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Studies Toward Improved Enantiocontrol in the Asymmetric Cu-Catalyzed Reductive Coupling of Ketones and Allenamides: 1,2-Aminoalcohol Synthesis

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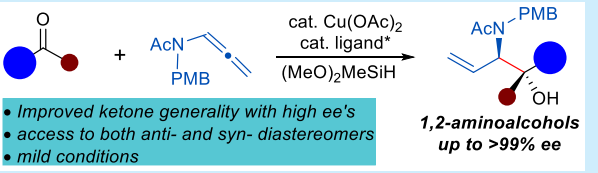
ABSTRACT: Herein, we report the development of an improved system for the Cu-catalyzed enantioselective reductive coupling of ketones and allenamides through the optimization of the allenamide to avoid an on-cycle rearrangement. High enantioselectivities could be obtained for a variety of ketones. Use of the acyclic allenamides described herein selectively generated *anti*-diastereomers in contrast to cyclic allenamides that were previously shown to favor the *syn*-form. A rationale for this change in diastereoselectivity is also presented.



Chiral vicinal aminoalcohols (**3**, Scheme 1A) are important motifs in organic chemistry due to their wide presence in nature, important biological activities, and application as potential pharmaceutical agents.[1] As a result, synthetic methodologies to access such compounds in an asymmetric fashion are warranted.[1b,d,2] One useful approach relies on the aminoallylation of carbonyl electrophiles from a *N*-substituted allyl organometallic (**1**) to arrive at **2** bearing an olefin functionality for further diversification to a variety of 1,2-aminoalcohol architectures in an efficient manner.[3] Surprisingly, this approach has been relatively underdeveloped until recently.[4−6]

Since the classical work of Barrett,[3] who generated preformed chiral *N*-substituted allylic boron reagents of **1** based on the Brown IPC-borane system, the Krische group elegantly applied their catalytic reductive coupling through hydrogen autotransfer[7] technology to the catalytic aminoallylation of aldehydes using Ru-[4b,d] or Ir-catalysis.[4a] In contrast, with ketone electrophiles it is typically more challenging to achieve highly enantioselective processes relative to aldehydes due to their decreased reactivity and the reduced steric differentiation between the two ketone substituents. Cu-catalyzed[5,6,8] reductive coupling methods have been shown to work well with ketones. The Malcolmson group has elegantly introduced 2-azadiene[6b,c] and 2-azatriene[6a] compounds as useful reagents for Cu-catalyzed reductive coupling reactions; however, these systems currently only allow access to saturated products when ketones are employed.[6b] Our group[5] has developed these processes using allenamides as precursors to **1** to access both 1,2- and 1,4-*N*,*O*-substituted organic compounds in a regio- and stereoselective manner. This led to the first enantioselective[5a] aminoallylation of ketones (Scheme 1 B). However, the ketone scope was limited in regards to enantioinduction due to a competitive on-cycle carbamate migration process (**8** → **9**) that leads to the erosion of enantioselectivity with certain ketones. This occurs because the allylcupration event is reversible, allowing for stereochemical erosion of **8** throughout the process. As a result, when the silylation of **8** to desired product *syn*-**5** is slow (k_1), significant amounts of product **6** were obtained, resulting in reduced yields and reduced enantioselectivities.[5a] To solve this issue, we hypothesized that improved ketone generality should be achieved if the carbamate migration step could be circumvented. Therefore, we began an investigation into the application of acyclic allenamides **11** whereby tuning of the R^3 substituent may be used to inhibit carbamate migration (Scheme 1C). Herein, we describe the results of these studies, leading to the development of an improved system for the enantioselective Cu-catalyzed aminoallylation of ketones in an *anti*-selective manner.[9]

In an effort to utilize an allenamide with the most convenient *N*-protective groups, we initially chose to investigate allenamide **11a** due to the high number of cleavage reactions available for both the *N*-Boc and *N*-Bn groups (Table 1).[10] Furthermore, we had hoped that the steric hindrance of the O^{t}Bu group of the *N*-Boc moiety (**11**, R^3 = O^{t}Bu) would hinder carbamate migration. Interestingly, the Walphos ligand family that was identified as optimal with cyclic allenamide **4** was ineffective with **11a** (entries 1 and 2, respectively). However, a survey of the Josiphos family (entries 3−5) identified Josiphos-002 (**J2**), which afforded the desired

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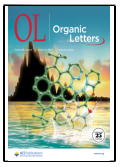

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Scheme 1. Enantioselective Aminoallylation

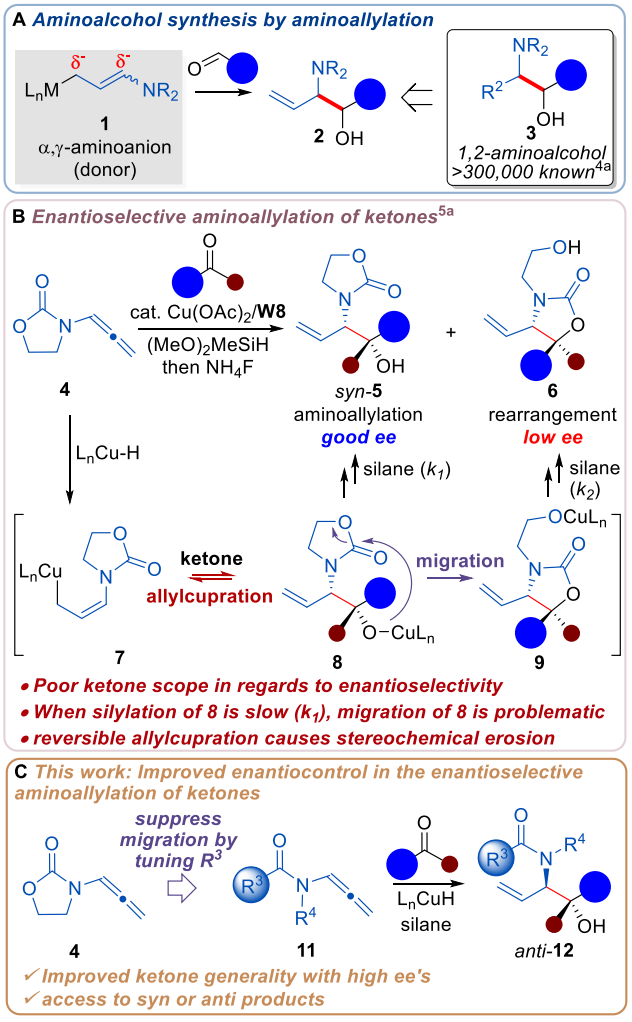
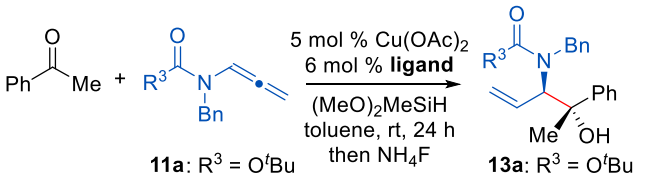


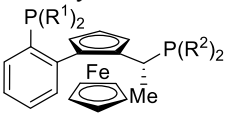
Table 1. Reaction Optimization[a]



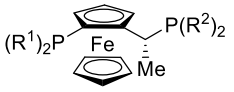
11a: R^3 = O^{t}Bu
11b: R^3 = Me
11c: R^3 = *i*-Pr

13a: R^3 = O^{t}Bu
13b: R^3 = Me
13c: R^3 = *i*-Pr

entry	ligand	11	% yield[b]	dr[c]	% ee[d]
1	**W8**	**11a**	10	2:>98	26[e]
2	**W3**	**11a**	45	45:55	20
3	**J1**	**11a**	47	43:57	86
4	**J2**	**11a**	76	51:49	94[j]
5	**J11**	**11a**	62	52:48	64
6[f]	**J2**	**11a**	81	54:46	92[k]
7[g]	**J2**	**11a**	81	58:42	90
8[h]	**J2**	**11a**	76	58:42	96
9[h,i]	**J2**	**11b**	87	90:10	94
10[h,i]	**J2**	**11c**	68	79:21	74



W3: R^1 = Ph, R^2 = Cy
W8: R^1 = Cy
R^2 = 3,5-$(CF_3)_2$-C_6H_4



J1: R^1 = Ph, R^2 = Cy
J2: R^1 = Ph, R^2 = *t*-Bu
J11: R^1 = 4-CF_3-C_6H_5

[a]Conditions are as follows: ketone (0.200 mmol), **11** (0.240 mmol), and $Me(MeO)_2SiH$ (0.400 mmol) in 0.50 mL of toluene; see the Supporting Information for details. [b]Combined yield of both diastereomers determined by quantitative ^{1}H NMR spectroscopy with dimethylfumarate as the standard. [c]*anti/syn* ratio determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture. [d]Value for the *anti*-diastereomer (**13a,b,c**) determined by HPLC. [e]Value of the *syn*-isomer. [f]THF was used as the solvent. [g]Dioxane was used as the solvent. [h]The reaction was run at 0 °C. [i]Dioxane/toluene (1:1) was used as the solvent. [j]30% ee for the minor diastereomer. [k]8% ee for the minor diastereomer.

product in high enantioselectivity, albeit with poor diastereocontrol (entry 4). Further optimization of reaction parameters (*e.g.*, solvent and temperature) employing **J2** did not lead to significant improvement in diastereocontrol (entries 6−8). At this point, the effect of the R^3 group of **11** on diastereoselectivity was next examined (entries 9 and 10). Maximum diastereoselectivity (90:10) was obtained using a small R^3 group (i.e., R^3 = CH_3, **11b**) and performing the reaction at 0 °C (entry 9) while still maintaining high enantioselectivity (94% ee).

The ketone scope in the Cu-catalyzed asymmetric aminoallylation reaction was next examined (Scheme 2). Allenamide **11d** was utilized due to the additional deprotection options available for the *N*-PMB group over the *N*-Bn group. Gratifyingly, of the 20 ketones examined, 19 generated products in high enantioselectivities (80−96% ee), demonstrating the improved generality of the current system over our previous report employing **4**.[5a] In general, diastereoselectivities were similar across all ketones examined. Both electron-deficient (**14b** and **14c**) and electron-rich (**14d−g**) aryl ketones having a *para*-substitution afforded high enantioselectivities. Such substitution patterns previously led to reduced enantioselectivities in reactions with allenamide **4**.[5a] Aryl ketones containing a *meta*-substitution (**14i−n**), including a free phenolic moiety (**14n**), were also equally effective, and heterocyclic ketones (**14o−r**) were also well tolerated. Problematic ketones included a symmetrical ketone that afforded low enantioinduction (**14t**), sterically demanding aryl ketones having an *ortho*-substitution that were unreactive, and propiophenone, which afforded a low yield and enantioselectivity.

Synthetic manipulation of the *N*-protective group on the aminoallylation products was investigated to confirm the absolute and relative stereochemistries of the reaction products (Scheme 3). The *N*-Ac group of **14a** could be cleaved to afford free secondary amine **15** using LAB.[11] From **15**, inversion of the carbinol stereocenter could be achieved by Boc-protection, followed by a known internal substitution of the hydroxyl group through neighboring-group participation using $SOCl_2$ activation.[12] This afforded inverted carbamate **17** that was compared to the same compound prepared from authentic material[10] reported in the literature. Conversion of **15** to **16** (*i.e.*, the opposite diastereomer of **17**) through expected retention was also performed as a control. Notably, this dichotomy allows for access to either diastereomer of the vicinal aminoalcohol surrogate using the described methodology.

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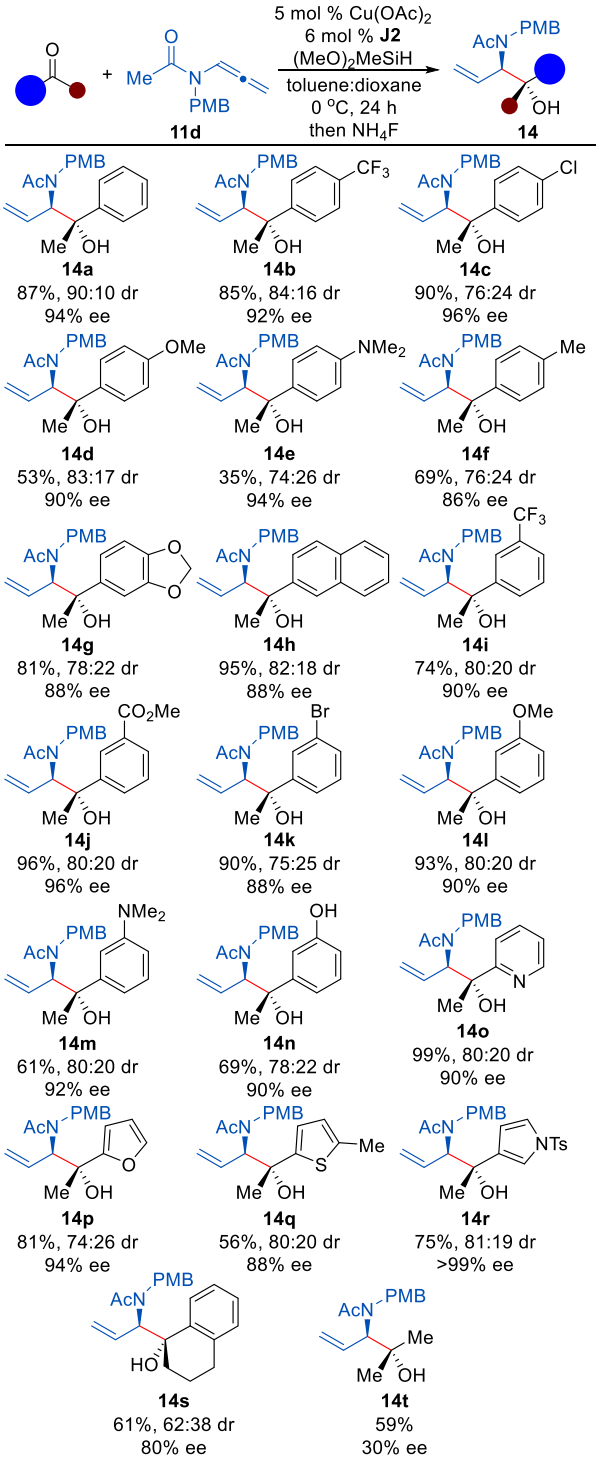
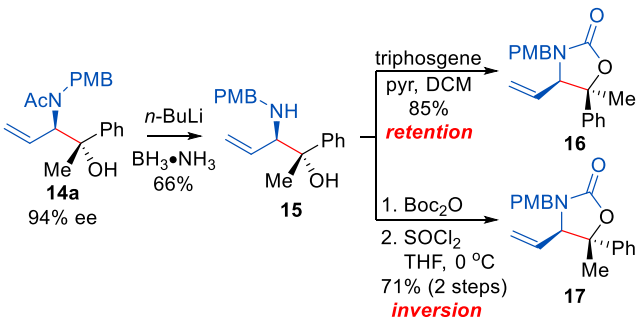
Scheme 2. Ketone Scope[a]



[a]The reaction utilizes 0.20 mmol ketone, see the Supporting Information. ee represents the value of the major (*anti*) diastereomer.

Scheme 3. Protecting Group Removal



The nature of the diastereodivergency obtained in these reactions based on the *N*-substituents of the allenamide warrants further discussion. While reactions employing cyclic carbonate-derived allenamides (e.g., **4**) consistently provide high *syn*-diastereocontrol,[5] the acyclic carbamate- and amide-derived allenamides (**11**) investigated in this work typically favor the *anti*-diastereomer. A stereochemical model to rationalize these preferences in stereoselectivity based on the allenamide structure is given in Scheme 4. Considering that the Cu-catalyzed reductive coupling of dienes with both carbonyl[5,8d] and imine[5e] electrophiles has been established to proceed through chairlike Zimmerman−Traxler transition states under Curtin−Hammett kinetic control, formation of the *syn- vs anti*-diastereomers results as a function of the alkene geometry of the nucleophilic *N*-substituted Cu(*σ*-allyl) reagent.[13] For example, with cyclic carbonate **4** (Scheme 4A), the reaction of the (*E*)-Cu(*σ*-allyl) intermediate with a ketone through (*E*)-**CC-TS** leads to the formation of *anti*-**5**, whereas (*Z*)-Cu(*σ*-allyl) should afford *syn*-**5** through (*Z*)-**CC-TS**. Because reaction with **4** ultimately affords *syn*-selectivity, (*Z*)-**CC-TS** represents the lowest-energy pathway. While it is unclear when comparing (*Z*)-**CC-TS** and (*E*)-**CC-TS** why this may be the case, it is arguably more conducive to analyze the corresponding Newman projections, sighting down the C−C bond being formed (*i.e.*, (*Z*)-**CC-TS-N** *vs* (*E*)-**CC-TS-N**). This analysis clearly shows that the (*Z*)-**CC-TS-N** transition structure leading to the *syn*-isomer of the product is expected to be lower in energy due to a reduction in the number of gauche interactions in (*Z*)-**CC-TS-N** compared to (*E*)-**CC-TS-N**, since the gauche interaction between the oxazolidinone and the ketone carbonyl of (*Z*)-**CC-TS-N** is expected to be less severe than the oxazolidinone/R_s gauche interaction present in (*E*)-**CC-TS-N**.

Extending this analysis to allenamides bearing acyclic carbonates (**AC**, Scheme 4B), transition structure (*E*)-**AC-TS-N** is expected to afford *anti*-**12**, whereas the *syn*-form would occur through (*Z*)-**AC-TS-N**. Because acyclic-derived allenamides afford *anti*-selectivity, this implies that structure (*E*)-**AC-TS-N** is the preferred pathway over (*Z*)-**AC-TS-N**, which is counterintuitive because (*E*)-**AC-TS-N** may be expected to have increased steric strain over (*Z*)-**AC-TS-N** from the greater number of gauche interactions present. An explanation of this apparent paradox can be achieved when considering that Newman projections of (*Z*)-**CC-TS-N** and (*Z*)-**AC-TS-N** do not account for $A^{1,3}$ strain present in the (*Z*)-isomer of the reactive Cu(*σ*-allyl) nucleophile (*i.e.*, (*Z*)-**18** and (*Z*)-**19**). Previous studies of (*Z*)-substituted enamides have demonstrated that these structures are not planar and exist as "twisted" amides due to the presence of $A^{1,3}$ strain.[14] Therefore, the Cu(*σ*-allyl) nucleophiles generated from both cyclic and acyclic allenamides (*i.e.*, (*Z*)-**18** and (*Z*)-**19**, respectively) are proposed to be more consistent with the "twisted" forms (*Z*)-**18-T** and (*Z*)-**19-T**, respectively. As a result, the *syn*-diastereomer of product is more accurately predicted to occur through (*Z*)-**CC-TS-T** and (*Z*)-**AC-TS-T** for cyclic *vs* acyclic allenamides, respectively. Accordingly, for acyclic allenamides, the amide twist leads to steric shielding of

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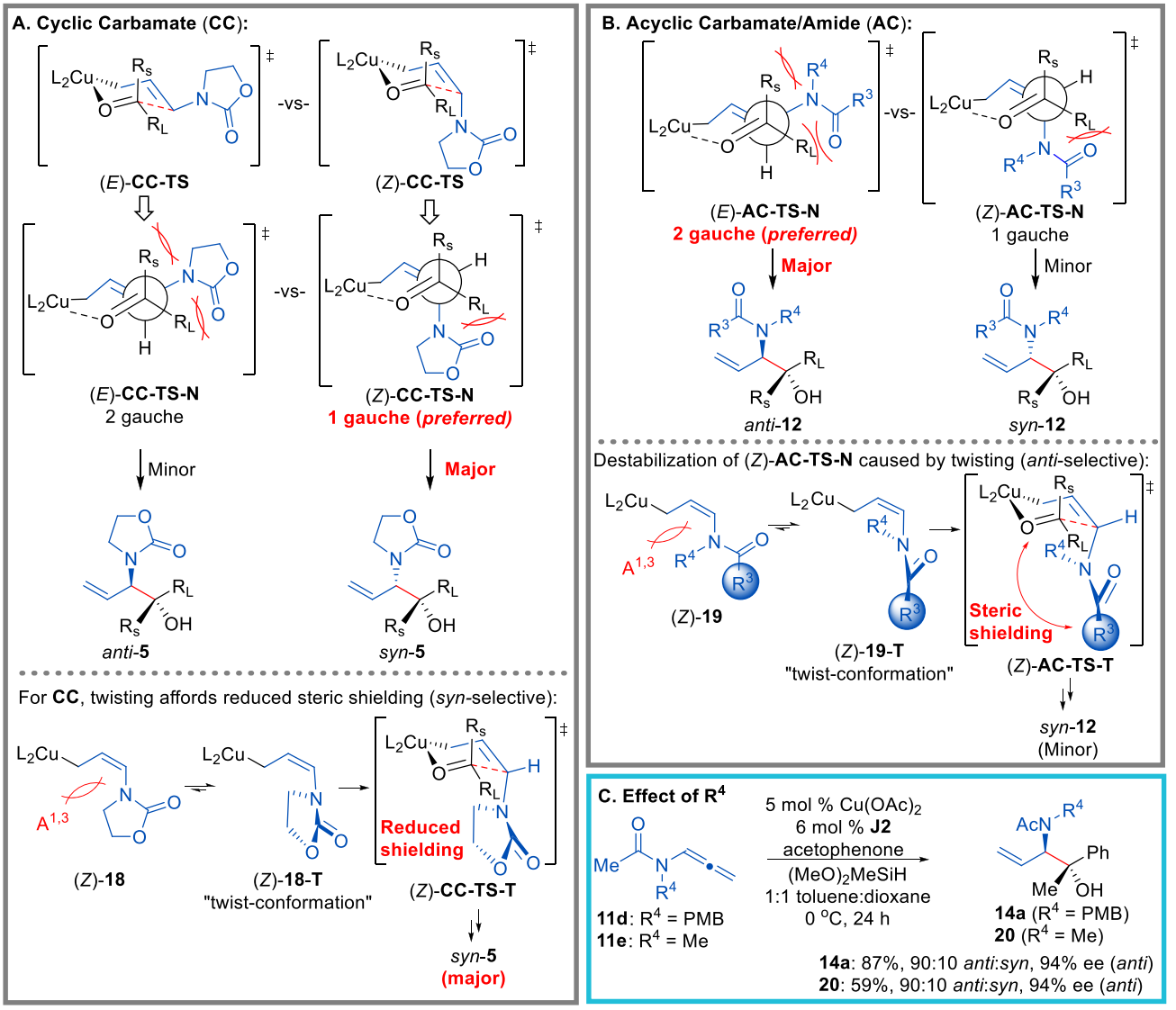
Scheme 4. Stereochemical Rationale



the π-face of the nucleophile along the ketone approach vector by the R^3-substituent (*i.e.*, (*Z*)-**AC-TS-T**) that destabilizes the transition structure, leading to the *syn*-isomer and allowing the process to be *anti*-selective through (*E*)-**AC-TS-N**. In contrast, for cyclic allenamides, twisting is still expected, but the steric shielding of the nucleophile π-face is substantially reduced relative to that in the acyclic analogues because the carbon substituents are locked in a ring and rotated away from the approaching ketone (*i.e.*, (*Z*)-**CC-TS-T**).

Further support for this proposed model can be observed in the effect of the R^3 substituent of **11**. For example, modest *anti*/*syn* selectivity was obtained when R^3 = O^{t}Bu (**13a**, 58:42, Table 1, entry 7) or *i*-Pr (**13c**, 79:21, Table 1, entry 10), but the selectivity improved to 90:10 when switching to a smaller R^3 group (*i.e.*, Me, **13b**, and **14a**). Presumably, the Me group is still large enough to block the ketone approach through (*Z*)-**AC-TS-T** but can further stabilize (*E*)-**AC-TS-N** due to a reduction in the gauche interaction penalty with the smaller Me-group over the bulkier *t*-BuO or *i*-Pr groups.[15] Along these lines, we also reasoned that further improvements in diastereoselectivity may be possible by reducing the gauche interactions of (*E*)-**AC-TS-T** by decreasing the steric size of the R^4 group. However, the reaction of acetophenone with **11d** (R^4 = PMB) or **11e** (R^4 = Me) afforded identical dr values (Scheme 4C). In this case, we propose that while (*E*)-**AC-TS-N** is likely stabilized by the reduction in gauche strain energy using R^4 = Me over PMB, the competing transition structure (*Z*)-**AC-TS-T** may also be stabilized, since the extent of amide twisting will be reduced due to a decrease in the $A^{1,3}$ strain of (*Z*)-**19** with R^4 = Me vs PMB.

In conclusion, we have reported an improved system for the Cu-catalyzed enantioselective aminoallylation of ketones affording important chiral vicinal aminoalcohol surrogates in excellent levels of diastereo- and enantioselectivity by tuning the allenamide structure to prevent an on-cycle carbamate migration. Ultimately, either diastereomer of the amino-allylation product can be accessed through post-*N*-protecting group manipulations, and a rationale for the switch in relative diastereocontrol when employing cyclic *vs* acyclic allenamide starting materials was described.

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■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c00157.

Experimental procedures, characterization data for all compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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