* amino alcohols (−)-**50** and (+)-***ent*-50** and Alpine hydride gave *syn* amino alcohols (−)-**51** and (+)-***ent*-51**.[21] Installation of the *N*-tosyl carbamate was followed by stereodivergent allylic C—H amination using either Pd(II)/(±)-MeO-SOX/or Pd(II)/(±)CF_3-SOX catalysis. In all cases examined, Pd(II)/(±)-MeO-SOX amination afforded the *anti*-oxazinanone and Pd(II)/(±)-CF_3-SOX the *syn*-oxazinanone with preparative yields of the major diastereomer (54–73%, **52–55a, 52–55b**). This streamlined route to all possible stereoisomers is competitive with previous routes that use pre-oxidized intermediates (α-amino-γ-lactone,[22] enaminone,[15] epoxides,[23] etc.).

We first examined if the preference to form the more stable *anti*-heterocycle[5,6,10] originates from C—H amination or in an off-cycle Pd reaction. Pd(II)/SOX-catalyzed allylic C—H functionalization proceeds via heterolytic allylic C—H cleavage to afford a cationic π-allylPd(SOX) intermediate[9] that is subject to rapid π-σ-π isomerization[8a] (Figure 4a). The later indicates that C—N bond formation is the stereo-determining step in C—H amination. Evaluation of the diastereometric excess of $Pd(OAc)_2$/(±)-MeO-SOX/2,5-DMBQ reaction over time shows that it initially generates the *syn*-isomer with the *anti*-isomer becoming

favored after four hours when the reaction is at ca. 35% total yield (Figure 4b, See Supporting Information for full reaction profile). In contrast, the $Pd(OAc)_2$/(±)-CF_3-SOX/BQ reaction profile shows no change in *syn*-stereoselectivity (Figure 4b). This data suggests that under both catalytic systems, the *syn*-oxazinanone is the preferred kinetic product of C—H amination and that a Pd(0)-isomerization to the thermody-namically favored *anti*-oxazinanone[5,6,10,24] occurs for the (±)-MeO-SOX but not for the (±)-CF_3-SOX system.

We hypothesized that the Pd(0)-catalyzed isomerizatioin may be more effectively promoted by the electron rich (±)-MeO-SOX than the electron deficient (±)-CF_3-SOX ligand. To test the ligand effect on Pd(0)-isomerization, pure *syn*-oxazinanone (±)-**1b** was exposed to $Pd_2(dba)_3$ in the presence of both (±)-MeO-SOX and/(±)-CF_3-SOX. Evaluation of the initial rates of *anti*-oxazinanone (±)-**1a** formation showed that $Pd_2(dba)_3$/(±)-MeO-SOX is ca. four times faster than $Pd_2(dba)_3$/(±)-CF_3-SOX in promoting isomerization from the *syn*- to the *anti*-oxazinanone (Figure 4c). Whereas no isomerization of *syn*-oxazinanone (±)-**1b** occurs without ligand, phosphine ligands have been reported to promote this isomerization with Pd(0) under anaerobic condition.[5,24]

We additionally hypothesized that the Pd(0)-catalyzed isomerization may be more effective with the sterically bulky 2,5-DMBQ than with BQ oxidant. The $Pd(OAc)_2$/(±)-MeO-SOX/ 2,5-DMBQ reaction was evaluated in the presence of 10% *syn*-oxazinanone (±)-**1b** (Figure 4d). Remarkably, *syn*-**1b** at low concentrations is competitive with suprastoichiometric 2,5 DMBQ in re-acting with Pd(0) as evidenced by its isomerization to favor *anti*-**1a** in comparable diastereomeric ratio to that observed under standard catalytic conditions (Figure 4d, entry 1, Table 1, entry 4). This suggests that the Pd(0) species is relatively long-lived under these conditions due to sluggish reactivity with the sterically hindered quinone. Supporting this hypothesis, when BQ oxidant is used, the reaction favors formation of *syn*-**42** and *syn*-**1b** does not undergo isomerization (entry 2). In $Pd(OAc)_2$/(±)-CF_3-SOX catalysis, the use of 2,5 DMBQ erodes the *syn*:*anti* ratio under the reaction conditions in both product formation and in isomerization of *syn*-oxazinanone (±)-**1b**, but does not turn it over to favor the *anti*-product (entry 3,4). Collectively, the pairing of an electron rich SOX ligand with a sterically hindered quinone oxidant promotes Pd(0) opening of the *syn*-oxazinanone to enabled the first *anti*-selective allylic C—H amination. Alternatively, the Pd(0)-isomerization path-way can be attenuated to preserve the kinetic *syn*-oxazinanone product by using an electron deficient SOX ligand with an unhindered quinone oxidant.

We report a general method for stereodivergent synthesis of both *anti*- and *syn*-1,3 amino alcohol motifs via Pd(II)/SOX catalysis. The diastereoselectivity is tunable via the combination of SOX ligand and quinone oxidant. Mechanistic studies indicate that both Pd(II)/(±)-MeO-SOX and Pd(II)/(±)-CF_3-SOX catalysis promotes C—H amination to the kinetic *syn*-oxazinanone whereas Pd(0)/(±)-MeO-SOX using sterically hindered 2,5 DMBQ oxidant can promote isomerization of the carbamate heterocycle to the thermodynamic *anti*-isomer. The SOX ligand's capacity for supporting concurrent Pd(II) and Pd(0) processes is notable and will be the topic of further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS:

Financial support NIGMS MIRA (R35 GM122525). We thank R. Quevedo for repeating our experimental procedure in Table 2, **25**.

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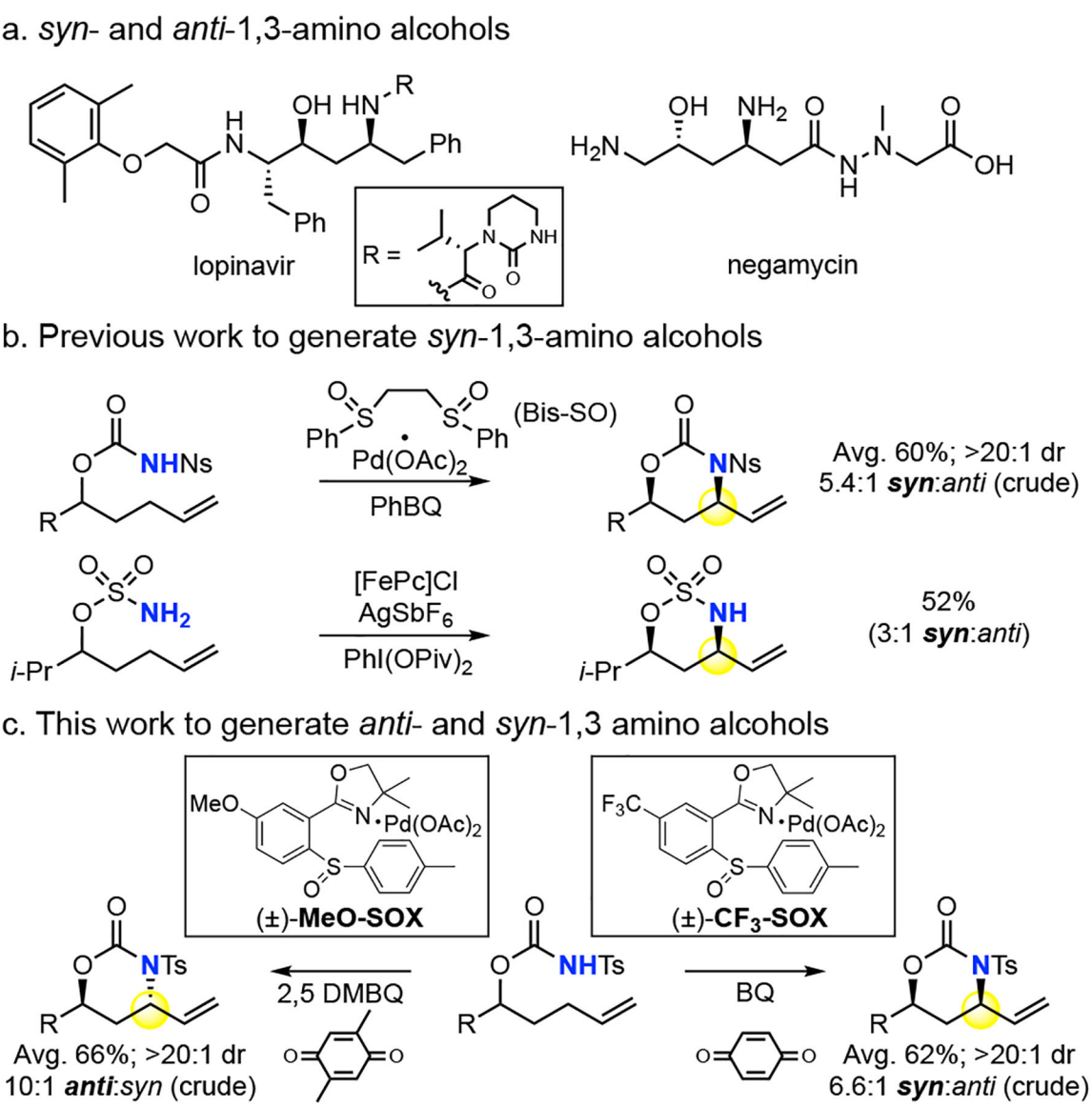


Figure 1.
C—H aminations for 1,3 amino alcohol motifs

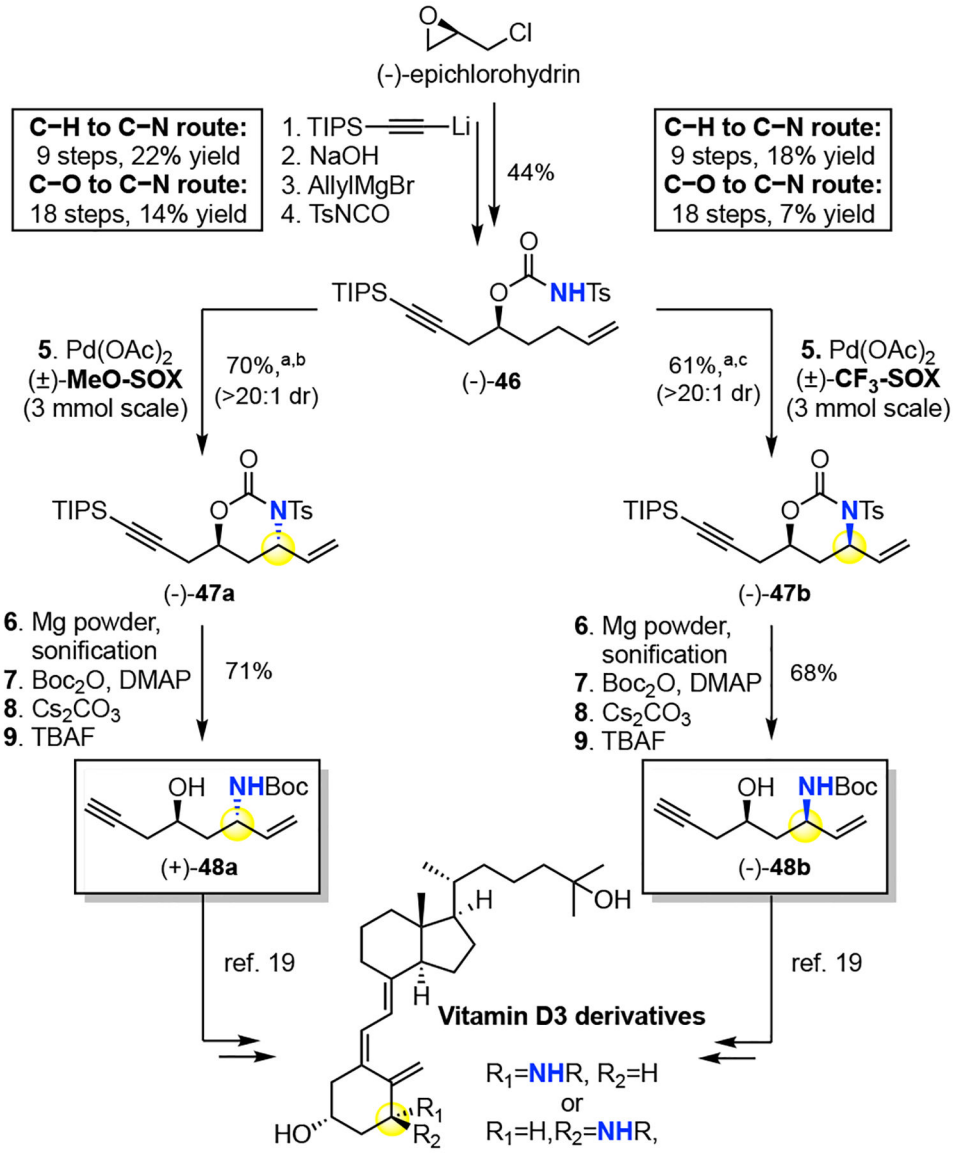


Figure 2.

Streamlining synthesis.

[a]Isolated yield(>20:1 dr) over 2 runs. Crude yield and dr determined by ^{1}H NMR:

[b]78%,19:1 dr. [c]81%, 4.1:1 dr.

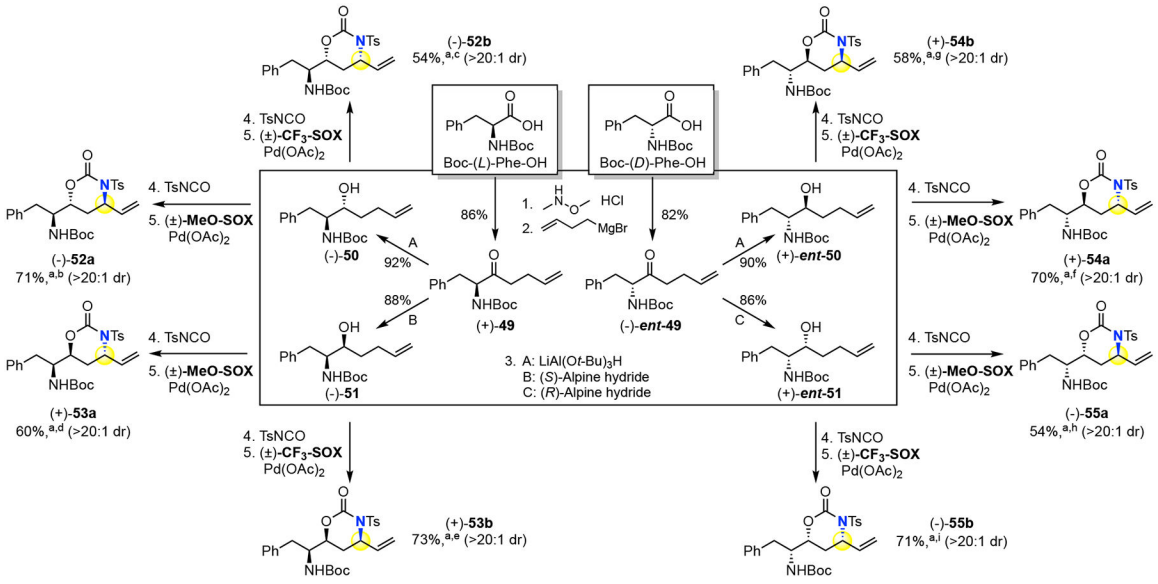
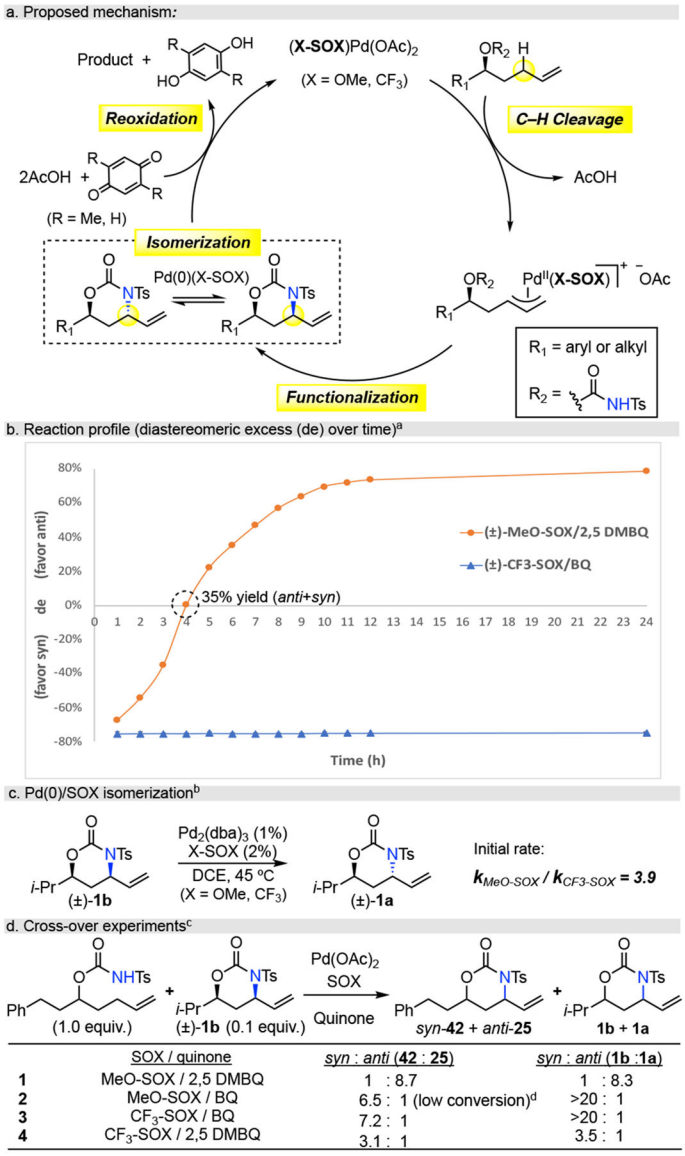


Figure 3.

Stereodivergent synthesis of diamino alcohol motifs.

[a]Isolated yield of major diastereomer (>20:1 dr) over two steps. Crude yield and dr determined by ^{1}H NMR: [b]89%, 9.1: dr. [c]68%, 6.5:1 dr. [d]85%, 3.3:1 dr. [e]86%, 13:1 dr. [f]84%, 9.3:1. [g]72%, 7.4:1 dr. [h]79% 3.5:1 dr. [i]82%, 14:1 dr.



	SOX / quinone	*syn* : *anti* (**42** : **25**)	*syn* : *anti* (**1b** :**1a**)
1	MeO-SOX / 2,5 DMBQ	1 : 8.7	1 : 8.3
2	MeO-SOX / BQ	6.5 : 1 (low conversion)[d]	>20 : 1
3	CF_3-SOX / BQ	7.2 : 1	>20 : 1
4	CF_3-SOX / 2,5 DMBQ	3.1 : 1	3.5 : 1

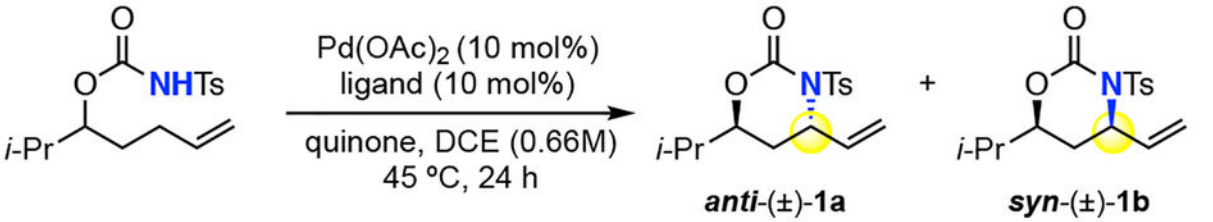
Figure 4.

Mechanistic studies

[a]de = ((*anti*−*syn*)/(*anti*+*syn*)×100)% [b]No isomerization observed without SOX ligand. [c]dr determined by HPLC. [d]BQ inhibits Pd(II)/MeO-SOX catalysis, also see Table 1, entry 5.

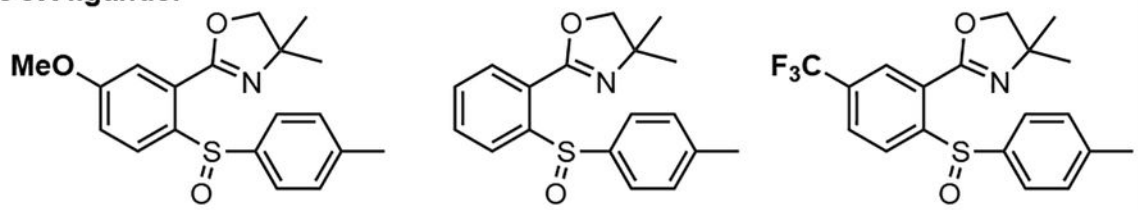
Table 1.

Reaction Development



Entry	Ligand	Quinone	Yield % (anti:syn)[a]	Yield % (isolated)[b]
1[c]	Bis-SO	Ph-BQ (2.0 eq.)	40 (1:4.7)	29 (syn)
2	(±)-MeO-SOX	Ph-BQ (2.0 eq.)	<5%	-
3	(±)-MeO-SOX	2,5 DMBQ (2.0 eq.)	88 (7.3:1)	72 (anti)
4	(±)-MeO-SOX[e,j]	2,5 DMBQ (1.2 eq.)	91 (7.8:1; 8.0:1[d])	78 (anti)
5	(±)-MeO-SOX	2,5 DMBQ + BQ[f]	12 (1:7.1[d])	8 (syn)
6	(±)-SOX	2,5 DMBQ (2.0 eq.)	86 (3.6:1)	61 (anti)
7	(±)-CF_3-SOX	2,5 DMBQ (2.0 eq.)	69 (1:4.3)	51 (syn)
8	(±)-CF_3-SOX	BQ (2.0 eq.)	76 (1:6.8)	60 (syn)
9	(±)-CF_3-SOX	BQ (1.6 eq.)	87 (1:6.7; 1:7.0[d])	71 (syn)
10	(±)-CF_3-SOX	BQ (1.2 eq.)	72 (1:6.7)	57 (syn)
11[g]	(±)-MeO-SOX	2,5 DMBQ (1.2 eq.)	88 (6.4:1)[h,j]	72 (anti)
12[g]	(±)-CF_3-SOX	BQ (1.6 eq.)	92 (1:4.0)[i,j]	69 (syn)
13[c]	Bis-SO	2,5 DMBQ (1.2 eq.)	60 (1:5.5)	46 (syn)
14[c]	Bis-SO	BQ (1.6 eq.)	53 (1:4.6)	38 (syn)

SOX ligands:



[a] Yield and dr determined by crude ^{1}H NMR.

[b] Isolated yield of pure diastereomer with >20:1 dr.

[c] Commercial 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate catalyst ($Pd(OAc)_2$/Bis-SO) used with additional 5% Bis-SO ligand.

[d] Determined by HPLC.

[e] Using enantiomeric pure (−)-(*S*)-MeO-SOX ligand, no significant kinetic resolution observed. See Scheme S9 in Supporting Information.

[f] 1.2 equiv 2.5 DMBQ and 0.1 equiv BQ was used.

[g] 10% $Ph_2P(O)OH$ was added; 6h.

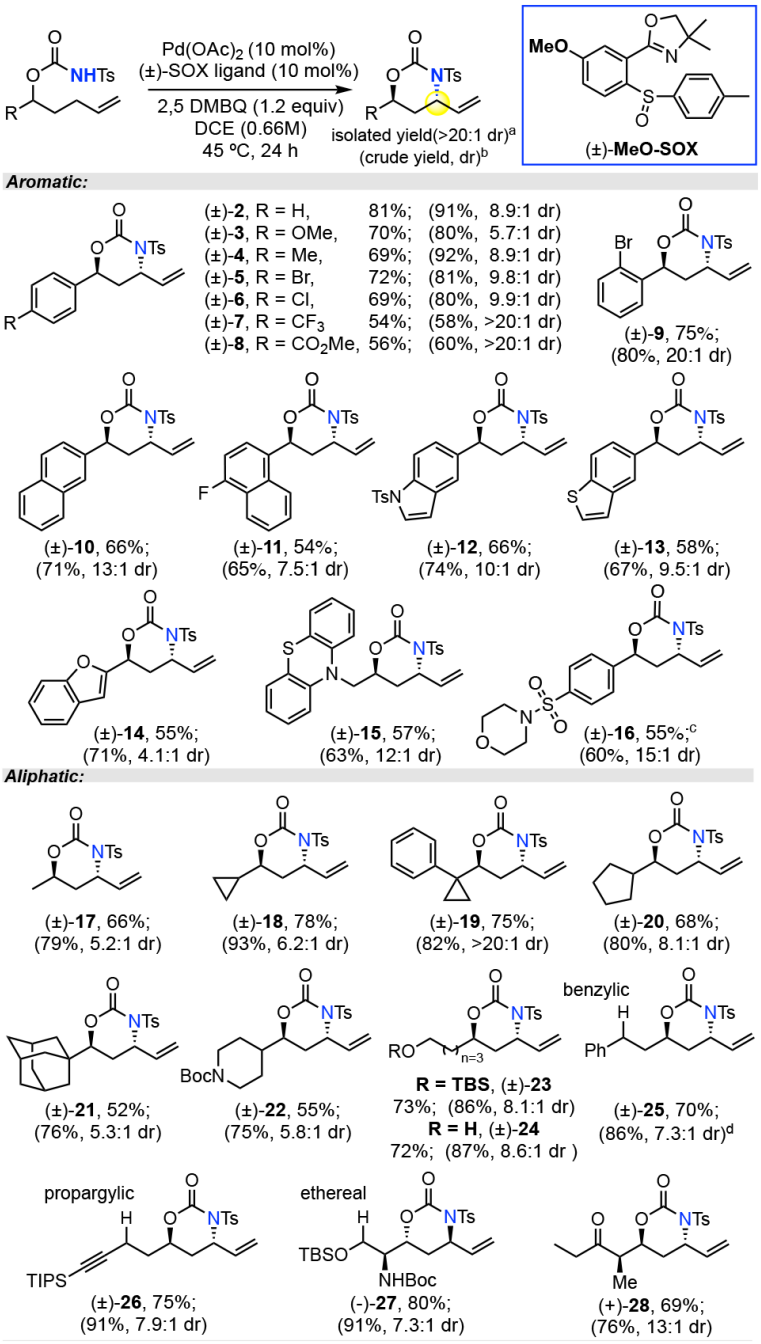
[h] No acid: 58% (2.0:1); isolated: 35% (*anti*).

[i] No acid: 80% (1:6.8); isolated: 67% (*syn*).

[j] See Supporting Information.

Table 2.

Scope for *anti*-1,3 Amino Alcohol Motifs



[a]Isolated yield of *anti* diastereomer (>20:1 dr) over 3 runs.

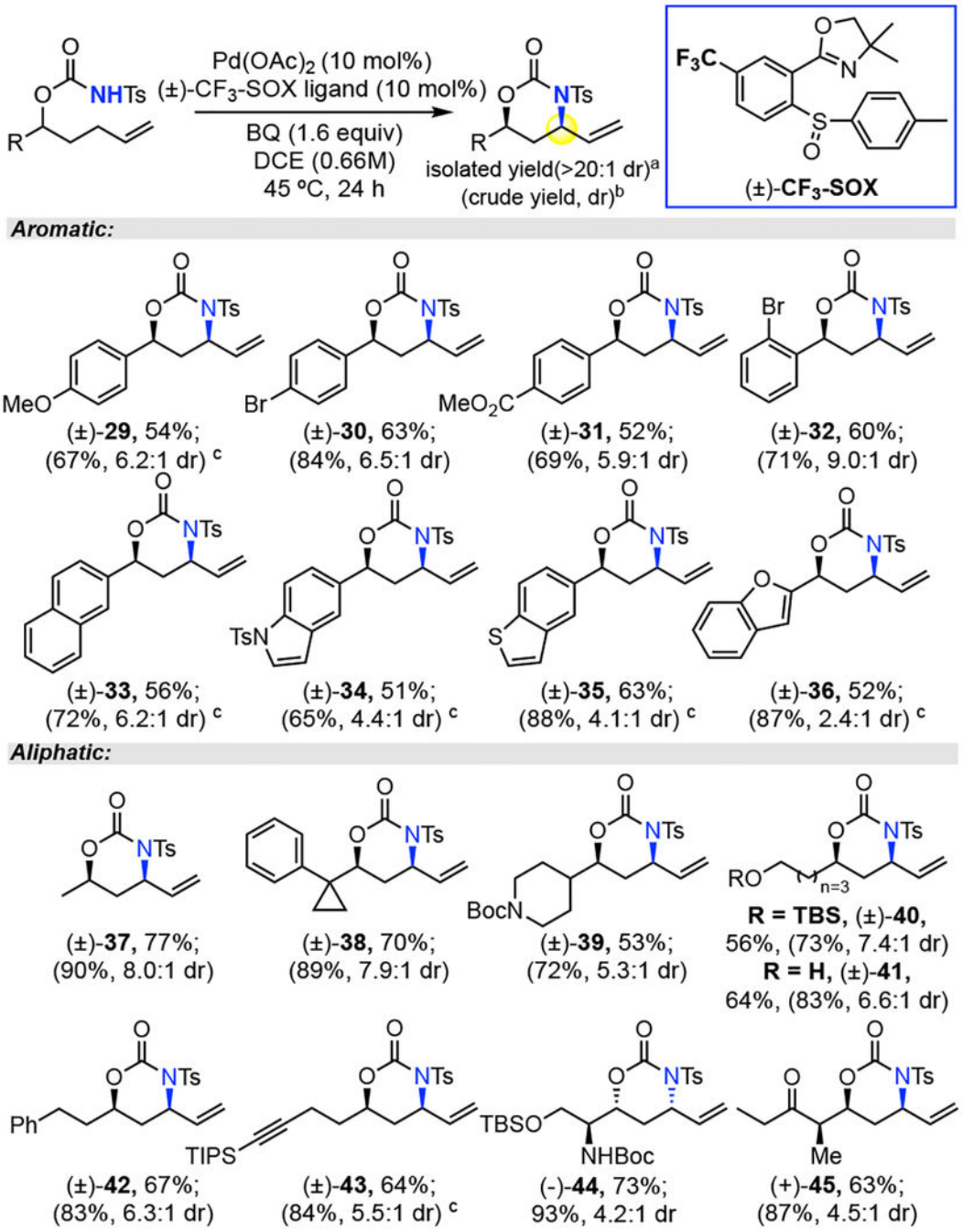
[b]Crude yield and dr determined by ^{1}HNMR.

[c] 10% $Ph_2P(O)OH$ added to increase reactivity.

[d] 8.6:1 dr by HPLC

Table 3.

Scope for *syn*-1,3 Amino Alcohol Motifs



[a] Isolated yield of *syn* diastereomer (>20:1 dr) over 3 runs.

[b] Crude yield and dr determined by ^{1}HNMR.

[c] 10% $Ph_2P(O)OH$ added to increase reactivity.