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Practical, Broadly Applicable, α-Selective, Z-Selective, Diastereoselective, and Enantioselective Addition of Allylboron Compounds to Mono-, Di-, Tri-, and Polyfluoroalkyl Ketones

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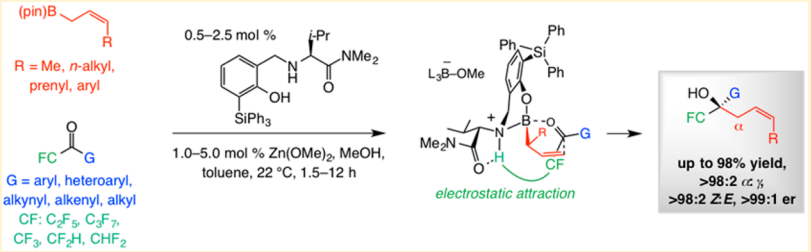
Supporting Information



ABSTRACT: A practical method for enantioselective synthesis of fluoroalkyl-substituted *Z*-homoallylic tertiary alcohols has been developed. Reactions may be performed with ketones containing a polylfluoro-, trifluoro-, difluoro-, and monofluoroalkyl group along with an aryl, a heteroaryl, an alkenyl, an alkynyl, or an alkyl substituent. Readily accessible unsaturated organoboron compounds serve as reagents. Transformations were performed with 0.5−2.5 mol % of a boron-based catalyst, generated in situ from a readily accessible valine-derived aminophenol and a *Z*- or an *E*-γ-substituted boronic acid pinacol ester. With a *Z* organoboron reagent, additions to trifluoromethyl and polyfluoroalkyl ketones proceeded in 80−98% yield, 97:3 to >98:2 α:γ selectivity, >95:5 *Z*:*E* selectivity, and 81:19 to >99:1 enantiomeric ratio. In notable contrast to reactions with unsubstituted allylboronic acid pinacol ester, additions to ketones with a mono- or a difluoromethyl group were highly enantioselective as well. Transformations were similarly efficient and α- and *Z*-selective when an *E*-allylboronate compound was used, but enantioselectivities were lower. In certain cases, the opposite enantiomer was favored (up to 4:96 er). With a racemic allylboronate reagent that contains an allylic stereogenic center, additions were exceptionally α-selective, affording products expected from γ-addition of a crotylboron compound, in up to 97% yield, 88:12 diastereomeric ratio, and 94:6 enantiomeric ratio. Utility is highlighted by gram-scale preparation of representative products through transformations that were performed without exclusion of air or moisture and through applications in stereoselective olefin metathesis where *Z*-alkene substrates are required. Mechanistic investigations aided by computational (DFT) studies and offer insight into different selectivity profiles.

1. INTRODUCTION

Small organic molecules bearing a fluoroalkyl-substituted carbon stereogenic center are central to development of therapeutics,[1] agrochemicals,[2] and materials.[3] Practical, efficient, cost-effective, and broadly applicable catalytic methods that generate such entities with high enantioselectivity are much sought after. Although such processes can deliver valuable and readily modifiable building blocks in high enantiomeric purity, they remain relatively uncommon.[4−7] The limited number of reported studies entail additions of allyl units to a small set of trifluoromethyl ketones, need significant amounts[4a,b] (at times several equivalents)[4a] of costly indium salts, can require days to reach completion,[4b] and selectivities do not exceed 90:10 er (enantiomeric ratio).[4c] Part of the challenge in developing such transformations is the comparatively small difference in the size of the carbonyl substituents and high electrophilicity causing nonselective background addition. Thus, high enantioselectivity must be attained by incorporation of well-defined electronic factors.

We have demonstrated that valine-derived chiral organoboron catalysts (Scheme 1),[8] which probably exist in solution as ammonium salt derivatives, promote the addition of symmetric allyl− and allenyl−B(pin) compounds[9] (pin = pinacolato) as well as silyl-protected propargyl−B(pin) reagents to trifluoromethyl ketones efficiently and with high α- and enantioselectivity (up to >98:2 α:γ and 99:1 er; Scheme 1a).[10] A collection of experimental and computational data suggests that in the favored mode of addition **i** (Scheme 1) there is minimization of electron−electron repulsion caused by the nonbonding electrons of the ketone oxygen and the fluorine atoms through electrostatic interaction with the catalyst's ammonium group. We later showed that with a phosphinoylimine and the more Lewis acidic $Zn(OMe)_2$ (vs NaO*t*-Bu) reaction of γ-substituted allyl−B(pin) compounds proceeds more efficiently and with far higher γ selectivity (Scheme 1b).[11] Preferential formation of the γ addition products likely arises from the ability of the Lewis acidic Zn salt to cause 1,3-boryl shift[12] (**ii** → **iii** → *Z*-**iv**, Scheme 1b) to occur faster than the

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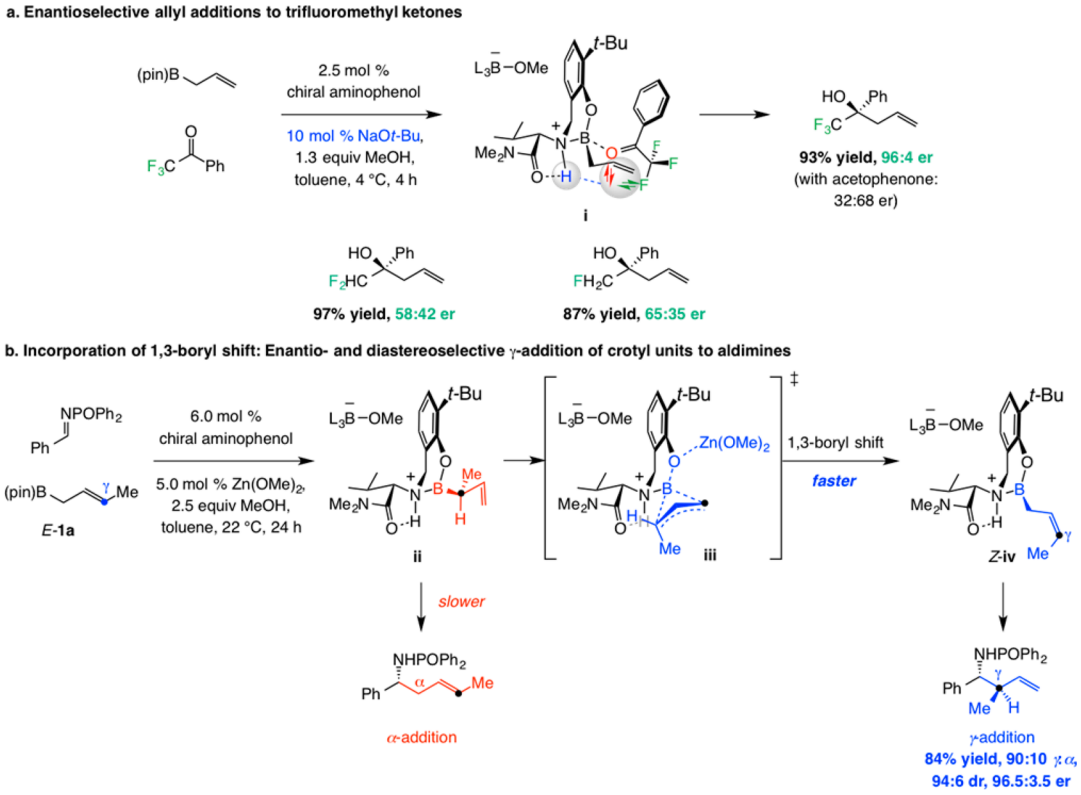
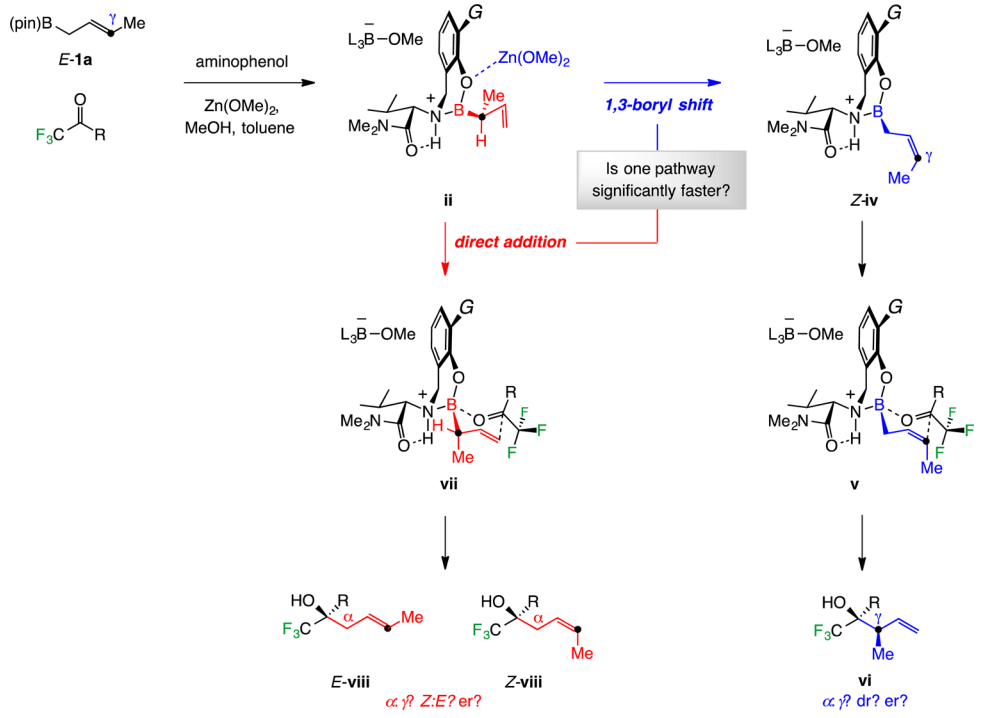
Scheme 1. Relevant Previous Observations



Scheme 2. Goals of this Study



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addition of the initially generated chiral allylboron intermediate to an imine (i.e., in Scheme 1b: **ii** → α-addition product).

The above findings raise the following key questions: Would the 1,3-borotropic shift give rise to a preference for formation of the γ-addition product (**vi** via **v**, Scheme 2), or would the corresponding α-addition product **viii** (via **vii**) be generated preferentially in the case of more electrophilic trifluoromethyl ketones? If γ-selective, then would the diastereomeric ratio (dr) and er be high? If α-selective, would er be high or would the product contain an *E*- or a *Z*-alkene? To what degree would *E*:*Z* selectivity be under catalyst control and/or depend on the stereochemistry of the organoboron reagent? Would additions to the less electrophilic difluoro- and monofluoromethyl ketone analogues occur with much lower enantioselectivity, as they did when symmetric allyl−B(pin) compounds were used or will the new method offer broader scope?[10]

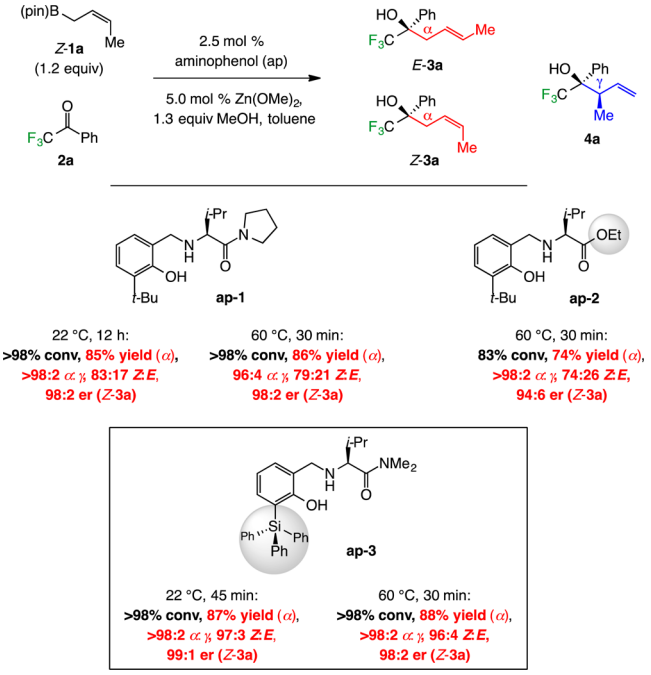
Here, we describe the results of studies designed to address the above questions. We detail the development of a practical, broadly applicable, highly efficient, α-selective, *Z*-selective, and enantioselective additions to fluoroalkyl ketones. The considerable scope of the catalytic protocol, its utility in chemical synthesis, the role of the stereochemical identity of the organoboron reagent, the origin of high α-, *Z*-, and enantioselectivity as well as the mechanistic basis for the observed trends in reactivity and selectivity are presented below.

2. RESULTS AND DISCUSSION

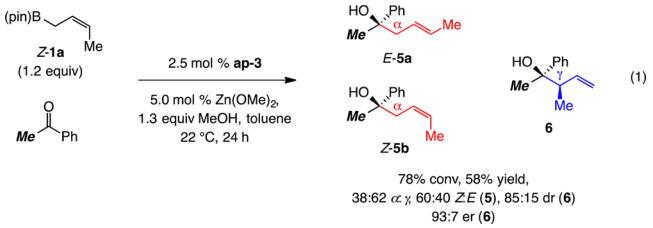
2.1. Initial Evaluation. We first examined the addition of organoboron reagent *Z*-**1a** to trifluoroacetophenone **2a** (Scheme 3). With ligand **ap-1** (ap = aminophenol), reaction was complete in 12 h at 22 °C, affording **3a** in 85% yield, >98:2 α:γ ratio, 83:17 *Z*:*E* selectivity, and 98:2 er. The transformation was much faster at 60 °C (>98% conv, 30 min), and **3a** was isolated in 86% yield and 98:2 er, with only slightly lower α:γ selectivity (96:4). However, *Z* selectivity was reduced significantly (79:21 *Z*:*E*). The transformation with **ap-2** was similarly efficient and selective, which was unexpected since previous studies had indicated transformations with a carboxylic ester (vs dialkyl amide) are less efficient and less enantioselective.[8] With more sterically demanding triphenylsilyl-substituted **ap-3**,[6k,10] efficiency (87−88% yield), α selectivity (>98:2), and er (≥98:2) remained high (Scheme 3), along with a boost in reaction rate (45 min) and *Z* selectivity, regardless of the reaction temperature (≥96:4 vs 74:26−83:17 *Z*:*E* with **ap-1**,**2**). The importance of this finding vis-à-vis utility in synthesis aside, the clear influence of catalyst structure on *Z*:*E* selectivity is notable (see below for analysis). When NaO*t*-Bu was used instead of $Zn(OMe)_2$, there was only 12% conversion after 28 h (22 °C, >98:2 α:γ, 97:3 *Z*:*E*, 98:2 er). As discussed previously,[11] the positive effect of the Zn(II) salt on efficiency is probably tied to its coordination to the catalyst's amide carbonyl; this reduces carbonyl−boron coordination, resulting in higher catalyst activity.

With acetophenone (vs the trifluoromethyl variant) and **ap-3**, the γ-addition product was slightly favored (62% **6**, eq 1). This suggests that with a less electrophilic ketone, Lewis acid catalyzed 1,3-borotropic shift becomes more competitive (see **ii** → *Z*-**iv** vs **ii** → **vii**, Scheme 2). The near-complete erosion of *Z* selectivity (60:40 vs 97:3 *Z*:*E*; eq 1) indicates that the presence of the trifluoromethyl group is key to the formation of the higher energy alkene isomer. The mechanistic origins of this effect and whether a difluoro- or a monofluoromethyl group would have a similar influence on various selectivity issues remained to be determined.

Scheme 3. Initial Examination of Reactivity and Selectivity[a]



[a]Reactions carried out under N_2 atm. Conversion and α:γ ratios determined by analysis of ^{19}F NMR spectra of unpurified product mixtures (±2%). Yields for purified α-addition products (±5%). The er was determined by HPLC analysis (±1%). Experiments were run in duplicate or more. See the Supporting Information for details.



(1)

3. SCOPE

3.1. Additions to Trifluoromethyl Ketones. With 0.5 mol % **ap-3**, 1.0 mol % $Zn(OMe)_2$, and 1.2 equiv of commercially available *Z*-**1a** (used as received), additions to aryl-substituted trifluoromethyl ketones proceeded to completion at 22 °C in 1.5−12 h (Scheme 4). Products were isolated in 87−98% yield, ≥98:2 α:γ selectivity, 88:12 to >98:2 *Z*:*E* selectivity and 96:4 to >99:1 er. Substrates containing a sterically congested (e.g., **3b**, **3d**−**f**, Scheme 4), electron-rich (e.g., **3c**, **3h**, **3o**), or electron-deficient (e.g., **3l**, **3f**) aryl group were suitable. Dimethylaminophenyl-substituted **3n** and methylthiophenyl-substituted **3p** were readily generated with exceptional efficiency and selectivity.

Heterocyclic substrates can be converted to the corresponding homoallylic alcohols (Scheme 5). Indole- (**7**), furyl- (**8a**-**b**), thienyl- (**9a**-**b**), and pyridyl-substituted (**10**) homoallylic alcohols were isolated in up to 98% yield, >98% α selectivity, 98% *Z* selectivity, and >99:1 er. The lower er in the reactions with 2-furyl and 2-thienyl ketones compared to those with their 3-substituted analogues are consistent with formerly disclosed observations regarding allyl−B(pin) and allenyl−B(pin) additions.[10]

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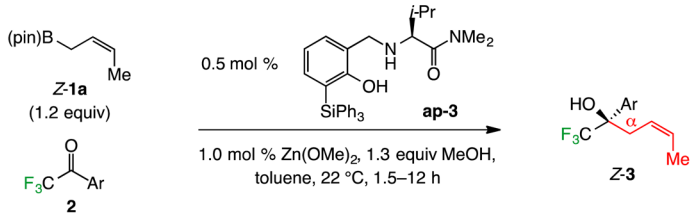
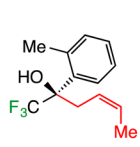
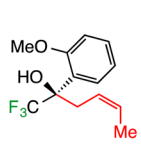
Scheme 4. Reactions with Aryl-Substituted Trifluoromethylketones[a]

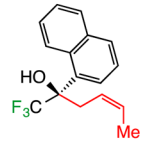




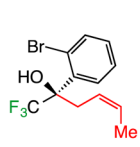
Z-3b
2 h, >98% conv, 91% yield, >98:2 α:γ, 96:4 Z:E, 98:2 er



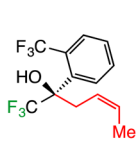
Z-3c
3 h, >98% conv, 92% yield, >98:2 α:γ, 98:2 Z:E, >99:1 er



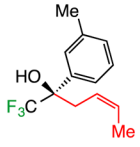
Z-3d
1.5 h, >98% conv, 95% yield, >98:2 α:γ, >98:2 Z:E, 97:3 er



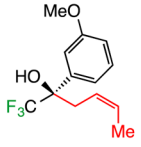
Z-3e
3 h, >98% conv, 91% yield, 98:2 α:γ, 90:10 Z:E, 98:2 er



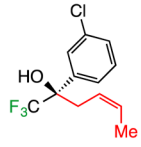
Z-3f
2 h, >98% conv, 93% yield, 98:2 α:γ, 88:12 Z:E, 98:2 er



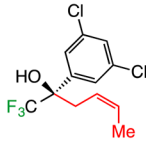
Z-3g
2 h, >98% conv, 92% yield, >98:2 α:γ, 97:3 Z:E, 99:1 er



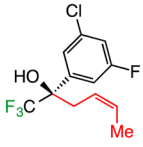
Z-3h
4 h, >98% conv, 95% yield, >98:2 α:γ, 97:3 Z:E, 99:1 er



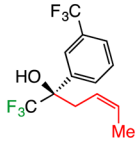
Z-3i
3 h, >98% conv, 87% yield, >98:2 α:γ, 96:4 Z:E, 98:2 er



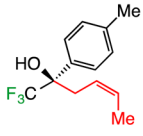
Z-3j
12 h, >98% conv, 93% yield, 98:2 α:γ, 97:3 Z:E, 96:4 er



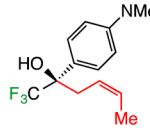
Z-3k
3 h, >98% conv, 96% yield, >98:2 α:γ, 97:3 Z:E, 97:3 er



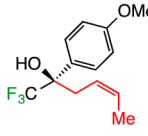
Z-3l
4 h, >98% conv, 93% yield, >98:2 α:γ, 95:5 Z:E, 98:2 er



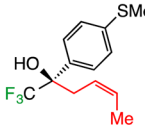
Z-3m
1.5 h, >98% conv, 92% yield, >98:2 α:γ, 96:4 Z:E, >99:1 er



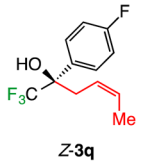
Z-3n
4 h, >98% conv, 98% yield, >98:2 α:γ, 97:3 Z:E, >99:1 er



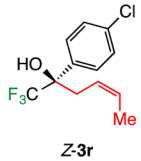
Z-3o
3.5 h, >98% conv, 97% yield, >98:2 α:γ, 97:3 Z:E, >99:1 er



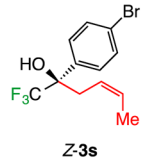
Z-3p
4 h, >98% conv, 98% yield, >98:2 α:γ, 96:4 Z:E, >99:1 er



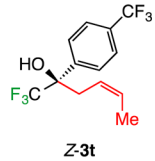
Z-3q
1.5 h, >98% conv, 94% yield, >98:2 α:γ, 96:4 Z:E, >99:1 er



Z-3r
1.5 h, >98% conv, 92% yield, >98:2 α:γ, 96:4 Z:E, 99:1 er



Z-3s
2 h, >98% conv, 93% yield, >98:2 α:γ, 96:4 Z:E, >99:1 er



Z-3t
1.5 h, >98% conv, 92% yield, >98:2 α:γ, 94:6 Z:E, 99:1 er

[a]Reactions carried out under N_2 atm. Conversion, α:γ and Z:E ratios determined by analysis of ^{19}F NMR spectra of unpurified product mixtures (±2%). Yields for purified α-addition products (±5%). The er was determined by HPLC analysis (±1%). All experiments run in duplicate or more. See the Supporting Information for details.

Regarding pyridyl product **10**, 2.5 mol % **ap-3**, 5.0 mol % $Zn(OMe)_2$, 12 h, and 60 °C were required for >98% conversion; this might be in part because the corresponding hydrate was the starting material. The X-ray structure secured for *Z*-**10** allowed us to establish the absolute stereochemical identity of the major product.[13]

Additions to other alkyl-substituted trifluoromethyl ketones (**11a–c**, Scheme 6), including cyclohexyl-substituted **11c**, proceeded to >98% conversion with 0.5 mol % **ap-3** (one case at 2.5 mol %) at 22 °C in 4 h (Scheme 6). Transformations were efficient (80–97% yield), generating the α-addition products with considerable selectivity (97:3 to >99:1 α:γ). Levels of *Z*-selectivity were surprisingly variable: Benzyl-substituted **11b** formed in 79:21 *Z*:*E* ratio (vs 92:8 and >98:2 for **11a** and **11c**, respectively). There was a less dramatic fluctuation in enantioselectivity with cyclohexyl-substituted **11c** (90:10 er vs 96:4 for **11a** and **11b**; see below for mechanistic analysis).

Reaction of the α,β-unsaturated trifluoromethyl-substituted ketones afforded dienes **12a–c** (Scheme 6) in 93–97% yield, >98:2 α:γ selectivity, ≥98:2 *Z*:*E* selectivity, and 99:1 er. Reactions affording 1,5-enynes **13a–c** were similarly efficient and α- and *Z*-selective (Scheme 6), but enantioselectivities were notably lower (81:19–85:15 er; see below for rationale).

3.2. Additions to Polyfluoroalkyl Di- and Monofluoromethyl Ketones. Polyfluorinated products **14** and **15** were generated efficiently and with excellent α selectivity, *Z* selectivity, and er. The highly enantioselective formation of difluoro- and monofluoro-substituted **16a–c** and **17a–c**, in contrast, were unexpected (96:4–98.5:1.5 er, Scheme 7); this was because addition of allyl–B(pin) to these same ketones was minimally enantioselective (Scheme 1a).[10] The X-ray structure of *p*-bromobenzoate derivative **18** showed that there is no change in the sense of stereochemical induction (vs the trifluoromethyl analogs). Moreover, these data show that the number of fluorine

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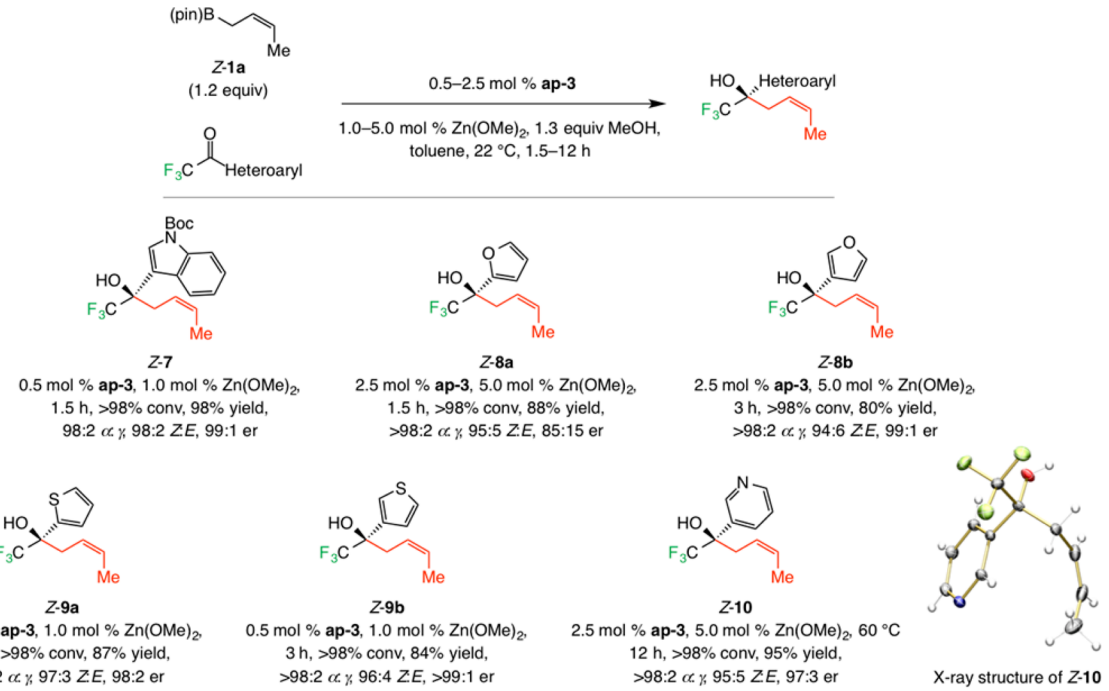
Scheme 5. Reactions with Heteroaryl-Substituted Trifluoromethyl Ketones[a]



[a]Reactions carried out under N_2 atm. Conversion, α:γ and Z:E ratios determined by analysis of ^{19}F NMR spectra of unpurified product mixtures (±2%). Yields for purified α-addition products (±5%). The er was determined by HPLC analysis (±1%). All experiments run in duplicate or more. See the Supporting Information for details.

atoms adjacent to the ketone unit has considerable influence on Z-selectivity of the process: The Z:E ratio descended in the order of 97:3 (Z-**3a**, Scheme 3) to 91:9 (Z-**16a**, Scheme 7) to 78:22 (Z-**17a**) with three, two, and one fluorine atoms on the α-alkyl site, respectively. The outcome of the reactions with di- and monofluoromethyl-substituted ketones constitutes one of the more distinct advantages of the present approach to reactions with allyl–B(pin),[10] where low er was observed with substrates containing a smaller number of fluorine atoms (see below for additional examples and analysis).

3.3. Reactions with Other Organoboron Reagents.[14] Transformations with *n*-heptyl-substituted Z-**1a** delivered products **19a–c** efficiently (86–95% yield, Scheme 8); although, in some cases longer reaction times were needed for complete conversion (24 h for **19a**,**b**). Z selectivity ranged from 90–94%, and α selectivities and enantioselectivities remained high (97:3 to >98:2 and 98:2 to >99:1 er, respectively). With the larger E-phenyl-substituted and γ,γ'-dimethyl-substituted allyl–B(pin) compounds (**20** and **21**, respectively; Scheme 8), products were isolated in 89–90% yield, but extended times were again required, especially in the former case (72 h). When the reaction was performed at 60 °C, there was complete conversion after 6 h, and the product was isolated in 90% yield. However, selectivity levels were lower (92:8 α:γ, 76:24 Z:E, 80:20 er). Enantioselectivity was lower in the latter two instances (85:15 and 89:11 er, respectively), and **21** was formed with 82:18 Z:E selectivity.

3.4. Reactions with (*E*)-Crotyl–B(pin). The somewhat diminished er for the reaction leading to prenyl alcohol **21** (Scheme 8) suggested that the corresponding transformation involving E-crotyl–B(pin) (E-**1a**, Scheme 9) might be less enantioselective: Z-**3a** was indeed generated in 91:9 er under the aforementioned conditions. The process was less efficient compared to that when Z-**1a** was used (24 h vs 45 min for >98% conv); nonetheless, the expected homoallylic alcohol was isolated in 86% yield and with exceptional α:γ and Z:E ratios (>98:2).

Transformations with E-**1a** and other trifluoromethyl ketones generated variable selectivity patterns (Scheme 9; compared to that with Z-**1a**, Scheme 4). With electron-rich aryl moieties, enantioselectivity was moderate with preference for the same enantiomer as Z-**1a** (i.e., **3c** in 85:15 vs >99:1 er). However, *o*-tolyl product **3b** was formed in 44:56 er (vs >99:1 er with Z-**1a**). For *o*-bromophenyl alcohol **3e**, the opposite enantiomer was slightly favored (24:76 er vs 98:2 er with Z-**1a**). Remarkably, in the case of *o*-trifluoromethyl-substituted **3f**, there was near complete reversal of enantioselectivity (6:94 vs 98:2 er with Z-**1a**). High er (albeit moderate 85:15) in favor of the same major enantiomer as Z-**1a** was observed with *m*- and *p*-substituted products **3l** and **3t** and alkyl-substituted **11a** (96:4 and 97:3 er, respectively). There were two other curious sets of data: (1) Z selectivity was high in all instances, except for *o*-tolyl-substituted **3b** (83:17 vs 96:4 to >98:2 Z:E, respectively; Scheme 9). (2) There was reversal in the sense of enantioselectivity in the additions involving trifluoromethyl acetophenone compared to its di- and monofluoromethyl analogues (i.e., Z-**3a** vs Z-**16a** and Z-**17a**). Moreover, whereas addition to *o*-tolyl-substituted trifluoromethyl ketone led to the formation of Z-**3b** in nearly racemic form (44:56 er), corresponding di- and monofluoromethyl derivatives Z-**16b** and Z-**17b** were generated in 9:91 and 4:96 er, respectively. The basis of these selectivity trends will be discussed below.

3.5. *E*- and *Z*-Organoboron Compounds React via Different Intermediates. We began by examining why the same major enantiomer (in most cases) and Z olefin isomer (in all instances) were being formed, regardless of whether Z- or E-**1a** is used. One explanation could be rapid isomerization

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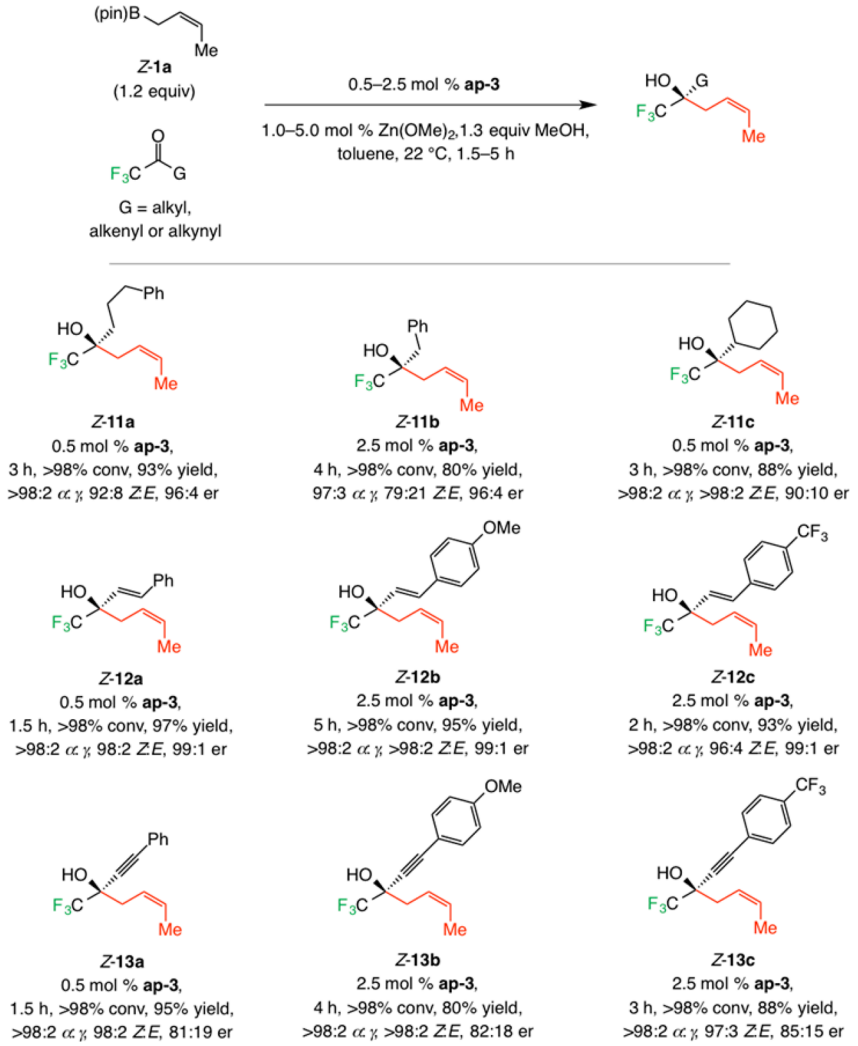
Scheme 6. Reactions with Alkyl-, Alkenyl-, and Alkynyl-Substituted Trifluoromethyl Ketones[a]



[a]Reactions carried out under N_2 atm. Conversion, α:γ and Z:E ratios determined by analysis of ^{19}F NMR spectra of unpurified product mixtures (±2%). Yields for purified α-addition products (±5%). The er was determined by HPLC analysis (±1%). All experiments run in duplicate or more. See the Supporting Information for details.

between the organoboron isomers. Nonetheless, spectroscopic studies indicated that *Z*- or *E*-**1a** do not readily interconvert (<2% in the presence of 5.0 mol % $Zn(OMe)_2$, 1.3 equiv of MeOH, toluene-d_8, 22 °C, 16 h).[15] Moreover, reaction with *rac*-**22** afforded **23a** in 85:15 dr[16] (Scheme 10; 84% yield, >98:2 α:γ, 92:8 er for the anti diastereomer, 91:9 er for the syn isomer). The stereochemical identity of the aforementioned products was ascertained by obtaining the X-ray structure of *p*-bromobenzoate derivative **24** (Scheme 10).[13] These data indicate that each organoboron isomer reacts by a distinct pathway; otherwise an equal mixture of syn and anti isomers would be formed (see below for further analysis).

3.6. Reactions with a Racemic Allylboron Reagent. Aryl-, heteroaryl-, alkenyl-, and alkyl-substituted trifluoromethyl ketones may be used in diastereo- and enantioselective reactions with *rac*-**22** (Scheme 10), although selectivity is moderate in some cases. This is a notable method because of the low catalyst loading (0.5 mol %), accessibility of the chiral catalyst, brief reaction times (1.5−3 h), mild conditions (22 °C), high yields, and exceptional α selectivity, as well as since to the best of our knowledge related catalytic enantioselective protocols have not been reported before. The organoboron compound (*rac*-**22**) can be accessed in a single step;[15] with enantiomerically enriched **22**, which can be synthesized by a number of methods,[17] considerably higher stereoselectivity should be expected.[15]

4. UTILITY

The method is amenable to gram-scale operations (Scheme 11). The application to pyridine-substituted **10** again shows that a basic pyridine moiety is tolerated. The er with which **3j**, precursor to antiparasitic agent Bravecto[18] (presently sold as the racemate) is formed in er higher than that with the addition of allyl−B(pin) (96.5:3.5 vs 95:5 er).[10] It is especially notable that the gram-scale reactions shown in Scheme 11 were performed without exclusion of air and/or moisture.

The *Z*-homoallylic alcohols are suitable substrates for a variety of directed, highly diastereoselective transformations.[19] Because the homoallylic ether products contain a *Z*-alkene, they can be readily converted to the corresponding *Z*-alkenyl halide derivatives through stereoretentive catalytic cross-metathesis reactions.[20] The stereoselective synthesis of alkenyl chloride **27** (Scheme 12) and its subsequent conversion to indole-containing **29** via boronic

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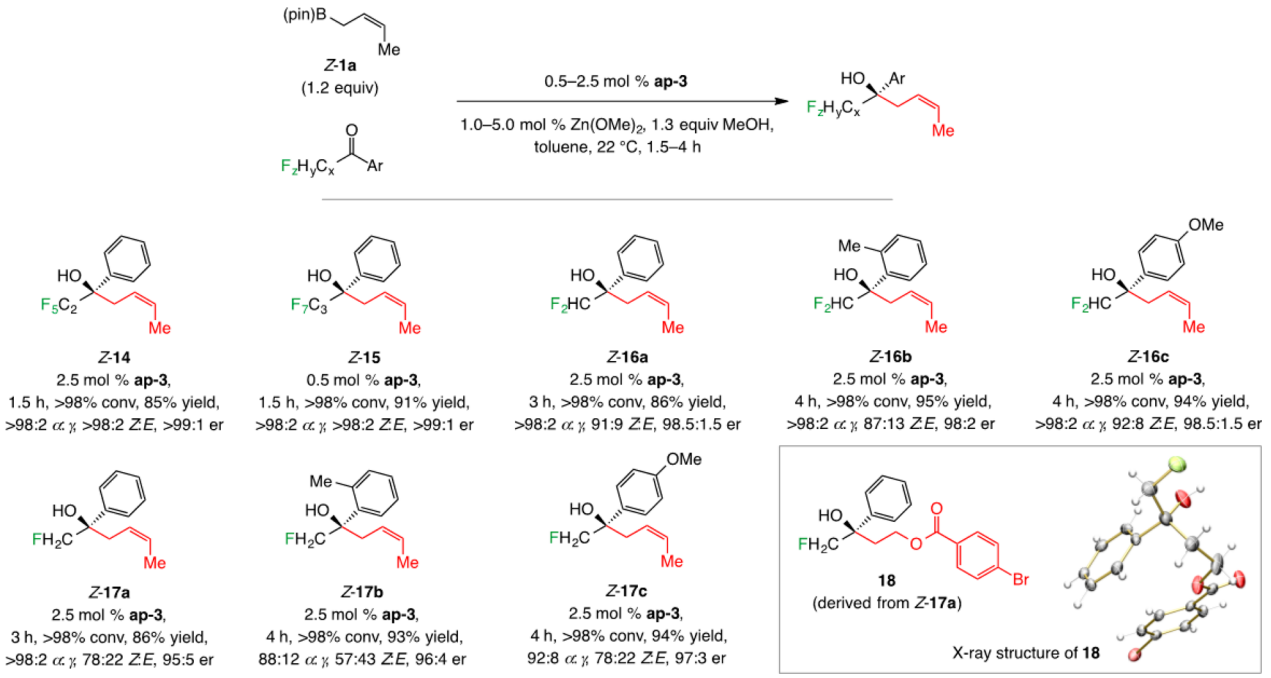
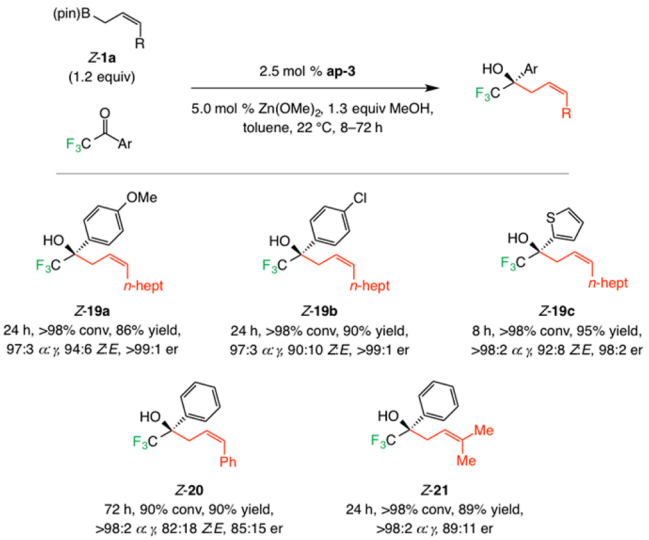
Scheme 7. Reactions with Other Fluoroalkyl-Substituted Ketones[a]



[a]Reactions carried out under N_2 atm. Conversion, α:γ and Z:E ratios determined by analysis of ^{19}F NMR spectra of unpurified product mixtures (±2%). Yields for purified α-addition products except for **17b–c** (±5%). The er was determined by HPLC analysis (±1%). All experiments run in duplicate or more. See the Supporting Information for details.

Scheme 8. Reactions with Other γ-Substituted Allyboron Reagents[a]



[a]Reactions carried out under N_2 atm. For Z-**20**, the E-allyl–B(pin) reagent was used. Conversion, α:γ and Z:E ratios determined by analysis of ^{19}F NMR spectra of unpurified product mixtures (±2%). Yields are for purified α-addition products (±5%). The er was determined by HPLC analysis (±1%). All experiments run in duplicate or more. See the Supporting Information for details.

acid **28** is a case in point. The Z-1,2-substituted alkene is crucial to cross-metathesis efficiency.[20] Reaction of the corresponding terminal alkene substrate was inefficient when a monoaryloxide pyrrolide complex was used (~40% conv, >98:2 Z:E)[21] and did not afford any product with monoaryloxide chloride complex **Mo-1**.

Another example (Scheme 12) performed with complex **Ru-1**[22] involves the use of an unprotected enantiomerically enriched tertiary alcohol (Z-**3a**) with commercially available unsaturated alcohol **30**; the desired product (**31**) was obtained after 8 h at room temperature in 89% yield and >98:2 Z:E selectivity. Here, the presence of the Z-methyl-substituted alkenes is required for high efficiency, and stereoselectivity is considerably higher compared to that when a terminal alkenes is involved.[23] Such transformations are valuable because by a combination of catalytic cross-metathesis and cross-coupling reactions a convenient route for the synthesis of otherwise difficult-to-access enantiomerically enriched compounds becomes feasible.

5. STEREOCHEMICAL MODELS

5.1. Reactions with Organoboron Compound Z-1a.

On the basis of DFT calculations (ωB97XD),[15] the high enantioselectivity in the transformations with Z-**1a** is due to reaction via intermediate **ix** and complex **I** in preference to **II** (Scheme 13). In **II** there is electron–electron repulsion between the halogen atoms of the trifluoromethyl group and the catalyst's aryloxide, and a near-eclipsing interaction between the methyl substituent and the catalyst's B–O bond. Furthermore, Coulombic attraction[10] between the trifluoromethyl moiety and the catalyst's ammonium group is only possible in **I**.[10] Another competing mode of reaction, represented by **III** (Scheme 13), would deliver the same sense of enantioselectivity as **I** but with an E-alkene. As illustrated in **III**, the stabilizing Coulombic attraction between the CF_3 and the ammonium groups would be countered by two significant repulsive interactions.

Variations in aminophenol structure and the associated changes in Z selectivity and er provide further insight (Table 1). While there is notable decrease in Z:E ratios with smaller catalyst substituents (from 97:3 to 83:17 to 84:16 with **ap-3**, **ap-4**, and **ap-5**, respectively), there is less significant diminution in er (from 99:1 to 98:2 to 97:3, respectively). As steric hindrance

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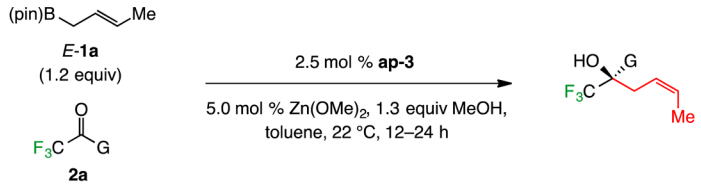
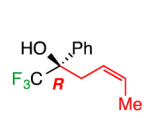
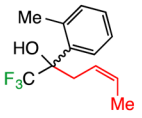
Scheme 9. Reactions with Crotylboron Compound *E*-1a: Substantial Variations in Enantioselectivity[a]

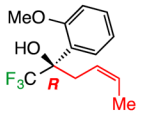




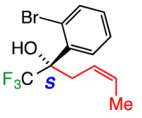
Z-3a
24 h, >98% conv, 86% yield,
>98:2 α:γ **>98:2 Z:E, 91:9 er**



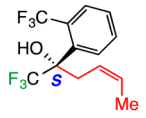
Z-3b
24 h, >98% conv, 91% yield,
>98:2 α:γ **83:17 Z:E, 44:56 er**



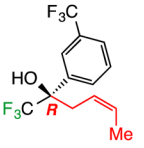
Z-3c
24 h, >98% conv, 89% yield,
>98:2 α:γ **98:2 Z:E, 85:15 er**



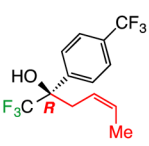
Z-3e
12 h, >98% conv, 96% yield,
98:2 α:γ **96:4 Z:E, 24:76 er**



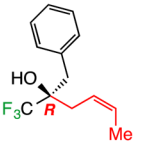
Z-3f
24 h, >98% conv, 93% yield,
>98:2 α:γ **>98:2 Z:E, 6:94 er**



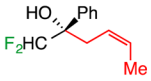
Z-3l
24 h, >98% conv, 92% yield,
>98:2 α:γ **>98:2 Z:E, 85:15 er**



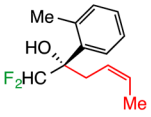
Z-3t
24 h, >98% conv, 90% yield,
>98:2 α:γ **>98:2 Z:E, 96:4 er**



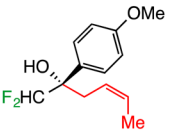
Z-11a
24 h, >98% conv, 82% yield,
>98:2 α:γ **>98:2 Z:E, 97:3 er**



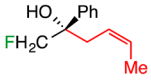
Z-16a
24 h, >98% conv, 93% yield,
>98:2 α:γ **>98:2 Z:E, 22:78 er**



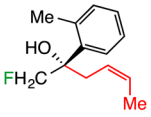
Z-16b
24 h, >98% conv, 89% yield,
>98:2 α:γ **98:2 Z:E, 9:91 er**



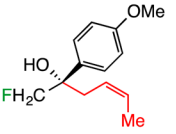
Z-16c
24 h, >98% conv, 95% yield,
>98:2 α:γ **>98:2 Z:E, 19:81 er**



Z-17a
24 h, >98% conv, 92% yield,
>98:2 α:γ **>98:2 Z:E, 9:91 er**



Z-17b
24 h, >98% conv, 95% yield,
98:2 α:γ **98:2 Z:E, 4:96 er**

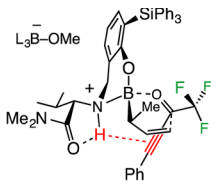


Z-17c
24 h, >98% conv, 98% yield,
>98:2 α:γ **>98:2 Z:E, 9:91 er**

[a]Reactions carried out under N_2 atm. Conversion, α:γ and *Z*:*E* ratios determined by analysis of ^{19}F NMR spectra of unpurified product mixtures (±2%). Yields for purified α-addition products (±5%). The er was determined by HPLC analysis (±1%). All experiments were run in duplicate or more. See the Supporting Information for details.

caused by the substrate's phenyl group and the aminophenol substituent (G) is diminished in **III**, more of the *E*-alkene isomer is formed. In contrast, repulsion between the ketone's trifluoromethyl group, which is smaller than Ph, and the same catalyst moiety, is not as significant; therefore, the impact on er is less.

The lower enantioselectivities (81:19–85:15 er) for enynes **13a–c** (Scheme 6) might be attributed to competing electrostatic attraction between the catalyst's ammonium unit and the alkynyl group (**IV**). The slightly higher er for more electron-poor *p*-trifluoromethylphenyl-substituted **13c** (85:15 vs 81:19 er for **13a**) provide some support, but together with nearly the same enantioselectivity for *p*-methoxyphenyl-substituted **13b**, these probably indicate that the change in electron density at the C–C triple bond is not significant enough for a stronger effect. Although interactions involving a C–C triple bond have been investigated only to a limited extent,[24] related associations between an ammonium moiety and aryl groups have been examined extensively[25] and proposed to account for the outcome of different types of transformations.[26] Such interactions are unlikely to be as strong with the corresponding *E*-alkenes since a nonlinear geometry should translate to less effective electrostatic attraction.



IV
possible competing interaction
with alkynyl substrates
(see **13**, Scheme 6)

5.2. Reactions with Organoboron Compound *E*-1a.

Enantioselectivities with *E*-crotyl–B(pin) are lower because of the smaller energy difference between **V** and **VI** (Scheme 14). The reason *Z* selectivity remains high in the reactions with *E*-**1a** is because of two counts of steric and electron–electron

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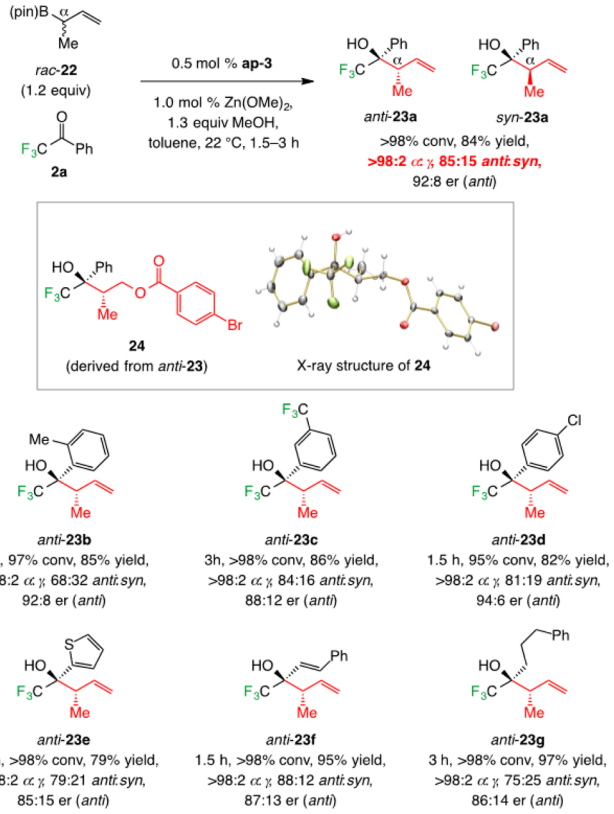
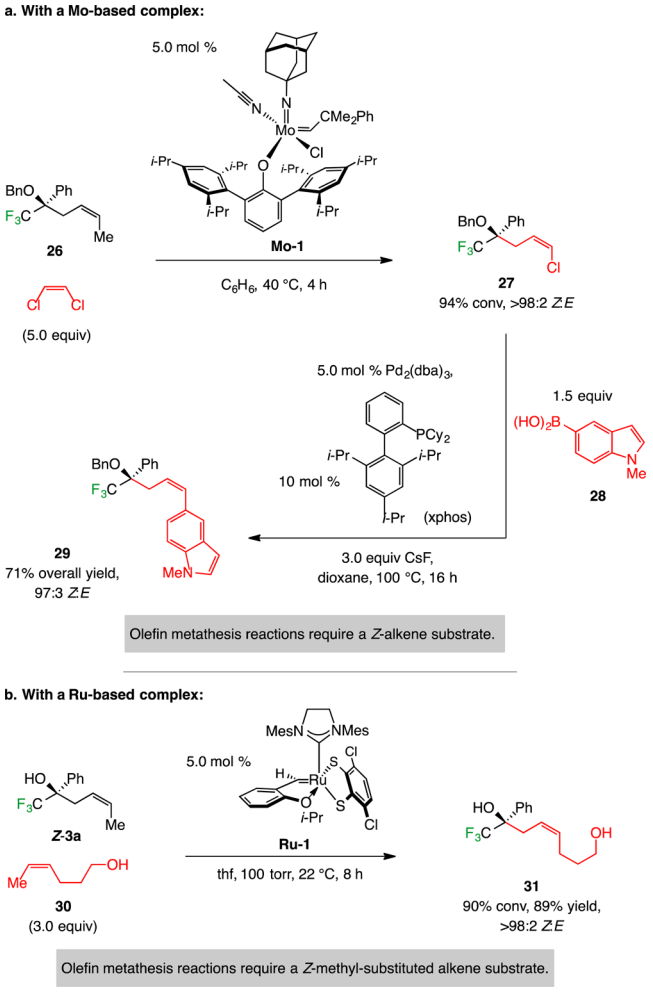
Scheme 10. Diastereo- and Enantioselective Additions with *rac*-22[a]



[a]Reactions carried out under N_2 atm. Conversion, α:γ and *Z*:*E* ratios determined by analysis of ^{19}F NMR spectra of unpurified product mixtures (±2%). Yields for purified α-addition products (±5%). The er was determined by HPLC analysis (±1%). All experiments run in duplicate or more. See the Supporting Information for details.

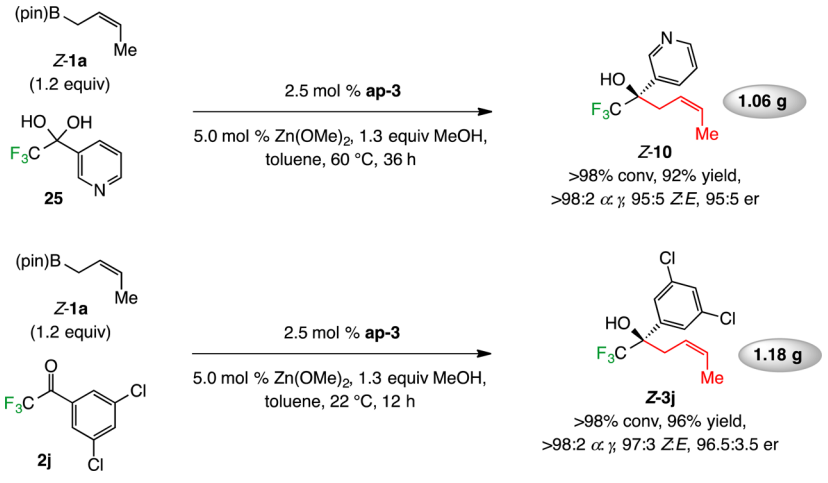
Scheme 12. In Combination with Catalytic *Z*-Selective Cross-Metathesis[a]



[a]Conversion and *Z*:*E* ratios determined by analysis of ^{19}F NMR spectra of unpurified product mixtures (±2%). Yields are for isolated and purified α-addition products (±5%). All experiments were run in duplicate or more. See the Supporting Information for details.

repulsion in **VII**, which render it less competitive. Reducing the size of the catalyst's aryl substituent (G), as shown by the data in Table 2, diminishes *Z*-selectivity to a small degree, suggesting that the electronic repulsion and steric interaction involving the

Scheme 11. Reactions on Gram Scale[a]



[a]Reactions carried out without inert atmosphere. Conversion, α:γ and *Z*:*E* ratios determined by analysis of ^{19}F NMR spectra of unpurified product mixtures (±2%). Yields for purified α-addition products (±5%). The er was determined by HPLC analysis (±1%). All experiments run in duplicate or more. See the Supporting Information for details.

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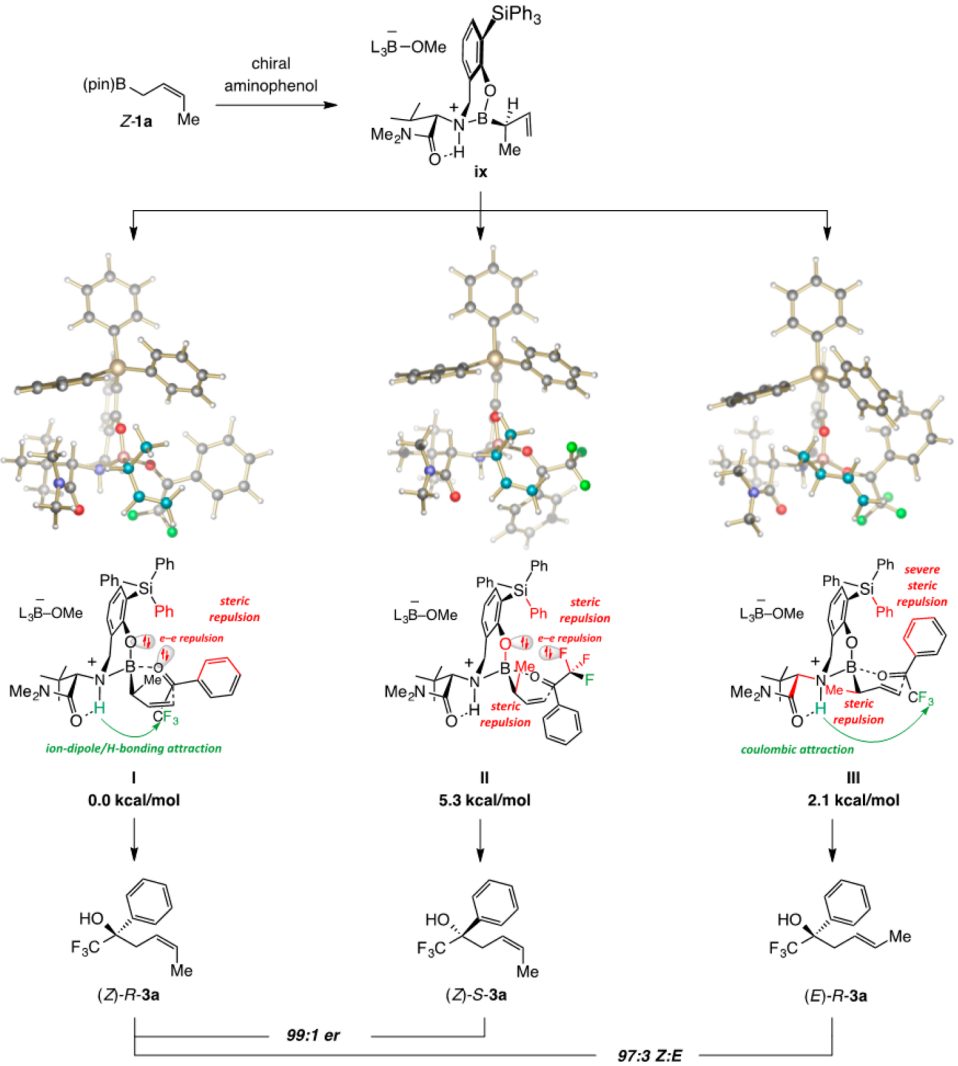
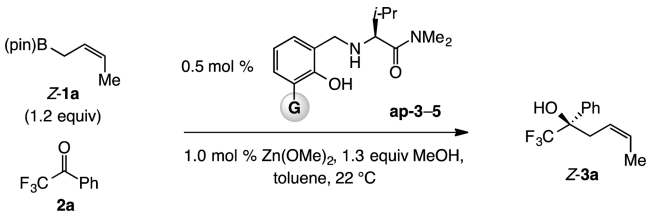
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Scheme 13. Stereochemical Models Based on DFT Studies with *Z*-Crotyl–B(pin)[a]



[a]DFT calculations were performed at the ωB97XD/DEF2TZVPP//ωB97XD/DEF2SVP$_{toluene(SMD)}$ level. Free energy values for transition states are relative to the most favorable alternative. See the Supporting Information for details.

Table 1. Effect of Ligand Structure on Stereoselectivity with *Z*-Crotyl–B(pin)[a]



entry	G	time (h); conv (%)[b]	α:γ[b]	*Z*:*E*[b]	yield (%)[c]	er[d]
1	$SiPh_3$ (**ap-3**)	1.5; >98	>98:2	***97:3***	87	99:1
2	*t*-Bu (**ap-4**)	12; >98	>98:2	***83:17***	85	98:2
3	H (**ap-5**)	48; 45	>98:2	***84:16***	32	97:3

[a]Reactions were carried out under N_2 atm. [b]Determined through analysis of ^{19}F NMR spectra of the unpurified product mixtures (±2%). [c]Yields are for isolated and purified α-addition products (±5%). [d]The er was determined through HPLC analysis (±1%). See the Supporting Information for details.

pseudo-equatorial methyl group in **VII** is the stronger factor (i.e., repulsion between the ketone and Ph group of the triphenylsilyl unit is less influential, as indicated by the *Z*:*E* selectivity values). Analogous modification of catalyst structure has little impact on er (entries 1–3, Table 2), since there would likely be similar lowering of steric repulsion in **V** and **VI**. The preference for **V** is reflected in the adverse effect of a sizable ortho aryl substituent on *Z*:*E* ratio (e.g., **3e–f**, Scheme 4), which arises from an increase in steric repulsion (vs that with **VII** wherein there is a pseudoequatorial aryl moiety).

5.3. Reactions with Di- and Monofluoromethyl Ketones. We have previously shown that electrostatic attraction with the catalyst's ammonium site is less influential with di- and monofluoromethyl ketones.[10] When *Z*-**1a** was used, products such as difluoromethyl **16a** and monofluoromethyl **17a** were generated in high er, indicating that reaction via **VIII** is more favored (vs that with **IX**, Scheme 15a). This is in contrast to allyl–B(pin) additions to the same ketones because with the presence of the methyl substituent steric factors become more influential such that high er can be attained. However, *Z*-selectivity hinges on competition between **VIII** and **X** (Scheme 15a), involving addition to different enantiotopic faces of the ketone carbonyl, as confirmed through determination of absolute stereochemistry.[15] The lower *Z*:*E* ratios thus

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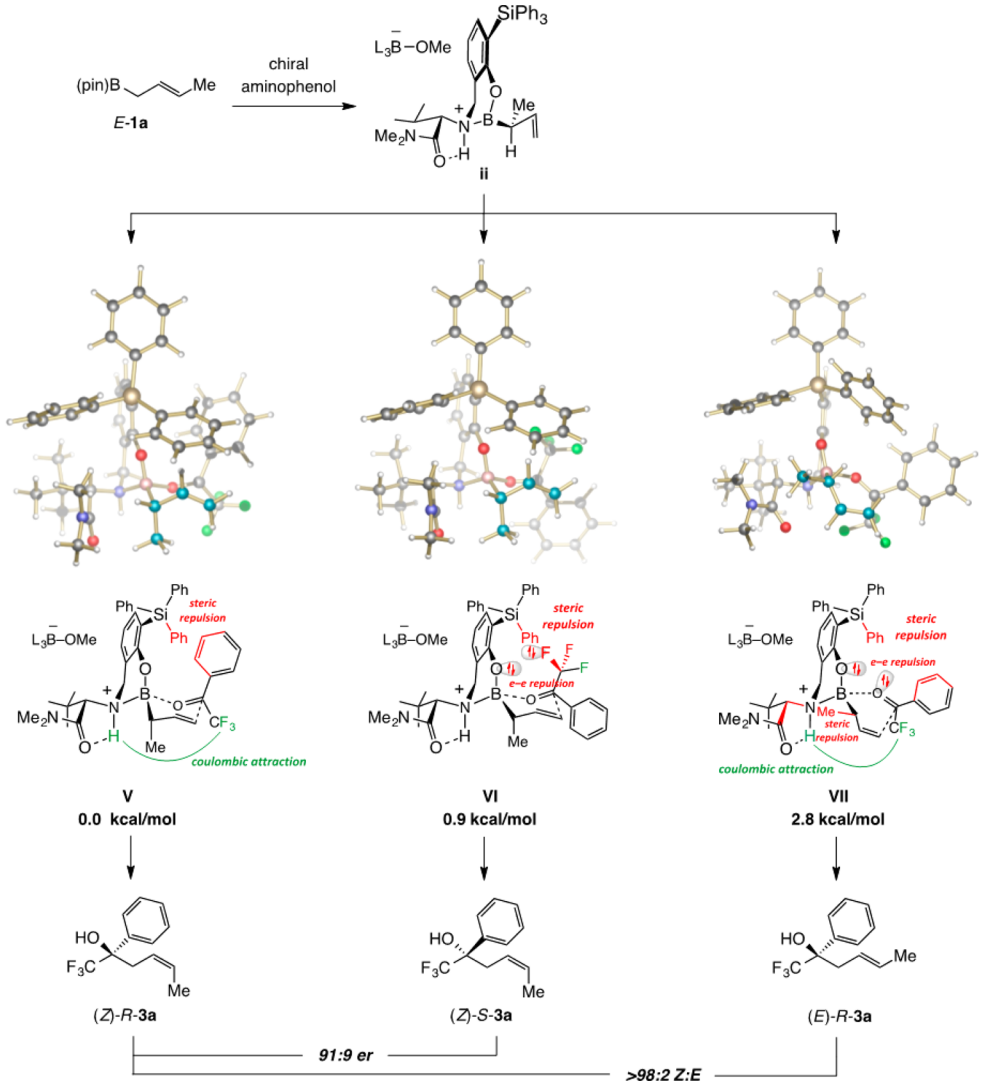
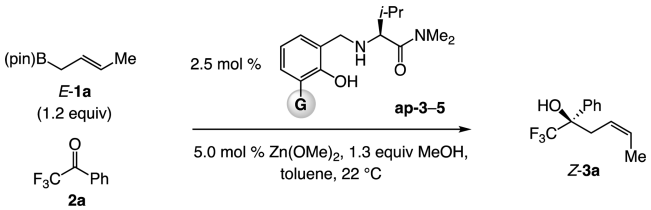
Scheme 14. Stereochemical Models Based on DFT Studies with *E*-Crotyl–B(pin)[a]



[a]DFT calculations were performed at the ωB97XD/DEF2TZVPP//ωB97XD/DEF2SVP$_{toluene(SMD)}$ level. Free energy values for transition states are relative to the most favorable alternative. See the Supporting Information for details.

Table 2. Effect of Ligand Structure on Stereoselectivity with *E*-Crotyl-B(pin)[a]



entry	G	time (h); conv (%)[b]	α:γ[b]	Z:E[b]	yield (%)[c]	er[d]
1	$SiPh_3$ (**ap-3**)	24; >98	>98:2	>98:2	86	91:9
2	*t*-Bu (**ap-4**)	24; >98	>98:2	97:3	84	93:7
3	H (**ap-5**)	24; 71	>98:2	96:4	60	89:11

[a]Reactions were carried out under N_2 atm. [b]Determined through analysis of ^{19}F NMR spectra of the unpurified product mixtures (±2%). [c]Yields are for isolated and purified α-addition products (±5%). [d]The er was determined through HPLC analysis (±1%). See the Supporting Information for details.

reflect the lower energy difference between the steric hindrance of the ketone substituent and the triphenylsilyl group in **VIII** as well as the pseudoequatorial methyl group and the catalyst framework in **X**. The slightly higher *Z* selectivity for difluoromethyl ketones (vs the monofluoromethyl derivative) might be the result of stronger electrostatic attraction between the fluoro-organic moiety and the ammonium group.

The sense of enantioselectivity is reversed with *E*-**1a** (Scheme 15b) because the reactions proceed via **XI** and **XII**. Without electrostatic attraction, **XII** is favored due to lower steric repulsion, a distinction more pronounced with a smaller monofluoroalkyl substituent (22:78 vs 9:91 er for **16a** and **17a**, respectively; Scheme 15b). It follows that with a more sterically demanding aryl substituent, **XI** becomes less favored, resulting in increased enantioselectivity to the extent that *o*-trifluoromethyl-substituted **3f** may be generated in 6:94 er (Scheme 9).

6. CONCLUSIONS

We put forth methods for efficient and enantioselective addition of readily accessible *Z*-γ-substituted boronic acid pinacol ester compounds to fluoroalkyl-substituted ketones. The approach

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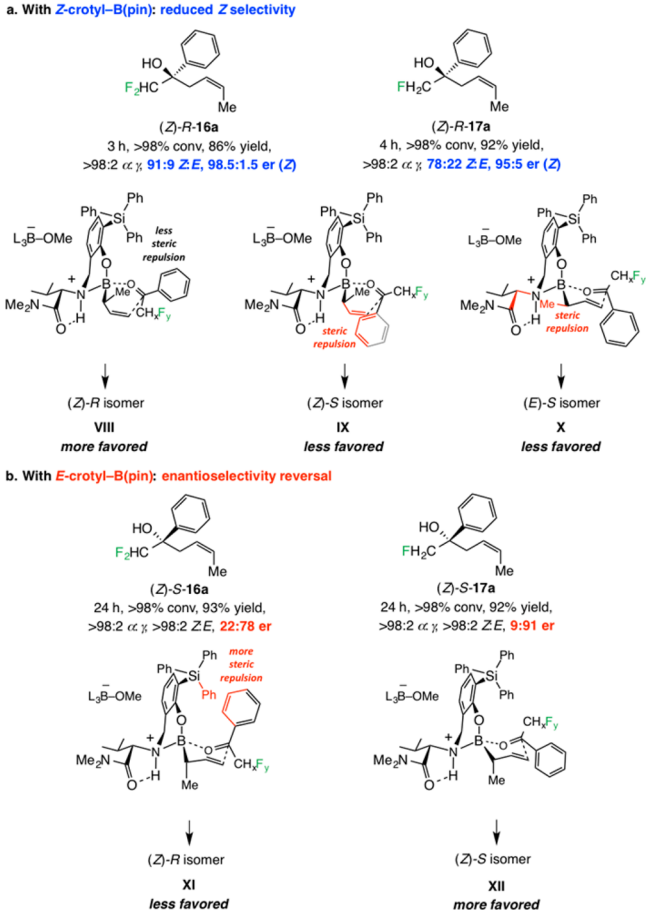
Scheme 15. Influence of Number of Fluorine Atoms on Stereoselectivity[a]



[a]Reactions carried out under N_2 atm. Conversion, α:γ and Z:E ratios determined by analysis of ^{19}F NMR spectra of unpurified product mixtures (±2%). Yields are for purified α-addition products (±5%). The er was determined by HPLC analysis (±1%). All experiments run in duplicate or more. See the Supporting Information for details.

has considerable range as aryl-, heteroaryl-, alkynyl-, alkenyl-, and alkyl-substituted ketones with a polyfluoro-, trifluoro-, difluoro-, and monofluoro-alkyl substituent can be used, affording products with up to 98% yield and >99:1 er (Schemes 4–8). Reactions can be catalyzed by 0.5–2.5 mol % of a complex generated in situ from valine-derived aminophenol ligand may be carried out at room temperature and are complete within a few hours. Contrary to reactions with unsubstituted allyl–B(pin), additions to mono- and difluoroalkyl substituted ketones are highly enantioselective. A noteworthy aspect of the transformations is that addition of the initial chiral organoboron intermediate to a fluoro-ketone is faster than 1,3-boryl shift, and as a result, α selectivity is often exceptionally high. Equally notable are the high Z:E ratios (up to >98:2), an attribute that is largely due to effective catalyst control of stereoselectivity. The assortment of possibilities for functionalization of the stereochemically defined alkene product, such as kinetically controlled Z-selective olefin metathesis reactions, add to the value of the approach.

We provide the first examples of efficient, diastereo-, and enantioselective synthesis of the corresponding γ-addition type products, where a racemic organoboron reagent adds to fluoroketones with >98% α selectivity (Scheme 12). Thus, by a combination of electronic (e.g., electrostatic attraction between the catalyst's ammonium group and the fluoroalkyl groups) and steric factors (e.g., induced by installation of a sizable triphenylsilyl group) tertiary homoallylic alcohols that contain a stereogenic carbon center with a hydroxyl and a fluoroalkyl substituent may be prepared in high yield, high Z-selectivity, and high enantiomeric purity. Mechanistic models based on DFT studies provide a rationale for different selectivity profiles and should be of value in future studies regarding this class of enantioselective catalysts (Schemes 13–15, Tables 1–2).

The present work allows facile access to many valuable enantiomerically enriched organofluorine compounds that might be used in the preparation of therapeutic candidates, novel materials, and/or more effective agrochemicals. Design and development of additional boron-based chiral catalysts and methods for enantioselective synthesis continue in these laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b05011.

Crystallographic information files for **Z-10**, **18**, and **24** (CIF, CIF, CIF)

Experimental details for all reactions and analytic details for all enantiomerically enriched products. Tables of electronic and free energies and geometries of computed structures. (PDF)

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Notes

The authors declare no competing financial interest.

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(16) The reason for the 85:15 dr is that the reaction of *R*- and *S*-**24** afford the same *anti*-**25a** predominantly but with different levels of diastereo- and enantioselectivity, as indicated by investigations detailed in the Supporting Information.

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