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Diastereoconvergent synthesis of *anti*-1,2-amino alcohols with N-containing quaternary stereocenters *via* selenium-catalyzed intermolecular C–H amination†

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We report a diastereoconvergent synthesis of *anti*-1,2-amino alcohols bearing N-containing quaternary stereocenters using an intermolecular direct C–H amination of homoallylic alcohol derivatives catalyzed by a phosphine selenide. Destruction of the allylic stereocenter during the selenium-catalyzed process allows selective formation of a single diastereomer of the product starting from any diastereomeric mixture of the starting homoallylic alcohol derivatives, eliminating the need for the often-challenging diastereoselective preparation of starting materials. Mechanistic studies show that the diastereoselectivity is controlled by a stereoelectronic effect (inside alkoxy effect) on the transition state of the final [2,3]-sigmatropic rearrangement, leading to the observed *anti* selectivity. The power of this protocol is further demonstrated on an extension to the synthesis of *syn*-1,4-amino alcohols from allylic alcohol derivatives, constituting a rare example of 1,4-stereoinduction.

Introduction

The prevalence of stereodefined 1,2- and 1,4-amino alcohol motifs in pharmaceuticals and asymmetric catalysts has generated a need for stereocontrolled synthesis of these structures.[1] Direct C–H functionalization is now a state-of-the-art strategy for the synthesis of 1,2-amino alcohols, allowing introduction of new C–N or C–O bonds without prefunctionalization at that carbon atom.[2] In this context, a variety of transition-metal catalyzed[3] and radical-mediated[4] C–H amination approaches to 1,2-amino alcohols have been reported. Although these methods provide efficient access to these compounds, little attention has been paid to the diastereoselectivity[1,3a–c,5] of these transformations, especially intermolecular aminations, or to the construction of quaternary heterosubstituted stereocenters.[6] Additionally, diastereoselective synthesis of 1,4-amino alcohols *via* direct C–H functionalization has not been reported.

We previously reported a metal-free allylic amination catalyzed by phosphine selenides that proceeds *via* a mechanism distinct from most other C–H functionalizations.[7] Initial ene reaction between an imidoselenium species cleaves the C–H bond and transposes the alkene, and a subsequent [2,3]-sigmatropic rearrangement delivers the new C–N bond (Scheme 1A). This "flip-flop" mechanism has several distinct properties that enable new modes of diastereocontrol without requiring intramolecular delivery of the nitrogen group: (i) C–H bond cleavage and C–N bond formation occur in separate steps, (ii) both steps are concerted and proceed suprafacially, (iii) initial activation of the C=C bond by Se takes place distal to the C–H bond being functionalized, and (iv) there is no allylic transposition of the intermediate, allowing either step to be stereodetermining depending on the substrate. Careful analysis of these key elements reveals that the presence of an oxygen-substituted stereocenter attached to either C1 or C3 of the allyl system would enable diastereoselective synthesis of 1,2- and 1,4-amino alcohols that are difficult to access using current C–H amination methods.

When the stereocenter is attached to C1 (Scheme 1B), the allylic stereocenter in starting material is destroyed in the ene reaction, and then formed anew in the stereodetermining [2,3]-sigmatropic rearrangement, thus enabling a diastereoconvergent process whereby a single diastereomer can be accessed from diastereomeric mixtures of the starting material. In contrast, the stereospecificity of most C–H nitrenoid insertion approaches[3d–o] would require diastereomerically pure starting materials that are often challenging to access[8] (Scheme 2A).

Second, the stereodetermining [2,3]-sigmatropic rearrangement now takes place in close proximity to the controlling stereocenter, allowing unprecedented diastereoselectivity *via* steric and/or electronic differentiation of the prochiral faces of the alkene (Scheme 1B). We hypothesized that an analog of the

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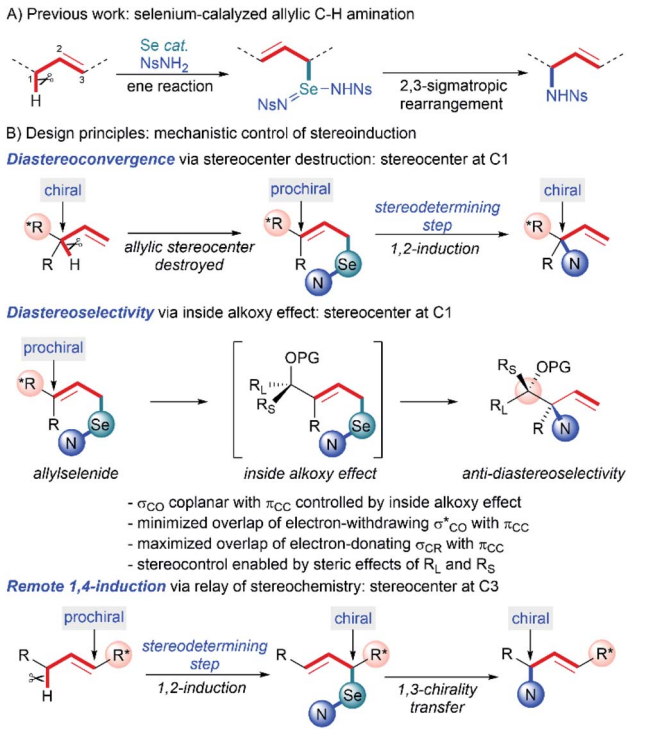
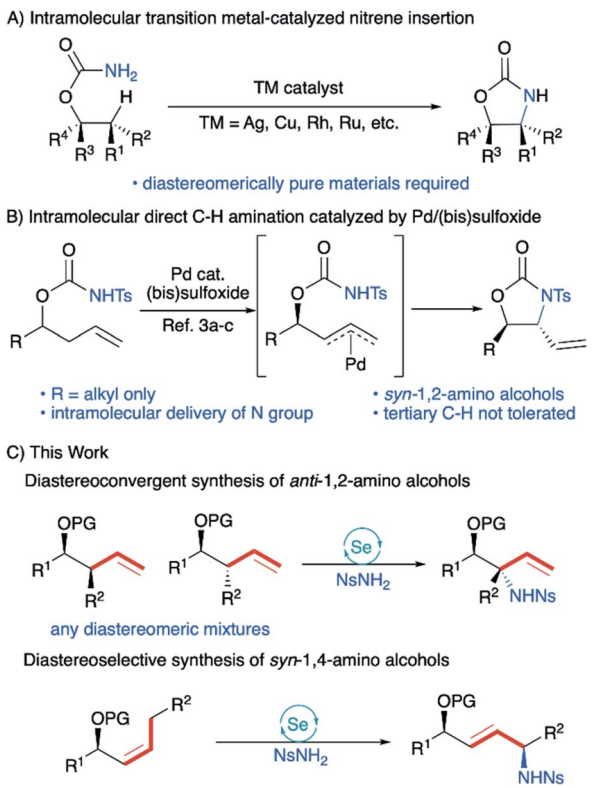


Scheme 1 Stereoselectivity analysis of selenium-catalyzed C–H amination.



Scheme 2 Diastereoselective synthesis of 1,2-amino alcohols *via* direct C–H functionalization.

"inside alkoxy effect"[9] might control the orientation of the C–O stereocenter in the transition state. Minimizing overlap of the σ^*_{C-O} orbital with the π system would stabilize the relatively electron-poor transition state, allowing delivery of the nitrogen to the less sterically hindered face and thereby giving high *anti* selectivity. This is complementary to the *syn* selectivity observed for known methods[3a–c,10] resulting from intramolecular delivery of a tethered nitrogen group (Scheme 2B).

Alternately, when the stereocenter is attached to C3, the stereodetermining step switches to the initial ene reaction. In this step, attack of the selenium now occurs alpha to the stereocenter, allowing diastereoselectivity *via* 1,2-induction (Scheme 1B). This stereochemistry is then selectively transferred to the distal center in the suprafacial [2,3]-rearrangement. In this scenario, initial 1,2-stereoselection is efficiently relayed into remote 1,4-induction. Remote stereoinduction of this type is difficult to achieve.[11]

Herein, we disclose a diastereoconvergent synthesis of *anti*-1,2-amino alcohols bearing N-containing quaternary stereocenters *via* intermolecular direct C–H amination of homoallylic alcohol derivatives under metal-free conditions. We show that high diastereoselectivity is observed in the formation of 1,2-amino alcohols without quaternary centers as well. We also demonstrate the application of this protocol to remote 1,4-induction, resulting in the synthesis of *syn*-1,4-amino alcohols from (*Z*)-allylic alcohol derivatives (Scheme 2C).

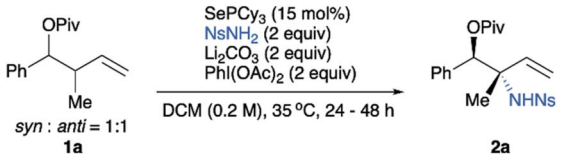
Results and discussion

To test the feasibility of this approach, we started with a 1 : 1 mixture of diastereomers of homoallylic ester **1a** as the model substrate. Our previously reported standard conditions for allylic amination gave the desired amination product, but in a disappointing 15% yield (Table 1, entry 1). Both conversion and overall mass recovery were low. Notably, we found that addition of an insoluble base is crucial to the success of the reaction. The role of this base is still unclear, but we hypothesize that trace acids formed under these conditions may partially decompose the starting material and/or product. A screen of basic additives revealed that Li_2CO_3 was optimal, giving product **2a** in 79% yield (Table 1, entry 2). Conversely, an acid additive lowers the conversion (Table 1, entry 5). Importantly, the starting 1 : 1 diastereomeric mixture in substrate **1a** was converted to a 10 : 1 mixture of diastereomeric products **2a**. The steric size of the protecting group has a minor effect on the diastereoselectivity, with acetate giving somewhat lower selectivity than pivalate (Table 1, entry 3).

Importantly, as hypothesized, the relative configuration of the starting material has no impact on the diastereoselectivity or yield of the reaction (Scheme 3). Even substrate **1a** enriched in the *anti*-diastereomer gives inversion of stereochemistry of the allylic stereocenter to give the same diastereomeric ratio with nearly identical yields. This highlights the advantage of this reaction in eliminating the need for preparing a single diastereomer of the substrate.

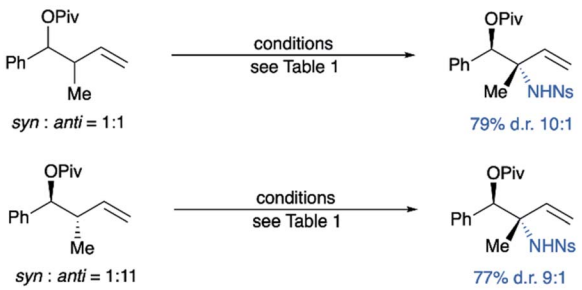
Next, we examined homoallylic alcohol substrates without substitution at the allylic position to see if our conditions would

Table 1 Optimization for *anti*-1,2-amino alcohols



Entry	Change	1a[a] (%)	Yield (%) d.r.[a]
1	Ref. 7a conditions	30	15
2	None	0	79 (10 : 1)
3	Ac instead of Piv	0	70 (6 : 1)
4	No Li_2CO_3	20	14
5	*p*-Nitrobenzoic acid instead of Li_2CO_3	42	15

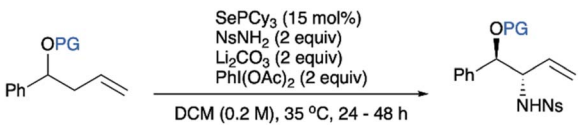
[a] Yields and diastereomeric ratio (d.r.) determined by ^{1}H NMR spectroscopy using 1,3-dinitrobenzene as internal standard.



Scheme 3 Diastereoconvergent formation of *anti*-1,2-amino alcohols.

also give stereoselectivity for these substrates. A screen of common alcohol protecting groups showed that most give good yields and diastereoselectivities, including acetyl (Ac), pivaloyl (Piv), benzyl (Bn), and *t*-butyldiphenylsilyl (TBDPS) (Table 2). For the best combination of yield and selectivity we chose to continue with pivaloyl protected substrates. Thus, we obtained an optimal unified protocol for amination of substrates both with and without allylic substituents.

Table 2 Screen of protecting groups



Entry	PG[b]	Yield[a] (%)	d.r.[a]
1	Ac	84	7 : 1
2	Piv	86	11 : 1
3	TBDPS	83	11 : 1
4	Bn	64	15 : 1

[a] Yields and diastereomeric ratio (d.r.) determined by ^{1}H NMR spectroscopy using 1,3-dinitrobenzene as internal standard. [b] PG = protecting group.

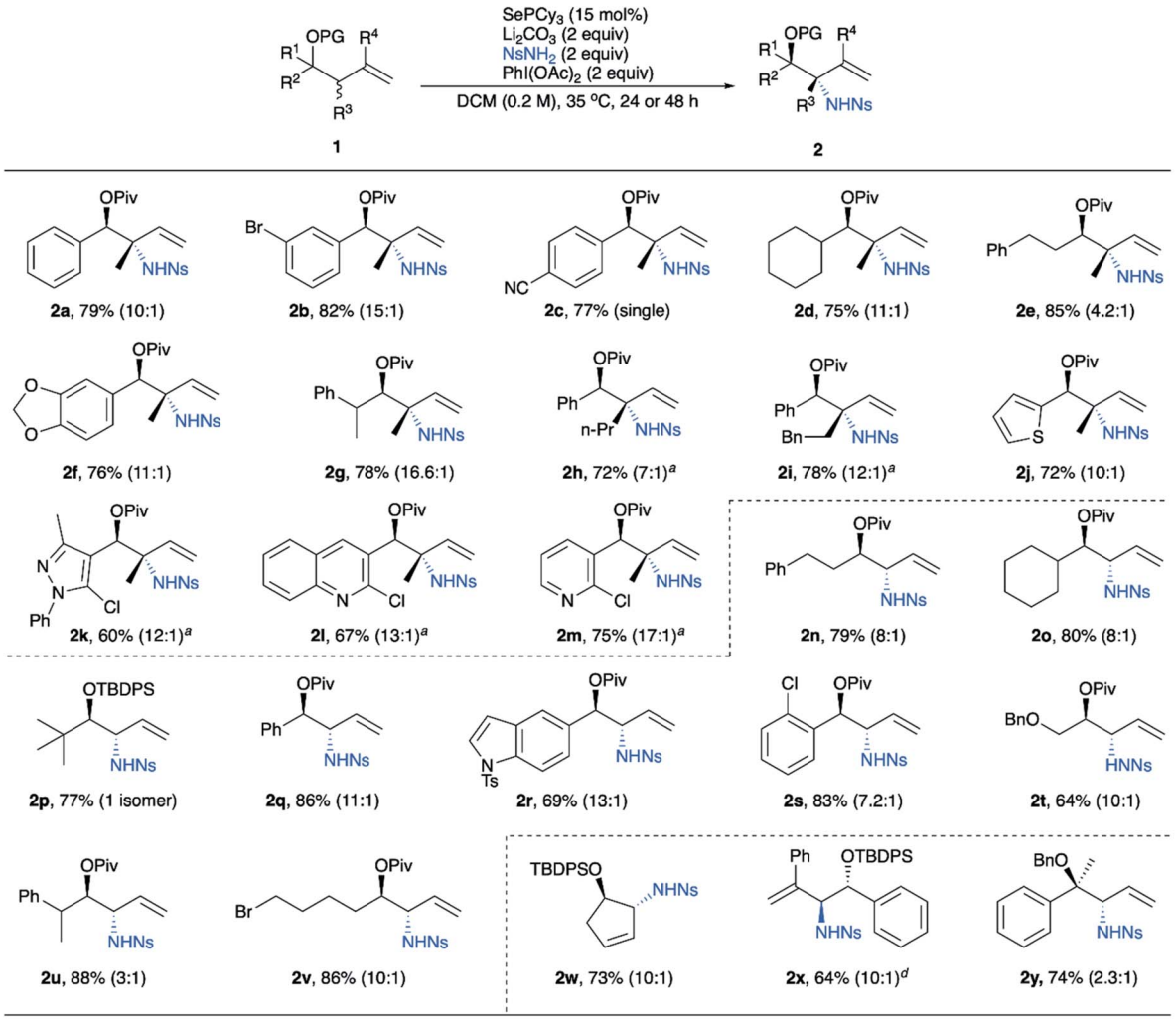
The optimized conditions were applied to a variety of homoallylic alcohol derivatives (Table 3). The reaction displays excellent compatibility with many functional groups including ester, alkyl halides, nitrile, aryl halides, ether, silyl ether, *etc.* Notably, our reaction tolerates a variety of heterocycles, especially nitrogen-containing heteroaromatics, including thiophene (**2j**), indole (**2r**), pyrazole (**2k**), quinoline (**2l**) and pyridine (**2m**). Additional substitution at the allylic position can be tolerated, giving aminated quaternary stereocenters in good yields and diastereoselectivities (**2h**, **2i**). The reaction also tolerates substituents with a wide range of steric demands at the homoallylic position, including primary, secondary, and tertiary alkyl groups, as well as aryl groups. Notably, diastereoselectivities are high even with minimal steric difference between the R group and OPiv group (**2n**, **2v**, **2t**), though diastereoselectivity increases as the homoallylic group becomes larger. These trends apply to both substrates without (**2n**, **2o**, **2q** and **2p**) and with allylic substituents (**2e**, **2a**, and **2d**). Furthermore, the reaction is also effective for 1,1-disubstituted alkenes (**2x**) and cyclic alkenes (**2w**).

We then investigated the diastereoselective synthesis of 1,4-amino alcohols starting from internal allylic alcohol derivatives. We started our exploration by subjecting (*E*)-alkene substrates **3a–d** to our previously published allylic amination conditions. Promisingly, the desired product was obtained in high yields, but no diastereoselectivity was observed using acetate as protecting group (Table 4, entry 1). A screen of protecting groups showed that larger groups gave only modest increases in diastereoselectivity (Table 4). We hypothesized that changing the alkene geometry to *Z* could improve the stereoselectivity by introducing 1,3-allylic strain,[12] thereby reducing the conformational flexibility at the allylic position (see Scheme 8A). To our delight, amination of (*Z*)-alkene **3e** gave a marked increase in diastereoselectivity to 4.9 : 1 (Table 4, entry 5). Though starting alkene **3e** had the *Z* configuration, product **4e** was found to be exclusively *E*, which was confirmed by observation of a coupling constant of 15.5 Hz between the alkene protons. The substrate scope for this 1,4-amino alcohol synthesis is given in Table 5. The reaction tolerates both primary and secondary groups on both sides of the alkene.

To probe the stereochemistry of the 1,2-amino alcohol products, **2p** and **2f** were deprotected and cyclized to **7** and **8**, respectively (Scheme 4). Comparison of the coupling constant in **7** to the known literature value[10b] reveals that the protons are cis, indicating that the reaction affords *anti*-amino alcohols when there are no allylic substituents. For substituted product **8**, an NOE was observed between the proton alpha to oxygen and the allylic methyl group, indicating that the major product bearing allylic substituents is also the *anti*-amino alcohol.

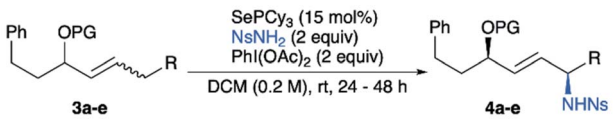
To explain the diastereoselectivity, a stereochemical model was built based on the proposed mechanism (Scheme 5), namely that the reaction proceeds *via* an ene reaction between a selenium bis(imide) and the alkene, followed by a [2,3]-sigmatropic rearrangement. The diastereoconvergence is explained by the fact that the allylic stereocenter is destroyed in the initial ene reaction, resulting in preferential formation of the *E* alkene intermediate from both diastereomers of the

Table 3 Substrate scope for *anti*-1,2-amino alcohols



[a] Reaction was performed using $SePCy_3$ (30 mol%) in DCE at 50 °C. [b] Isolated yields. [c] Diastereomeric ratio (d.r.) determined by ^1H NMR spectroscopy. [d] *It*BuSe was used as the catalyst. [e] PG = protecting group.

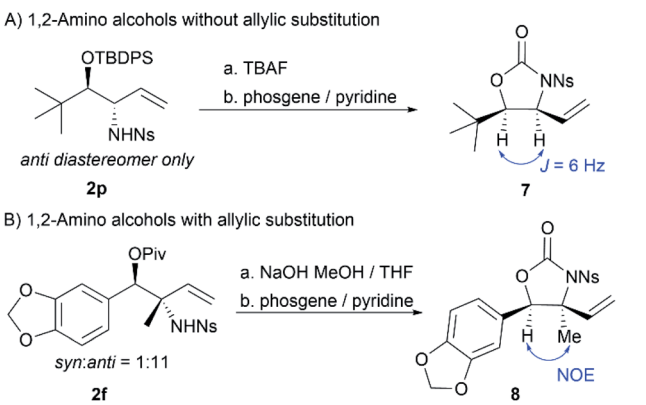
Table 4 Optimization for *syn*-1,4-amino alcohols



Entry	Substrate	PG[b] and R	*E* or *Z*	Yield[a] (%)	d.r.[a]
1	**3a**	Ac, Me	*E*	75	1 : 1
2	**3b**	Bz, Me	*E*	75	1.5 : 1
3	**3c**	TBDPS, Me	*E*	62	1.9 : 1
4	**3d**	Piv, Me	*E*	76	1.7 : 1
5	**3e**	Piv, *n*-Pr	*Z*	78	4.9 : 1

[a] Yields and diastereomeric ratio (d.r.) determined by ^1H NMR spectroscopy using 1,3-dinitrobenzene as internal standard. [b] PG = protecting group.

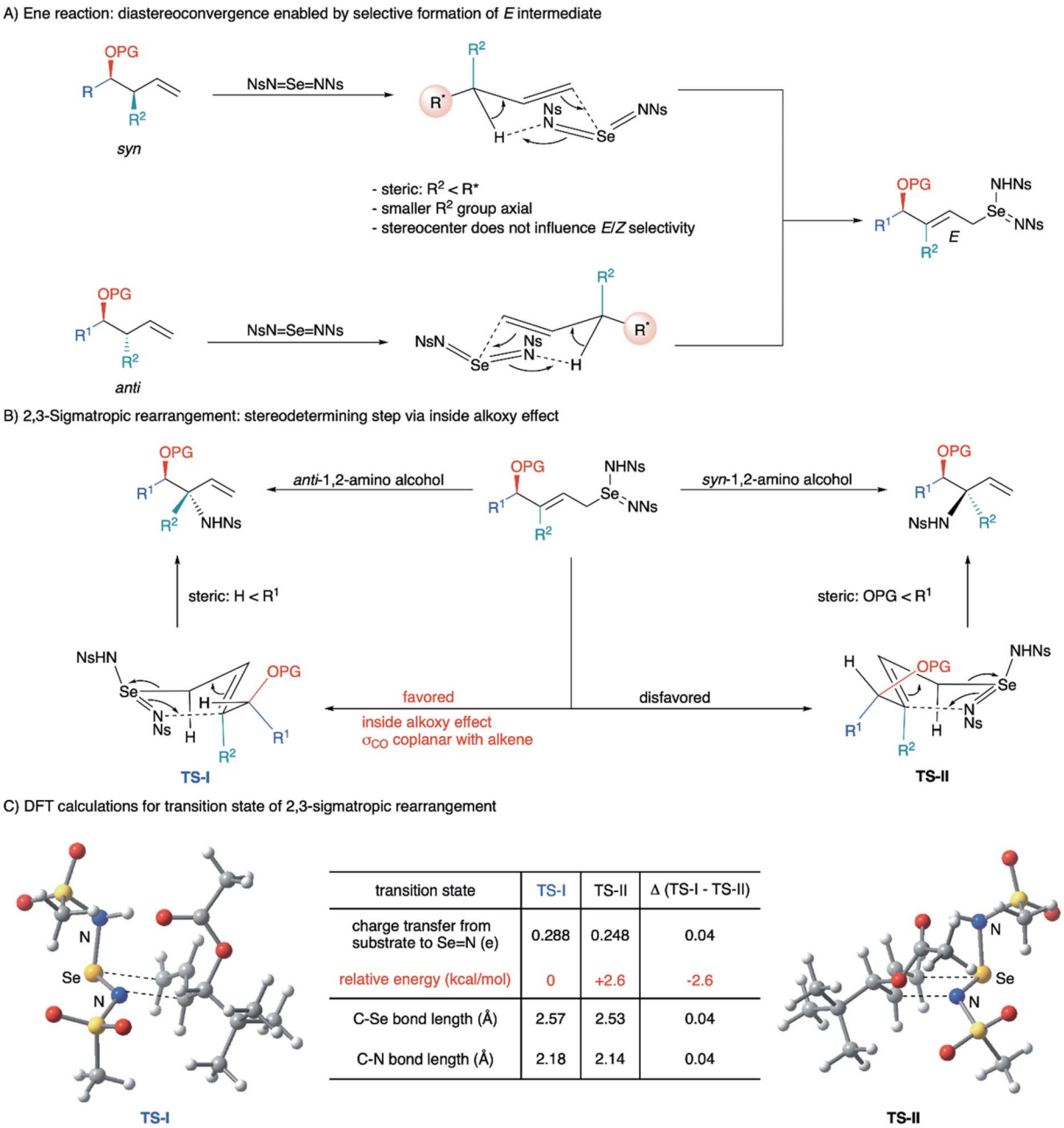
starting material (Scheme 5A). The allylic amine stereocenter is then formed in the [2,3]-sigmatropic rearrangement step. Importantly, the relative stereochemistry of the C–N and C–O



Scheme 4 Stereochemistry determination.

bonds is the same for both R^2 = H and R^2 = alkyl, indicating that the stereochemistry is being controlled only by the stereocenter attached to oxygen. To further test the importance of the inside alkoxy effect in controlling selectivity, ester **9** and homoallylic amine **11** were treated under our optimal reaction conditions, respectively (Scheme 6). Though the reactions proceeded in moderate yields, poor diastereoselectivity was observed, strongly supporting our hypothesis that the inside alkoxy effect[9] is the primary factor responsible for the high diastereoselectivity we observe for homoallylic alcohol derivatives.

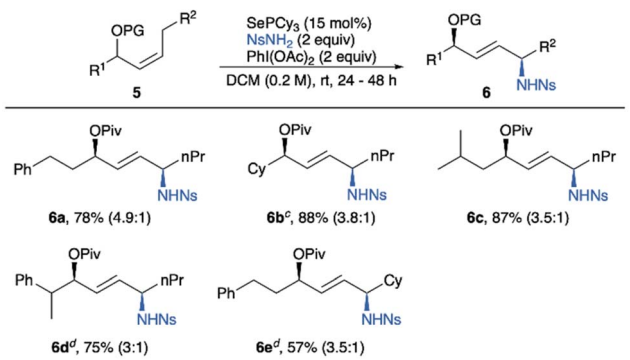
To gain further insights into the stereochemistry-determining [2,3]-sigmatropic rearrangement, a DFT computational study was performed (Scheme 5C).[13] Transition states for the [2,3]-sigmatropic rearrangement step leading to each diastereomeric product were found. The one leading to the *anti* product (TS-I) was lower in energy by 2.6 kcal mol^{-1} than the one leading to the *syn* product (TS-II), consistent with our experimental results. Careful examination of the two transition states did not reveal any obvious steric clashes. In both, approach of the nitrogen takes place on the opposite face of the bulky alkyl substituent. Interestingly, we observed that TS-I had



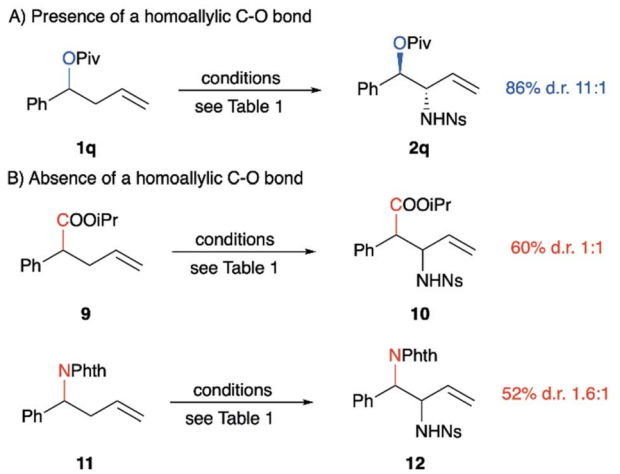
transition state	TS-I	TS-II	Δ (TS-I - TS-II)
charge transfer from substrate to Se=N (e)	0.288	0.248	0.04
relative energy (kcal/mol)	0	+2.6	-2.6
C-Se bond length (Å)	2.57	2.53	0.04
C-N bond length (Å)	2.18	2.14	0.04

Scheme 5 Stereochemical model for *anti*-1,2-amino alcohols.

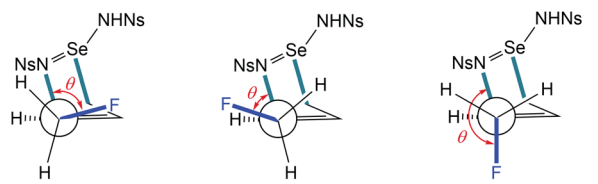
Table 5 Substrate scope for *syn*-1,4-amino alcohols



[a] Isolated yields. [b] Diastereomeric ratio (d.r.) determined by ^{1}H NMR spectroscopy. [c] Reaction time 70 h. [d] 30 mol% catalyst used.

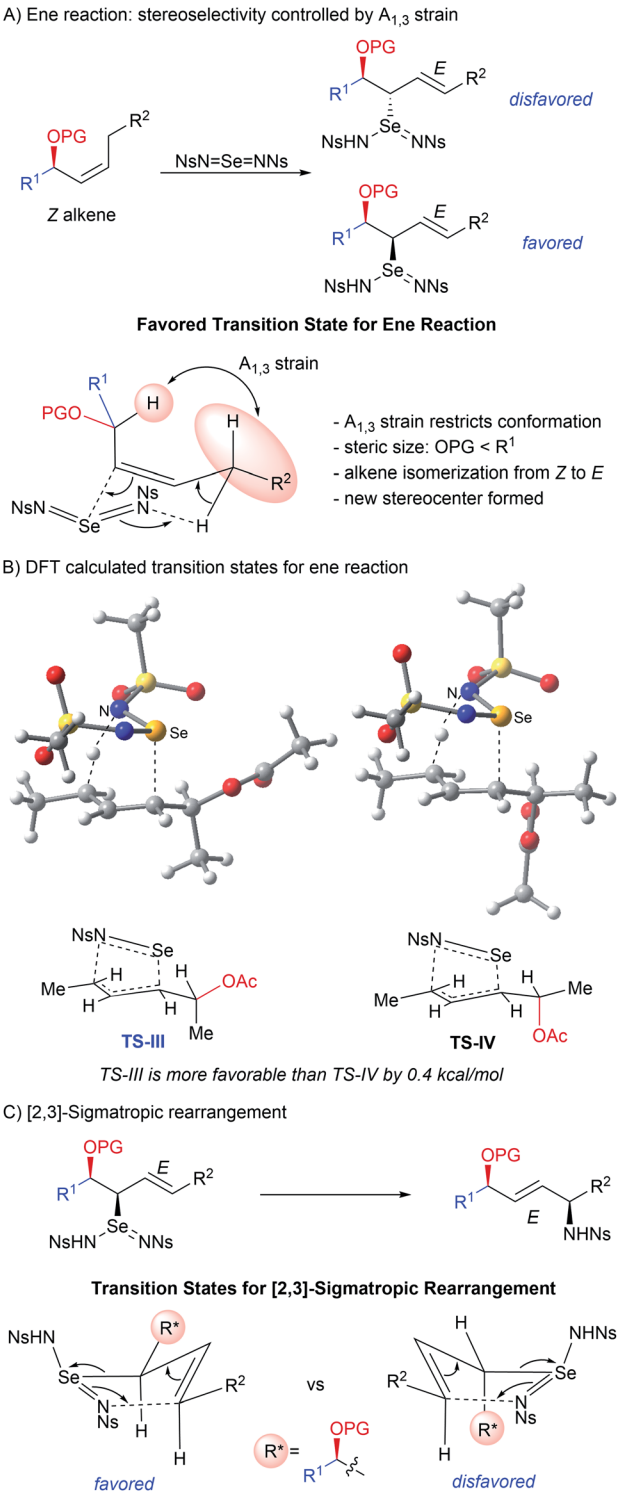


Scheme 6 Experimental evidence for inside alkoxy effect.



transition state	inside	outside	anti
θ(°)	-89	+64	+163
charge transfer from substrate to Se=N (e)	0.42	0.35	0.33
relative energy (kcal/mol)	0	0.6	1.8
C-Se bond length (Å)	2.68	2.60	2.62
C-N bond length (Å)	2.30	2.30	2.25
sum of bond lengths (Å)	4.98	4.90	4.87

Scheme 7 Computational study for homoallyl fluoride.



Scheme 8 Stereochemical model for *syn*-1,4-amino alcohols.

notably longer C–Se and C–N distances than TS-II ($\Delta \sim 0.04$ Å), indicating a looser transition state. This was accompanied by a greater degree of charge transfer from the allyl fragment to the selenium bis(imide) fragment ($\Delta q = 0.04$). These results are consistent with a stereoelectronic effect on the transition state similar to the known inside alkoxy effect[9] described for

cycloaddition reactions. NBO calculations show that the π system becomes electron-deficient during the rearrangement and that the orientation of the oxygen substituent affects the degree of charge transfer. In the most stable transition state (TS-I), the protected hydroxyl group is coplanar with the alkene, thereby minimizing the overlap of the electron-withdrawing σ^*_{CO} orbital with the π system. Simultaneously, this orientation maximizes the overlap of the electron-donating σ_{C-H} and σ_{C-C} bonds with the π system, enabling greater charge transfer and thereby stabilizing the transition state.

To isolate this stereoelectronic effect and more closely examine it, transition states for the [2,3]-sigmatropic rearrangement on a simple homoallyl fluoride substrate were found for three conformations about the C–C bond: anti, inside, and outside (Scheme 7). The inside fluoro transition state was again found to be the lowest in energy. As before, there is a clear correlation between the dihedral angle of the C–F bond and the amount of charge transfer from the substrate to the Se–N fragment, with the greatest charge transfer occurring in the inside fluoro transition state. Similarly, the transition states with more charge transfer were found to be looser, as indicated by the sum of the C–Se and C–N bond lengths, and had substantially more charge transfer to the selenium imide fragment. These calculated transition states confirm the importance of stereoelectronic control in the stereochemistry-determining [2,3]-sigmatropic rearrangement.

The stereoselectivity in the 1,4-amino alcohols was explored through DFT calculations using a similar stereochemical model to that developed for the *anti*-1,2-amino alcohols.[13] Unlike for 1,2-amino alcohols, however, the stereochemistry of this product is determined in the initial ene reaction. Avoidance of 1,3-allylic strain fixes the orientation of the allylic stereocenter as in Scheme 8A. DFT calculations reveal that the most stable transition state has the selenium bis(imide) approach from the same face of the alkene as the acyloxy group (TS-III), rather than adjacent to the alkyl group (TS-IV). Though small, the preference for TS-III over TS-IV of 0.4 kcal mol^{-1} is consistent with the relative steric size of these two groups and the observed diastereomeric ratio. The requirement for conformational restriction using 1,3-allylic strain explains the improved performance of *Z* alkenes over *E* alkenes.

In the subsequent [2,3]-sigmatropic rearrangement, orientation of the R* group in the equatorial position is favored, leading to the formation of the *syn*-1,4-amino alcohol bearing an *E* alkene as the major diastereomer (Scheme 8C). This is consistent with the observation that only *E* alkenes are formed, regardless of the initial configuration of the starting alkenes.

Conclusions

In summary, we have developed a diastereoconvergent synthesis of *anti*-1,2-amino alcohols bearing quaternary N-containing stereocenter *via* intermolecular direct allylic C–H amination catalyzed by phosphine selenides, complementary to existing approaches that give *syn*-1,2-amino alcohols. Experimental and computational studies reveal that the diastereoselectivity is controlled by a stereoelectronic effect similar to the inside alkoxy effect, in which the protected hydroxyl group avoids withdrawing electron density from the transition state of the [2,3]-sigmatropic rearrangement. The diastereoconvergent ene reaction step eliminates the need to prepare a single diastereomer of homoallylic alcohol derivatives to achieve high diastereoselectivity. We have also developed a synthesis of *syn*-1,4-amino alcohols *via* direct C–H amination, constituting a rare example of remote stereochemical induction in the preparation of these compounds.

Data availability

Data for this paper, including characterization data for all new compounds and structures and energies for all DFT computations, are provided in the ESI.†

Author contributions

T. Z. conducted all experiments. J. L. B. performed all DFT calculations. F. E. M. directed the research. T. Z. and F. E. M. wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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