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Regio- and Enantioselective Synthesis of Trifluoromethyl-Substituted Homoallylic α-Tertiary NH_2-Amines by Reactions Facilitated by a Threonine-Based Boron-Containing Catalyst

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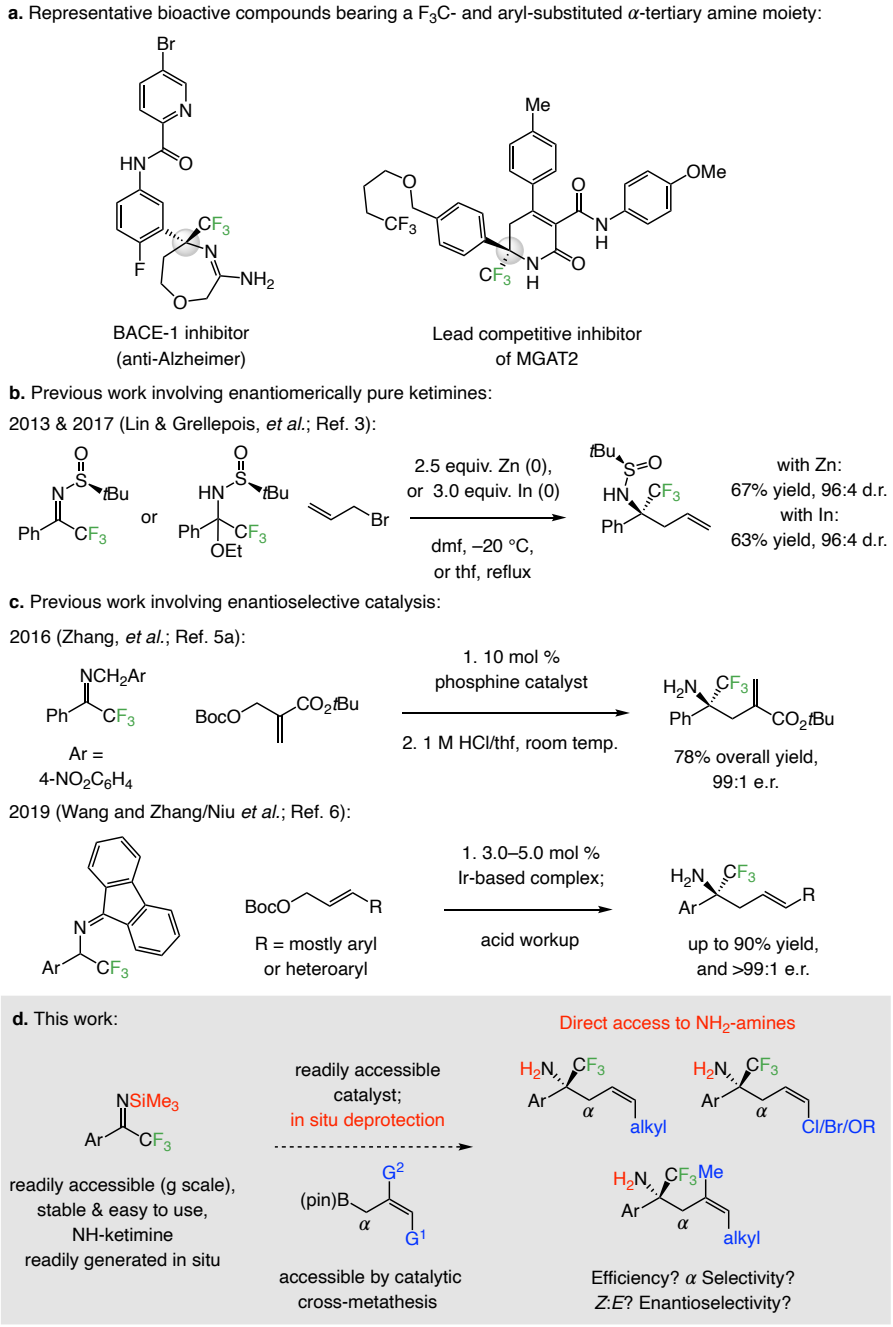
Dedicated to Professor Jean-Marie Lehn

Abstract: *A method for catalytic regio- and enantioselective synthesis of trifluoromethyl-substituted and aryl-, heteroaryl-, alkenyl-, and alkynyl-substituted homoallylic α-tertiary NH_2-amines is introduced. Easy-to-synthesize and robust N-silyl ketimines are converted to NH-ketimines in situ, which then react with a Z-allyl boronate. Transformations are promoted by a readily accessible L-threonine-derived aminophenol-based boryl catalyst, affording the desired products in up to 91% yield, >98:2 α:γ selectivity, >98:2 Z:E selectivity, and >99:1 enantiomeric ratio. A commercially available aminophenol may be used, and allyl boronates, which may contain an alkyl-, a chloro-, or a bromo-substituted Z-alkene, can either be purchased or prepared by catalytic stereoretentive cross-metathesis. What is more, Z-trisubstituted allyl boronates may be used. Various chemo-, regio-, and diastereoselective transformations of the α-tertiary homoallylic NH_2-amine products highlight the utility of the approach; this includes diastereo- and regioselective epoxide formation/trichloroacetic acid cleavage to generate differentiated diol derivatives.*

Introduction

Catalytic enantioselective transformations that furnish α-tertiary amines,[1,2] fragments found in many bioactive molecules (Scheme 1a), are small in number, rendering their development a compelling research objective. Strategies for preparation of α-tertiary homoallylic NH_2-amines with a trifluoromethyl and an aryl substituent are especially desirable, as the resulting products can be converted to a variety of organofluorine compounds that cannot be easily prepared otherwise in high diastereo- and enantioselectivity. Among the available

approaches, there are reactions of an enantiomerically pure *N-tert*-butylsulfinyl ketimine with an allylzinc or a costly allyl–In compound (Scheme 1b).[3,4] Two other strategies are catalytic enantioselective processes involving in situ generated allyl species and N-benzyl substrates (Scheme 1c).[5,6] Products either bear an alkene with an internal carboxylic ester unit[5] or an



Scheme 1. Bioactive compounds that contain a F_3C- and aryl-substituted α-tertiary amine moiety and methods that may be used to prepare them. Abbreviations = BACE-1: β-secretase-1; MGAT: monoacylglycerol acyltransferase.

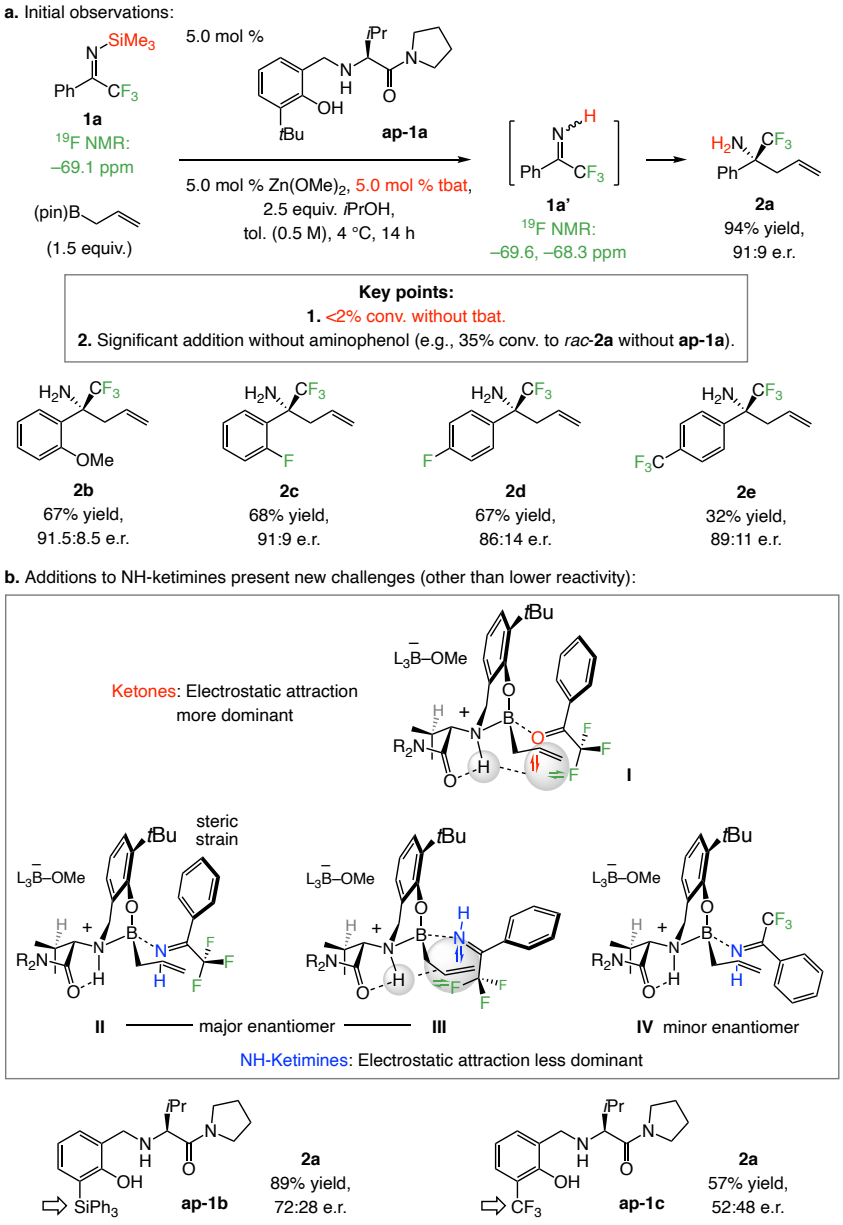
(*E*)-β-substituent.[6,7] These are significant advances no doubt, but the following issues remain unaddressed: 1) Direct formation of unprotected α-tertiary homoallylic amines would obviate the need for subsequent release of the NH_2-amine by acid treatment, which can be detrimental to the structural integrity of a sensitive benzylic C–N bond.[8] 2) Availability of catalysts that can be readily modified/optimized and do not require a costly and/or precious metal. 3) Regio- and diastereoselective product modification, a characteristic more easily accommodated with *Z*-homoallylic amine (vs. an *E*- or a monosubstituted olefin).[9]

A problem with directly accessing NH_2-amines is that F_3C-substituted NH-ketimines are unstable (moisture-sensitive).[10] We surmised that one might utilize N-protected ketimines that are readily available, robust, and can be converted to NH-ketimines in situ. We thus chose to investigate *N*-trimethylsilyl ketimines, stable entities accessible in multigram quantities by reactions between ketones and lithium bis(trimethylsilyl)amide (1.5 h, 50–95% yield) [11] in sufficiently high purity for *N*-trimethylsilyl ketimines to be directly usable (no purification). Whether in situ NH-ketimine formation would occur readily or the minimally electrophilic NH-ketimines would react efficiently and enantioselectively, we did not know. As catalysts, we opted for aminophenol-based boryl systems, easily to prepare and modifiable entities that at the time had been used for enantioselective additions to aldimines,[12] ketones, [13] and aldehydes,[14] but not the far less reactive NH-ketimines.

Results and Discussion

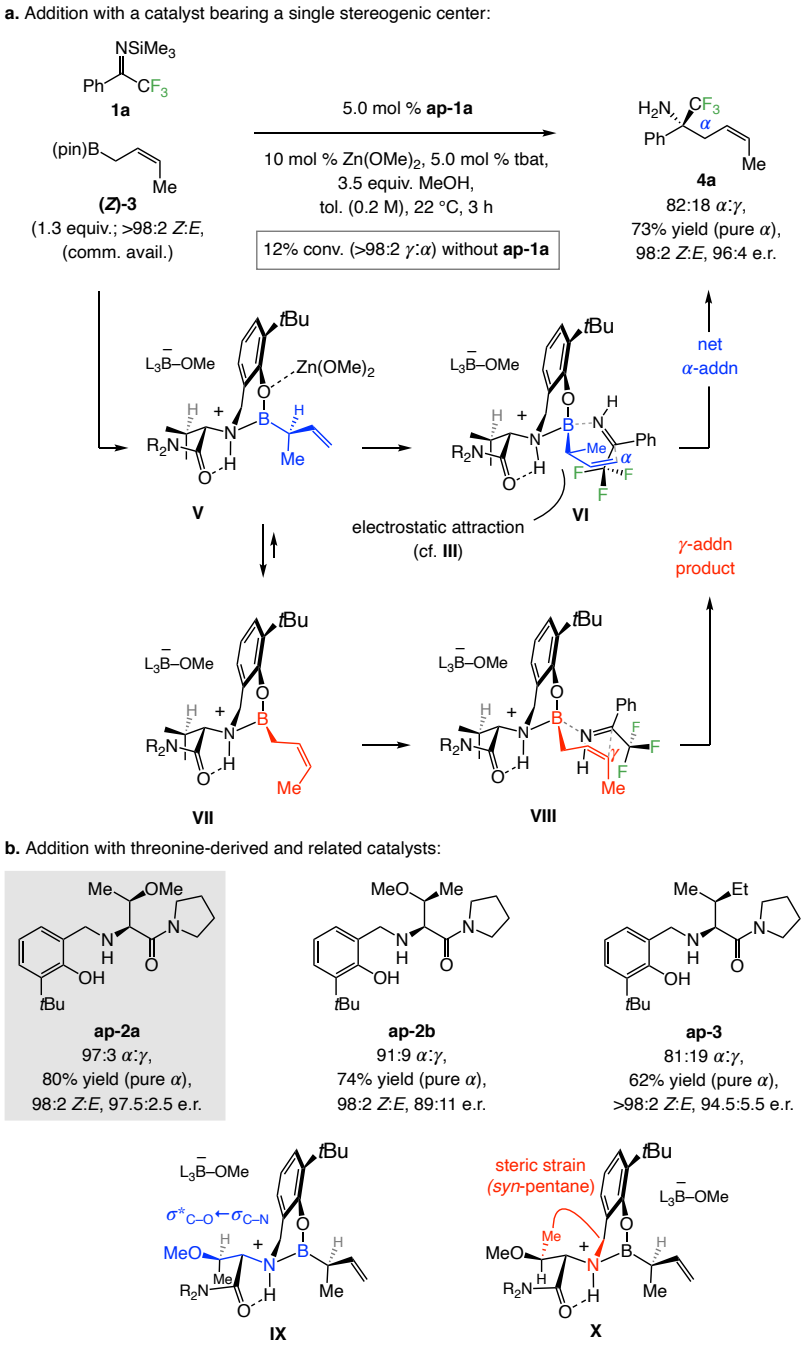
We began by probing the possibility of synthesizing **2a** (Scheme 2a) by reaction of silyl ketimine **1a** and allyl–B(pin) (pin = pinacolato) with 5.0 mol % **ap-1a** under the standard conditions (e.g., 5.0 mol % $Zn(OMe)_2$, 1.5–2.5 equiv. alcohol, tol., 0–22 °C), but none of **2a** was formed (<2%). We then examined the influence of different fluorides for in situ NH-ketimine generation,[15] establishing that with 5.0 mol % *tetra*-*n*-butylammonium difluorotriphenylsilicate (tbat, $(n\text{Bu})_4N(Ph_3SiF_2)$), **2a** can be generated in 94% yield and 91:9 enantiomeric ratio (e.r.). This was despite the fact there was 35% conversion to *rac*-**2a** without an aminophenol. By monitoring the transformation spectroscopically (^{19}F NMR; see data in Scheme 2a), we found that the NH-ketimine (**1a'**) is formed rapidly, indicating that silyl removal occurs in the course of the reaction (i.e., the addition does not directly involve silyl-ketimine **2a**). Investigation of other aminophenol ligands and/or silyl ketimines, did not result in any significant improvement in e.r.[15]

We found it intriguing that the e.r. values in Scheme 2a are lower than those for allyl additions to F_3C-substituted ketones (92.5:7.5–96:4 e.r.).[13b, 16] For a ketone (**I**, Scheme 2b), electrostatic attraction involving the ammonium unit diminishes electron–electron repulsion between the carbonyl oxygen and a C–F bond.[13a] With a ketimine, on the other hand, reaction via **II** or **III** can lead to the major enantiomer, but in the former (**II**), electrostatic attraction (see **I**



Scheme 2. Initial studies involving allyl–B(pin) and new challenges regarding reaction with NH-ketimines. See the Supporting Information for details. Abbreviation: tbat = $(n\text{Bu})_4\text{N}(\text{Ph}_3\text{SiF}_2)$.

and **III**) is not feasible because of the NH proton; steric factors in **II** thus become central and transformation via **IV** more competitive. In line with this scenario, when Ph_3Si-substituted **ap-1b** (Scheme 2b) was used, **2a** was formed in 72:28 e.r. (89% yield).



Scheme 3. Catalytic reactions with *Z*-crotyl–B(pin) are highly α- and enantioselective as a result of several favorable steric and electronic factors originating from *O*-methyl threonine-derived catalyst. See the Supporting Information for details.

The above findings insinuated that it might be possible to exploit steric factors to improve e.r. We recently showed that additions of *Z*-disubstituted allyl boronates to ketones or aldehydes

are more enantioselective probably because the substituent at the stereogenic carbon center of the chiral allyl boronate (e.g., Me unit in **VI**, Scheme 3a) prefers to be oriented pseudo-axially, away from the catalyst framework.[13d,14] Accordingly, we investigated the reaction with *Z*-crotyl–B(pin) ((*Z*)-**3**). Control experiments indicated that the non-catalytic pathway, while completely γ-selective, is inefficient (12% conv.; Scheme 3a), and, indeed, with 5.0 mol % **ap-1a** there was >98% conversion to **4a**, which was formed in 96:4 e.r. (vs. 91:9 e.r. for **2a**). Consistent with the proposed model, and similar to previous cases,[13c] reaction with (*E*)-**3** was inefficient (<10% conv. under otherwise identical conditions). Nevertheless, α:γ selectivity was moderate (82:18; 73% yield of the α isomer), implying that conversion of **V** to lower energy **VII** by borotropic shift and addition via **VIII** (Scheme 3a) to generate the γ isomer competes with reaction via **VI** to give **4a**.

We reasoned that one way to improve the α:γ selectivity might be to enhance the Lewis acidity of a chiral catalyst's B center. Our hope was that by enhancing ketimine activation, C–C bond formation could be accelerated to a greater extent than the alternative borotropic shift (**V**→**VII**). Somewhat surprisingly, however, a smaller (expected to lower steric repulsion in **II**) and electron-withdrawing CF_3 unit in **ap-1c** (Scheme 2b)[13e] adversely impacted the e.r. We therefore chose to investigate a threonine-based catalyst based on the logic that the C–O bond neighboring the C–N bond might increase Lewis acidity of the boron center and the ammonium unit to enhance electrostatic attraction (**III**, Scheme 2b) and facilitate catalyst-ketimine association (pre-empting borotropic shift).

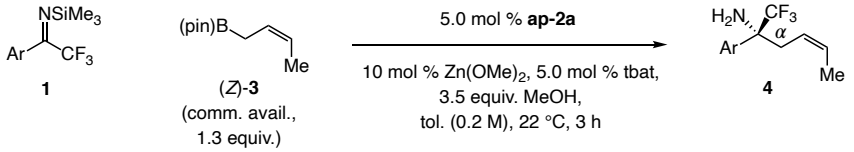
With *O*-methyl-L-threonine derived **ap-2a** (Scheme 3b), **4a** was generated in 97:3 α:γ selectivity (vs. 82:18, **ap-1a**) without any diminution in *Z*:*E* ratio or e.r. Equally important, with diastereomeric **ap-2b,** derived from *O*-methyl-D-threonine, **4a** was formed in lower α- and enantioselectivity (91:9 and 89:11, respectively). A rationale for the improvement in α selectivity in the reaction with **ap-2a** is that, as depicted in **IX**, proper alignment of the C–OMe and C–N bonds allows for effective $\sigma_{C-N} \rightarrow \sigma^*_{C-O}$ hyperconjugation, leads to diminished electron density at nitrogen. This is consistent with the reduced α:γ selectivity when **ap-2b** was used, as the requisite conformation would exacerbate steric pressure (**X**). The much lower α selectivity with **ap-3** (Scheme 3b) underscores the positive impact of the additional C–O bond.

Various aryl- and F_3C-substituted silyl ketimines may be converted to α-tertiary homoallylic NH_2-amines (**4b**-**m**, Table 1). In only four instances the pure α-addition isomer was not obtained (entries 1–2, 4, and 11). Reactions of hindered *o*-Cl and *o*-tolyl ketimines afforded

4c and **4e** in 79% and 52% yield, respectively (entries 2 and 4). In such instances or with strongly electron-rich aryl ketimines (e.g., **1m**), to maximize efficiency, in situ silyl removal was performed prior to charging the mixture with **ap-2a** and (*Z*)-**3**.[15] With ketimines that are less reactive due to steric (e.g., entries 2–4) or electronic factors (e.g., entries 4 and 12), borotropic shift became more competitive and α:γ selectivity suffered.

Heterocyclic α-tertiary amines were prepared in high *Z*:*E* ratios and enantioselectivities, as indicated by **4n-p** (Scheme 4). However, these processes presented additional challenges. Low stability of the silyl ketimine (hydrolysis to ketone) was one problem, and thus **4n**, bearing a more electron donating 2-furyl substituent, was isolated in 32% yield (vs. benzofuryl- and 2-thienyl-substituted **4o-p** in 77% and 84% yield, respectively). We could not obtain an indole-substituted silyl ketimine in sufficiently high purity, and attempts to promote addition to the 2- or 3-pyridyl variants were thwarted due solubility issues and/or rapid formation of the derived hemiaminal (reaction with MeOH). Efforts to carry out reactions with alkyl-substituted substrates led to the formation of hydrolyzed products (ketones), enamines, or hemiaminals (<5% desired product).

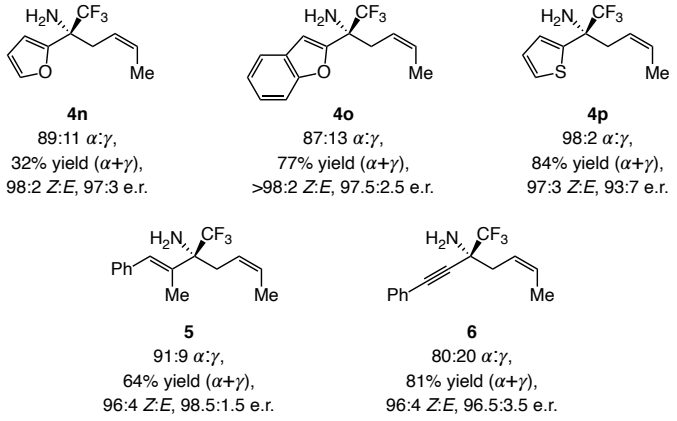
Table 1: Catalytic enantioselective additions to aryl-substituted ketimines.[a]



Entry	Ar	Conv. [%][a]	α:γ[b]	Yield (pure α) [%][c]	*Z*:*E*[b]	e.r.[d]
1	*o*FC_6H_4; **b**[d]	>98	96:4	89[f]	98:2	98.5:1.5
2	*o*ClC_6H_4; **c**[e]	>98	74:26	79[f]	98:2	96.5:3.5
3	*o*$MeOC_6H_4$; **d**	>98	96:4	70	98:2	>99:1
4	*o*MeC_6H_4; **e**[e]	>98	45:55	52[f]	98:2	95.5:4.5
5	*m*ClC_6H_4; **f**	>98	>98:2	90	97:3	96.5:3.5
6	*m*$F_3CC_6H_4$; **g**	>98	98:2	82	98:2	98:2
7	*p*FC_6H_4; **h**	>98	93:7	68	98:2	97:3
8	*p*ClC_6H_4; **i**	>98	95:5	87	95:5	96:4
9	*p*BrC_6H_4; **j**	>98	96:4	67	97:3	98:2
10	*p*$F_3CC_6H_4$; **k**	>98	98:2	61	96:4	97.5:2.5
11	*p*$MeOC_6H_4$; **l**	96	94:6	78[f]	98:2	98:2
12	*p*$Me_2NC_6H_4$; **m**[e,g]	98	87:13	50	98:2	96.5:3.5

[a] All reactions performed under N_2 atm. [b] Conv., d.r., and α:γ ratios determined by analysis of ^{19}F NMR spectra of unpurified mixtures; conv. (±2%) refers to disappearance of the silyl ketimine starting material. [c] Yield of isolated and purified material (±5%). [d] Enantioselectivity determined by HPLC analysis (±1%); the derived acetate was used in entry 1. [e] NH-Ketimine generated first. [f] Yield is for mixture of α- and γ-addition products. [g] Reaction time = 8 h. See the Supporting Information for details.

Allylic and propargylic α-tertiary amines **5** and **6** were isolated in 64% and 81% yield (α+γ isomers), respectively, and in high *Z* selectivity and e.r. The lower α:γ ratio (80:20) for **6** probably arises from increased stability of the hemiaminal derivative (~20% detected[15]), owing to a more diminutive alkynyl group, which lowers the barrier to borotropic shift (see Scheme 3a).



4n
89:11 α:γ,
32% yield (α+γ),
98:2 *Z*:*E*, 97:3 e.r.

4o
87:13 α:γ,
77% yield (α+γ),
>98:2 *Z*:*E*, 97.5:2.5 e.r.

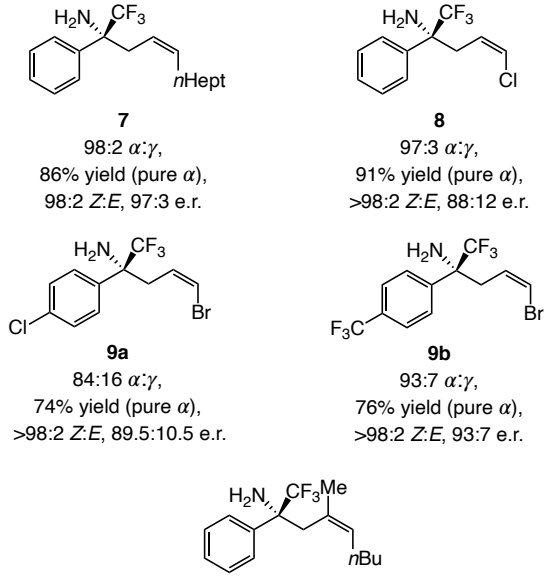
4p
98:2 α:γ,
84% yield (α+γ),
97:3 *Z*:*E*, 93:7 e.r.

5
91:9 α:γ,
64% yield (α+γ),
96:4 *Z*:*E*, 98.5:1.5 e.r.

6
80:20 α:γ,
81% yield (α+γ),
96:4 *Z*:*E*, 96.5:3.5 e.r.

Scheme 4. Heterocyclic, alkenyl-, and alkynyl-substituted ketimines may be used. Same conditions as in Table 1 were used, except for **4o** the NH-ketimine was generated first in situ. Yield of isolated and purified material (±5%); enantioselectivity determined by HPLC analysis (±1%). See the Supporting Information for further details.

Other *Z*-allyl boronates, accessible by catalytic cross-metathesis,[17] may be used, providing access to products with different alkenyl moieties (Scheme 5). We prepared α-tertiary



7
98:2 α:γ,
86% yield (pure α),
98:2 *Z*:*E*, 97:3 e.r.

8
97:3 α:γ,
91% yield (pure α),
>98:2 *Z*:*E*, 88:12 e.r.

9a
84:16 α:γ,
74% yield (pure α),
>98:2 *Z*:*E*, 89.5:10.5 e.r.

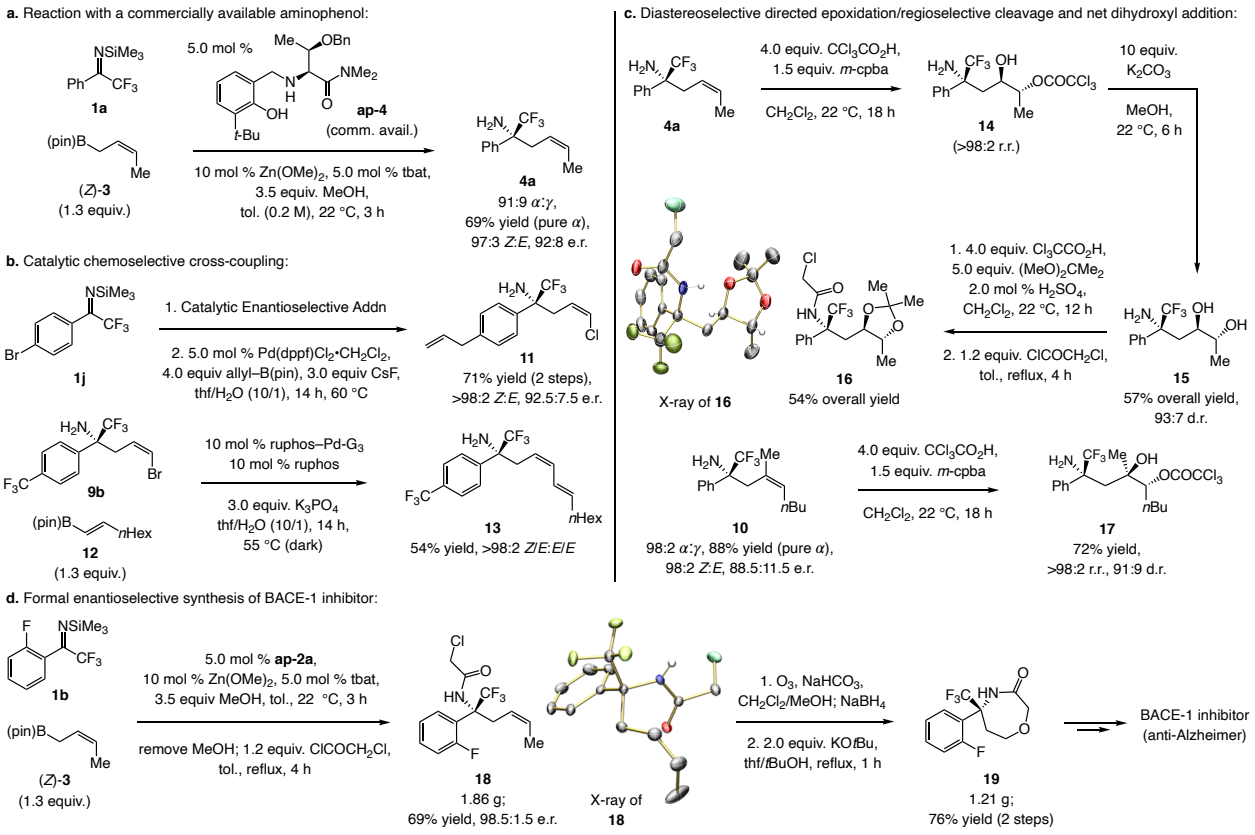
9b
93:7 α:γ,
76% yield (pure α),
>98:2 *Z*:*E*, 93:7 e.r.

10
98:2 α:γ,
88% yield (pure α),
98:2 *Z*:*E*, 88.5:11.5 e.r.

Scheme 5. The enantioselective approach is applicable to different allyl boronates, accessible by stereoretentive catalytic cross-metathesis. Same conditions as in Table 1 used, except that 14 h was needed for **8a-b** and **10**. For **8a-b** and **9a-b**, the silyl group was removed first. Yield of isolated and purified material (±5%); enantioselectivity determined by HPLC analysis (±1%). See the Supporting Information for further details. Abbreviation = MEM: methoxyethoxymethyl.

amines bearing an *n*-heptyl (**7**), a chloro (**8**), or a bromo (**9a-b**) substituent. Yields (56-91% for pure α isomers), regioselectivities (84:16–98:2 α:γ), and *Z*:*E* selectivities (≥98%) were generally high; enantioselectivity ranged from 88.5:11.5 to 97:3 e.r. Trisubstituted olefin **10** was obtained in 88% yield (pure α), >98:2 *Z*:*E* selectivity, and 88.5:11.5 e.r.

Another feature of the new strategy is that aminophenols can be easily prepared in multigram quantities from inexpensive starting materials,[18] and are commercially available. By using *O*-benzyl-L-threonine derived **ap-4**, which recently became commercially available, we were able to prepare **4a** in 69% yield (pure α), [97:3 *Z*:*E* and 92:8 e.r. vs. 80% yield (pure α, Scheme 6a), 98:2 *Z*:*E*, 97:3 e.r. with **ap-2a**]. The feasibility of synthesizing α-tertiary NH_2-amines with a halogen-substituted *Z*-alkene means that additional derivatives can be conveniently prepared by cross-coupling reactions, stereoretentive catalytic processes that do not require amine protection. A representative case is the two-step transformation of ketimine **1j** to **11** in 71% overall yield, >98:2 *Z*:*E* selectivity, and 92.5:7.5 e.r. (Scheme 6b). Another example is a cross-



Scheme 6. The practical nature and utility of the new catalytic enantioselective method. Yield of isolated and purified material (±5%); enantioselectivity determined by HPLC analysis (±1%). See the Supporting Information for further details.

coupling involving homoallylic α-tertiary NH_2-amine **9b** and alkenyl–B(pin) **12**, leading to the formation of 1,3-diene **13** in 54% yield (>98:2 *Z*/*E*:*E*/*E*).[15]

Thus, the possibility of generating products that contain a *Z*-alkenyl chloride, not only makes it possible to access a much wider range of other α-tertiary NH_2-amines, it can be done so with high chemoselectivity.

As noted earlier, a central attribute of the present method is that the products contain a *Z* alkene, transformations of which are considerably more diastereoselective than the corresponding *E* isomers or monosubstituted olefins.[9, 19] The following data highlight the importance of this feature. Directed epoxide formation/regioselective cleavage with *m*-chloroperbenzoic acid and trichloroacetic acid (Scheme 6c), according to a procedure introduced for reactions involving cyclic allylic tertiary alkylamines and γ-tertiary alkylamino α,β-unsaturated esters,[20] afforded **14** in >98:2 regiosiomeric ratio (r.r.); mild hydrolysis converted **14** to diol **15** in 57% overall yield and 93:7 diastereomeric ratio (d.r.). The X-ray structure of amide/acetonide derivative **16** confirmed the identity of the major stereoisomer. Similarly, **10** was converted to trichloroacetate **17** in 72% yield, >98:2 r.r., and 91:9 d.r.

The gram-scale synthesis of cyclic amide **19** (1.21 g) via **18** (Scheme 6d), previously converted to BACE-1 inhibitor (Scheme 1a), further highlights the utility of the approach. A homoallylic amine with a monosubstituted alkene can also be used in the same way for this last sequence. Nevertheless, the fact that precious metal salts are not needed, the aminophenol can be prepared in significant amounts at relatively low cost, and multigram quantities of *Z*-crotyl–B(pin) may be accessed by simple procedures and with inexpensive starting materials,[18] point to the truly practical nature of the approach.

Conclusion

We have described a method for enantioselective preparation of readily modifiable F_3C- and aryl-, heteroaryl-, alkynyl, or alkenyl-substituted α-tertiary *Z*-homoallylic NH_2-amines. Reactions involve an easy-to-handle N-silyl ketimine and a *Z*-allyl boronate, which might either be purchased or accessed in high stereoisomeric purity by catalytic cross-metathesis, and are promoted by a catalyst generated in situ from a readily accessible aminophenol. High α:γ selectivities arise from attractive electrostatic forces and the steric and stereoelectronic attributes of the catalyst's L-threonine residue. Development of additional catalytic protocols for

enantioselective synthesis of a broader range of α-tertiary NH_2-amines (e.g., F_3C-/alkyl-substituted) are in progress.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: catalysis, enantioselective synthesis, homoallylic amines, NH_2-amines, NH-ketimines

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