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Catalytic Enantioselective Addition of an Allyl Group to Ketones Containing a Tri-, a Di-, or a Monohalomethyl Moiety. Stereochemical Control Based on Distinctive Electronic and Steric Attributes of C−Cl, C−Br, and C−F Bonds

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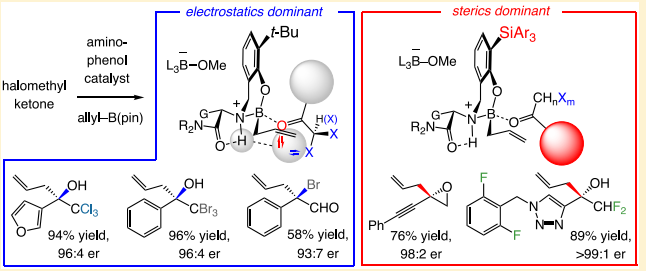
Supporting Information

ABSTRACT: We disclose the results of an investigation designed to generate insight regarding the differences in the electronic and steric attributes of C−F, C−Cl, and C−Br bonds. Mechanistic insight has been gleaned by analysis of variations in enantioselectivity, regarding the ability of electrostatic contact between a halomethyl moiety and a catalyst's ammonium group as opposed to factors lowering steric repulsion and/or dipole minimization. In the process, catalytic and enantioselective methods have been developed for transforming a wide range of trihalomethyl (halogen = Cl or Br), dihalomethyl, or monohalomethyl (halogen = F, Cl, or Br) ketones to the corresponding tertiary homoallylic alcohols. By exploiting electrostatic attraction between a halomethyl moiety and the catalyst's ammonium moiety and steric factors, high enantioselectivity was attained in many instances. Reactions can be performed with 0.5−5.0 mol % of an in situ generated boryl−ammonium catalyst, affording products in 42−99% yield and up to >99:1 enantiomeric ratio. Not only are there no existing protocols for accessing the great majority of the resulting products enantioselectively but also in some cases there are hardly any instances of a catalytic enantioselective addition of a carbon-based nucleophile (e.g., one enzyme-catalyzed aldol addition involving trichloromethyl ketones, and none with dichloromethyl, tribromomethyl, or dibromomethyl ketones). The approach is scalable and offers an expeditious route to the enantioselective synthesis of versatile and otherwise difficult to access aldehydes that bear an α-halo-substituted quaternary carbon stereogenic center as well as an assortment of 2,2-disubstituted epoxides that contain an easily modifiable alkene. Tertiary homoallylic alcohols containing a triazole and a halomethyl moiety, structural units relevant to drug development, may also be accessed efficiently with exceptional enantioselectivity.



1. INTRODUCTION

Organohalides are central to research in chemistry. Fluoroorganic molecules are important in medicine,[1] and, aside from being common electrophiles, chloro- and bromoalkyl moieties can be found in bioactive compounds.[2] Catalytic strategies for enantioselective synthesis of organohalides are thus highly desirable. And yet, there are only a small number of catalytic methods for generating halogen-containing organic molecules in high enantiomeric purity. One notable study appeared more than three decades ago by Corey in regard to enantioselective reductions of halo-substituted ketones.[3,4]

We have previously reported catalytic reactions between trifluoromethyl ketones and allylic boronates[5,6] where the enantioselectivity was an indicator of the extent of electrostatic attraction between an ammonium moiety and a C−F bond. We showed that, whereas additions to methyl ketones proceed with low selectivity (e.g., 68:32 enantiomeric ratio (er), Scheme 1a), transformations with trifluoromethyl ketones are much more enantioselective, affording the alternative stereoisomer preferentially (e.g., 4:96 er, Scheme 1a). This reversal might be expected on the basis of width (B_1) Sterimol parameters[7] (Ph, 1.71; CH_3, 1.52; CF_3, 1.97),[8] but the er differences would probably be significantly less. Length (L) Sterimol values (Ph, 6.28; CH_3, 3.00; CF_3, 3.32[8]) would predict a high er in both instances and with the *same* sense of enantioselectivity. We have proposed stereochemical models, on the basis of experimental as well as DFT studies, where electrostatic attraction between the trifluoromethyl group and the ammonium proton attenuates electron−electron repulsion (**I**, Scheme 1a).[5a] We have posited a rationale for several selectivity variations. For instance, the reason reactions with 2-furyl and 2-thienyl trifluoromethyl ketones are less enantioselective, in comparison to the 3-furyl and 3-thienyl derivatives, seems to be due to competitive electrostatic attraction in the former (**III**, Scheme 1a).

Reactions with difluoromethyl or monofluoromethyl ketones, on the other hand, are hardly enantioselective (≤65:35

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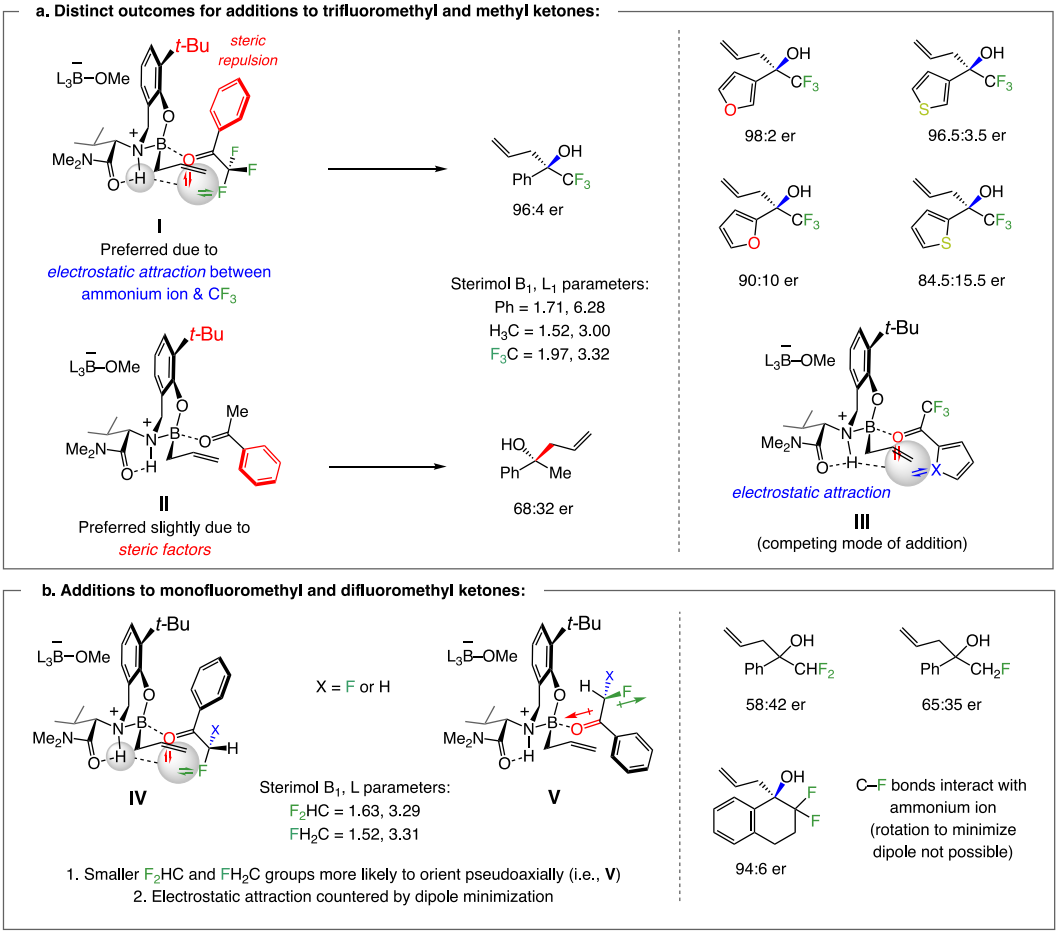
Scheme 1. Previous Findings



er, Scheme 1b), as might be expected on the basis of Sterimol B_1 or L differences (Scheme 1b). The lower er for difluoromethyl and monofluoromethyl ketones is likely a consequence of dipole minimization (cf. **IV** and **V**, Scheme 1b), which is not applicable to trifluoromethyl groups. Accordingly, we found that addition to a cyclic difluoroalkane, where the C–F bonds cannot orient anti to the carbonyl group, is highly selective (94:6 er, Scheme 1b). We were later able to achieve considerable enantioselectivity in reactions with mono- and difluoromethyl ketones by using (*Z*)-crotyl–B(pin) as the reagent;[5b] however, an additional Me (or any other) substituent was required. Achieving the same with allyl–B(pin) via a considerably more flexible transition state would be considerably more challenging.

The following key questions subsequently arose and are the subject of the present report:

(1) Would additions to trichloromethyl and tribromomethyl ketones be governed by electrostatic forces similar to those observed with trifluoromethyl variants, or do steric factors dominate (Scheme 2)? Although Cl and Br are much less electronegative than F (Pauling scale: F, 3.98; Cl, 3.16; Br, 2.96), C–Cl and C–Br bonds are longer and more polarized, implying that electrostatic attraction might be important (bond moments: C–F, 1.39 D; C–Cl, 1.47 D; C–Br, 1.42 D).[9] Still, CCl_3 and CBr_3 are significantly larger than CF_3 (Sterimol B_1 (L) values: Ph, 1.71 (6.28); CF_3. 1.97 (3.32); CCl_3, 2.64 (3.83); CBr_3, 2.87 (4.01[8])), and steric factors could well exert a greater influence on efficiency and/or enantioselectivity.

(2) Would additions to dichloromethyl and dibromomethyl ketones or monochloromethyl and monobromomethyl ketones be much less enantioselective in comparison to their trihalomethyl derivatives, as was the case with the F-substituted variants (Scheme 1b)? If the er were to be high with monohalomethyl or dihalomethyl ketones, considering the larger size of Cl and Br, it would mean that electrostatic interactions play an even more important role (favoring reaction via the chloro or bromo derivative of **IV**). If steric factors were to be dominant, the smaller difference in size between the mono- or dihalomethyl moieties and other ketone substituents would render enantiotopic differentiation more challenging.

(3) Considering that electronic factors do not play a major role with mono- and difluoromethyl ketones, and the importance of organofluorine compounds, might a strategy be developed for accessing the corresponding tertiary homoallylic alcohols in high er?

(4) The products of many of the above transformations would be synthetically versatile due to the higher reactivity of the C–Cl and C–Br bonds (vs C–F). What valuable and otherwise difficult to synthesize enantiomerically enriched organic molecules would become readily available through functionalization of

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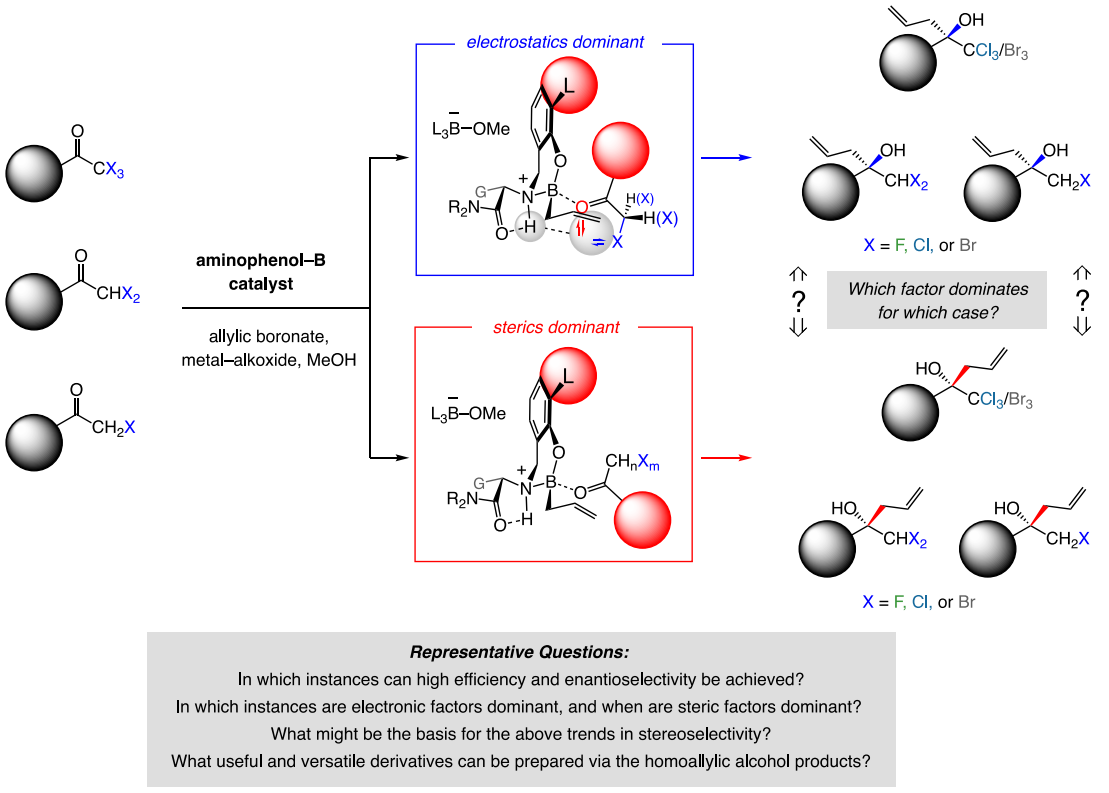
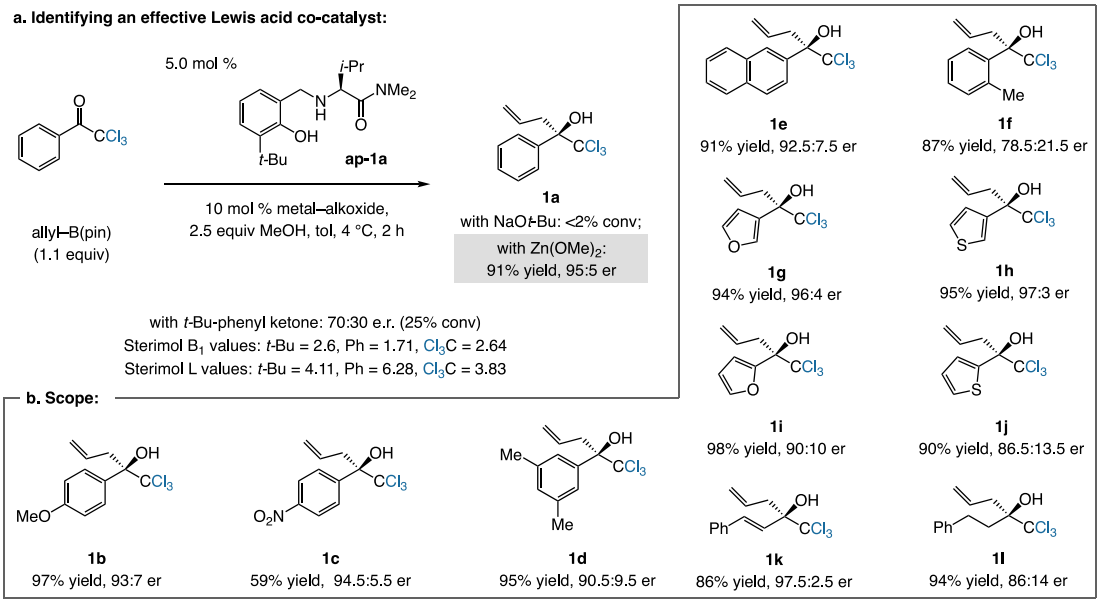
Scheme 2. Main Objectives of This Study



Scheme 3. Allyl–B(pin) Addition to Trichloromethyl Ketones[a]



[a]Reactions were run under an N_2 atmosphere. Conversion (>98% in all cases) was determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields are for the purified products (±5%). Enantioselecivity was determined by HPLC analysis (±1%). Experiments were run at least in triplicate. See the Supporting Information for details.

the above halomethyl-substituted tertiary homoallylic alcohols?

It should be emphasized that while catalytic enantioselective additions of allyl moieties to ketones have been widely investigated,[10] those involving the above set of halogen-substituted ketones (Scheme 2) are uncommon. This is likely because the sizes of a halomethyl group and the other ketone substituent are more similar and therefore steric differentiation is more difficult. Furthermore, in the case of dihalomethyl and monohalomethyl ketones, where the halogen is a chlorine or bromine atom, the strongly basic conditions needed for protocols that involve organometallic species can lead to undesirable pathways (e.g., enolization and self-condensation). As such, at least in certain cases, electronic factors that can

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J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

promote stereodifferentiation are required. While there is just a single report regarding enzyme-catalyzed aldol addition to a trichloromethyl ketone,[11] there are, to the best of our knowledge, no examples that involve a dichloromethyl, a tribromomethyl, or a dibromomethyl derivative. Moreover, although there are reported instances of catalytic enantioselective reactions between a C-based nucleophile and a monochloromethyl, a monobromomethyl, a monofluoromethyl, or a difluoromethyl ketone,[12,13] other than the two isolated examples of allyl additions to phenyl monochloromethyl ketone (i.e., a single substrate), no other corresponds to formation of a tertiary homoallylic alcohol.[14,15]

2. RESULTS AND DISCUSSION

2.1. Trichloromethyl and Tribromomethyl Ketones.

We began with the question of whether or not catalytic allyl addition to trichloromethyl or tribromomethyl ketones can be efficient and highly enantioselective and, if so, whether the sense of selectivity is the same as that observed with trifluoromethyl analogues (i.e., electronic factors play a significant role).

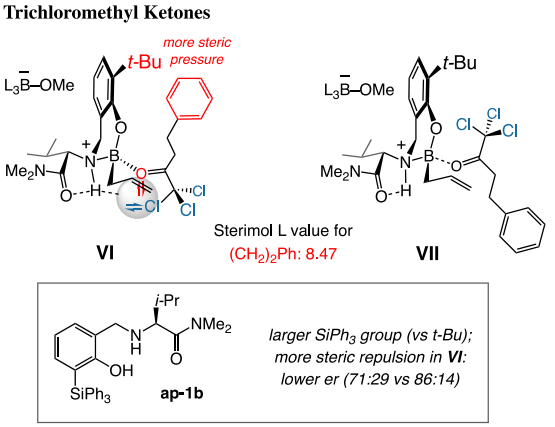
2.1.1. Trichloromethyl Ketones. With **ap-1a** and NaO-*t*-Bu, there was <2% reaction with trichloroacetophenone (Scheme 3a), but with the more Lewis acidic $Zn(OMe)_2$[16] we were able to isolate homoallylic alcohol **1a** in 91% yield and 95:5 er. The high er is noteworthy considering that, without **ap-1a**, there was ~70% conversion to *rac*-**1a**. Equally important, the major isomer arises from addition to the *same* enantiotopic face as a trifluoromethyl ketone (**I**, Scheme 1a), indicating that electronic factors remain dominant. The minor role of steric strain[17] is underscored by the low er for *tert*-butylphenyl ketone (70:30 er; Sterimol B_1 (L) values: *t*-Bu, 2.6 (4.11); Ph, 1.71 (6.28); Cl_3C, 2.64 (3.83)).

Aryl-substituted trichloromethyl ketones reacted efficiently and enantioselectively (Scheme 3b), including those with an electron-donating (**1b**), electron-withdrawing (**1c**), or a hindered moiety (**1d–f**). The reduced er for **1d** and particularly **1f**, which contain relatively hindered aryl substituents, may be attributed to increased steric pressure involving the catalyst's *t*-Bu group (see Scheme 2). Additions to 3-furyl- and 3-thienyltrichloromethyl ketones afforded **1g,h** in 94% and 95% yield and 96:4 and 97:3 er, respectively. As expected, and likely for the reasons noted above (**III**, Scheme 1a), **1i,j** were formed with lower enantioselectivity (90:10 vs 96:4 er for the 2-furyl and 3-furyl cases, respectively, and 86.5:13.5 vs 97:3 er for the 2-thienyl and 3-thienyl cases, respectively). These cases confirm that, despite its much larger size (vs a CF_3), a CCl_3 group can engage in electrostatic interaction with the catalyst's ammonium unit, especially considering that selectivities were similar to those of trifluoromethyl ketones.[5a] Higher polarization of a C–Cl bond (vs C–F) thus fully compensates for the increase in steric requirements. Efficient synthesis of allylic alcohol **1k** highlights the advantage of a non-transition metal catalyst,[18] where competitive conjugate addition can be a complication.

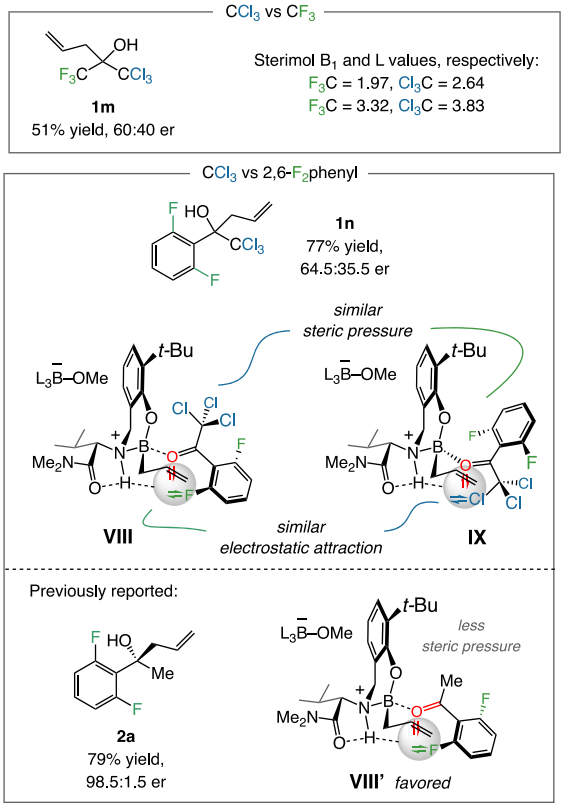
The lower er for phenethyl-substituted **1l** (86:14 er), in comparison to the tertiary benzylic alcohols and especially **1k** (97.5:2.5 er), might be because there is greater steric pressure with a more extended alkyl moiety (see **VI**; Scheme 4), a proposal that is supported by the large Sterimol L value calculated for a phenethyl moiety (8.47 vs 6.28 for Ph).[8] Hence, **1l** was formed in 71:29 er when the larger triphenylsilyl-substituted **ap-1b** was used (vs 86:14 with **ap-1a**).

Despite the major difference in size between a CF_3 and a CCl_3 group (Sterimol B_1 = 1.97 and 2.64, respectively), the addition to trifluoromethyl-substituted trichloromethyl ketone is minimally selective (**1m**, 60:40 er). This is revealing and lends credence to the ability of a CCl_3 unit to associate electrostatically with an ammonium group. Equally informative

Scheme 4. Factors Controlling Addition to Alkyl-Substituted Trichloromethyl Ketones



Scheme 5. Competition with an Organofluorine Group[a]



[a]Reactions were run under an N_2 atmosphere. Conversion (>98% in all cases) were determined by analysis of ^1H NMR spectra of unpurified product mixtures (±2%). Yields are for the purified products (±5%). Enantioselectivity was determined by HPLC analysis (±1%). Experiments were run at least in triplicate. See the Supporting Information for details.

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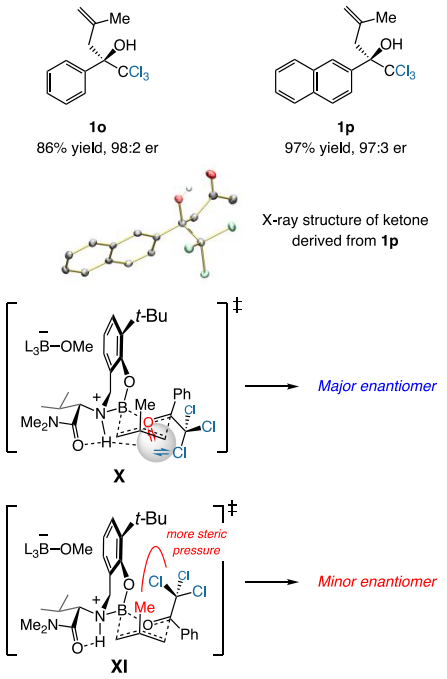
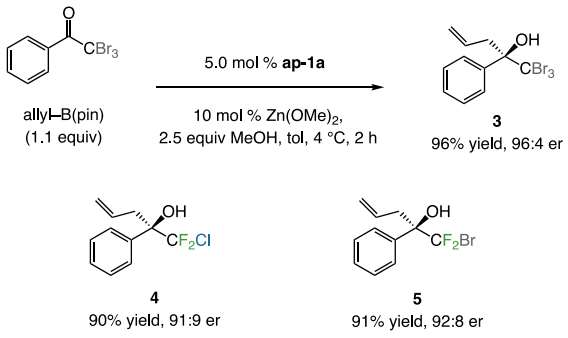
Scheme 6. Reactions with a C2-Substituted Allylboronate[a]



[a]Reactions were run under an N_2 atmosphere. Conversions (>98% in all cases) were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields are for the purified products (±5%). Enantioselectivity was determined by HPLC analysis (±1%). Experiments were run at least in triplicate. See the Supporting Information for details.

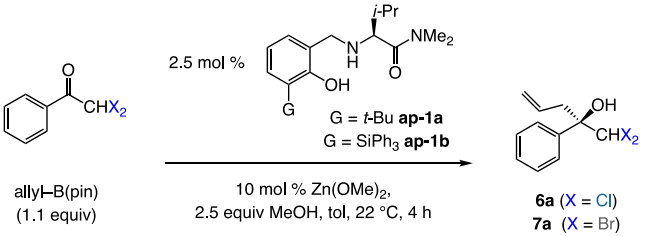
Scheme 7. Influence of a Tribromomethyl Group in Comparison to a Difluorochloromethyl and a Difluorobromomethyl Unit[a]



[a]Reactions were run under an N_2 atmosphere. Conversions (>98% in all cases) were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields are for purified products (±5%). Enantioselectivity was determined by HPLC analysis (±1%). All experiments were run at least in triplicate. See the Supporting Information for details.

is the low er for 2,6-difluorophenyl-substituted **1n** (64.5:35.5 er; Scheme 5) in comparison to the more enantioselective case of a 2,6-difluorophenyl-substituted ketone (**2a**, 98.5:1.5 er).[5a] There is probably analogous steric repulsion between the catalyst's *t*-Bu unit and a CCl_3 or a 2,6-difluorophenyl unit (**VIII** and **IX**, respectively, Scheme 5). However, unlike **2a**, a product derived from a methyl ketone for which **VIII′** represents the more favorable mode of addition, there are

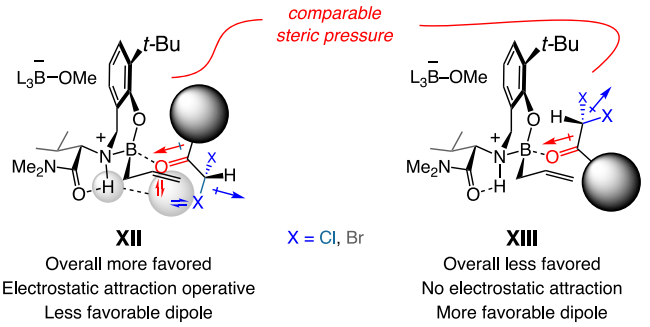
Table 1. Influence of Aminophenol Structure on Additions to Dichloromethyl and Dibromomethyl Ketones[a]



entry	X	aminophenol	yield (%)[b]	er[c]
1	Cl	**ap-1a**	96	86:14
2	Cl	**ap-1b**	98	76:24
3	Br	**ap-1a**	89	91:9
4	Br	**ap-1b**	93	84:16

[a]Reactions run were run under an N_2 atmosphere. Conversions (>98% in all cases) were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). [b]Yields are for purified products (±5%). [c]Enantioselectivity was determined by HPLC analysis (±1%). See the Supporting Information for details.

Scheme 8. Possible Reason for Lower Enantioselectivity of Reactions with Dichloromethyl and Dibromomethyl Ketones



similar electrostatic attractions and steric repulsions in **VIII** and **IX**.

A C2-methyl substituent within the allyl boronate thus causes the er to be higher (e.g., 98:2 vs 95:5 er for **1o** vs **1a** and 97:3 vs 92.5:7.5 er for **1p** vs **1e**; see Scheme 6 and Scheme 3); the alternative addition mode (**X** vs **XI**, Scheme 6) is destabilized because of more severe repulsion. Considering the repulsion between the naphthyl substituent and the catalyst's *t*-Bu moiety,[14] the high er for **1p** underscores the influence of electrostatic forces on enantioselectivity.

2.1.2. Other Trihalomethyl Ketones. Tribromomethyl-substituted tertiary alcohol **3** was obtained in 96% yield and 96:4 er after 2 h at 4 °C (Scheme 7; at 22 °C, 38% yield,[19] 87:13 er). The efficiency of addition to this significantly congested carbonyl group is especially noteworthy, as is the sense of enantioselectivity, which is the *same* as for trifluoromethyl and trichloromethyl ketones. In light of the much larger size of a CBr_3 group (Sterimol B_1 (L) values: CCl_3, 2.64 (3.83); CBr_3, 2.87 (4.01)]) and lower polarization in a C–Br bond (bond moments: C–Cl, 1.47 D; C–Br, 1.42 D), the high er more likely originates from steric factors, as the sizable trihalomethyl group is probably situated equatorially

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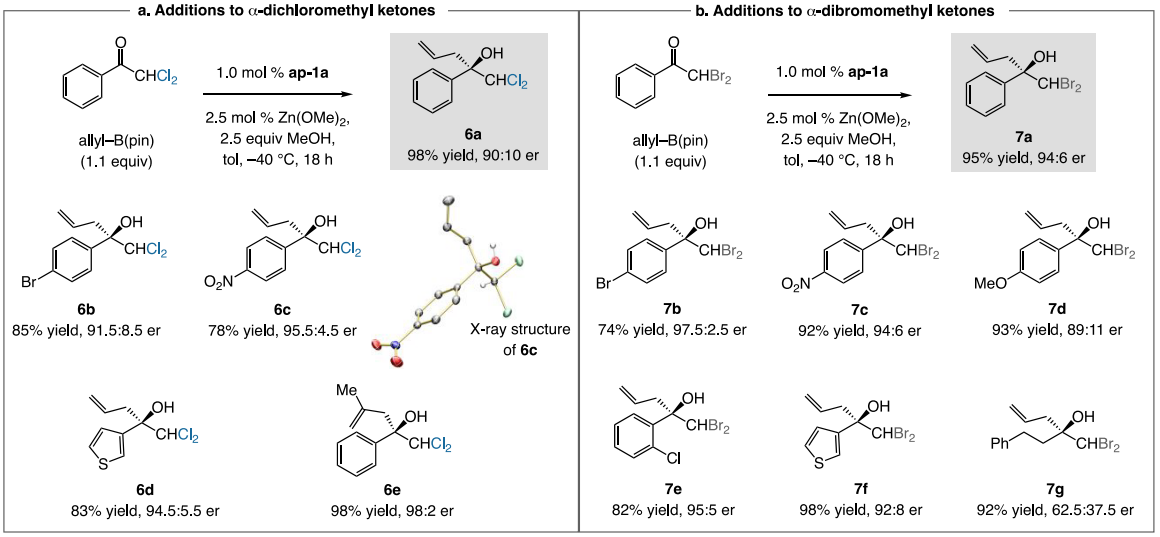
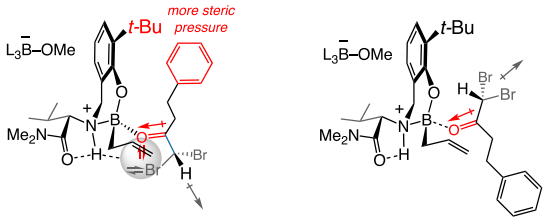
Scheme 9. Additions to Dichloromethyl and Dibromomethyl Ketones[a]



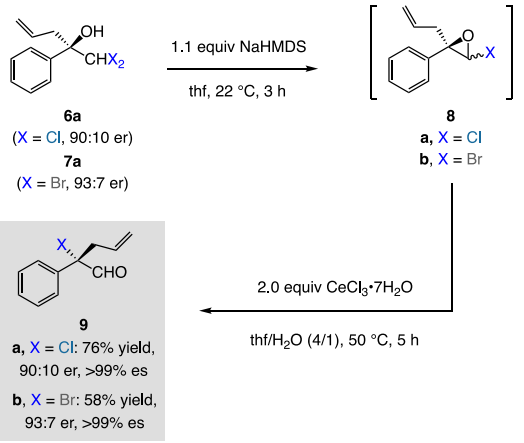
[a]Reactions were run under an N_2 atmosphere. Conversions (>98% in all cases) were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields are for purified products (±5%). Enantioselectivity was determined by HPLC analysis (±1%). Experiments were run at least in triplicate. See the Supporting Information for details.

Scheme 10. Impact of Electrostatic Interactions and Stereoelectronic Effects on Enantioselectivity



Smaller energy gap vs aryl- or heteroaryl-substituted variants: lower er

Scheme 11. Synthesis of α-Halo-γ,δ-Unsaturated Aldehydes[a]



[a]Reactions were run under an N_2 atmosphere. Conversions (>98% in all cases) were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields are for purified products (±5%). Enantioselectivity was determined by HPLC analysis (±1%). Experiments were run at least in triplicate. es = enantiospecificity ((product er)/(substrate er) × 100). See the Supporting Information for details.

(cf. **X**, Scheme 6). This is consistent with dominant steric effects, affording products in ≥95:5 er with methyl ketones that have a large aryl moiety (e.g., 1-naphthyl substituted), or those performed with aminophenol-based catalysts with a triphenylsilyl moiety instead of a *t*-Bu-aryl unit (e.g., **ap-1b**; see Scheme 4).[14] Formation of **4** and **5** (Scheme 7) in lower er in comparison to **3** shows that electrostatic attraction involving the C–F bonds is less controlling than the release of steric pressure resulting from the positioning of a CBr_3 moiety pseudoequatorially (cf. **IV**, Scheme 1b).

2.2. Dichloromethyl and Dibromomethyl Ketones. Reactions with dichloromethyl and dibromomethyl ketones (Table 1) were efficient (89–98% yield), revealing several key attributes. (1) The major enantiomer is derived from addition to the *same* enantiotopic face of the carbonyl group as with the trihalomethyl ketones. (2) Tertiary homoallylic alcohols **6a** and **7a** were generated in higher er (86:14 and 91:9 with **ap-1a**, entries 1 and 3) in comparison to their difluoromethyl derivative (58:42 er, Scheme 1b). (3) Enantioselectivities were lower than those when trihalomethyl ketones were used, not exceeding 91:9 er. (4) With silyl-substituted **ap-1b** the er was lower (entries 2 and 4 vs entries 1 and 2, Table 1). Stereochemical models **XII** and **XIII** (Scheme 8) offer a plausible rationale for these findings. Reaction via **XII** should be preferred due to electrostatic attraction between the dihalomethyl group and the ammonium moiety. However, unlike for the reactions of trihalomethyl ketones, addition via **XIII** can be more competitive because, although ammonium/X–C association is lost, dipolar repulsion is minimized. With the larger **ap-1b**, reaction via **XII** becomes less preferred because of steric repulsion between the silyl moiety and the ketone's aryl group. The lower er for the dichloromethyl and dibromomethyl ketones is probably a consequence of the diminished steric repulsion between these moieties and the *t*-Bu group in **XIII**, as reflected by the Sterimol *L* (but not B_1)

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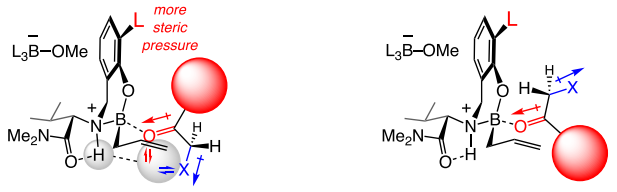
Scheme 12. Steric Effects and Dipole Minimization in Reactions with Monohalomethyl Ketones



XVI

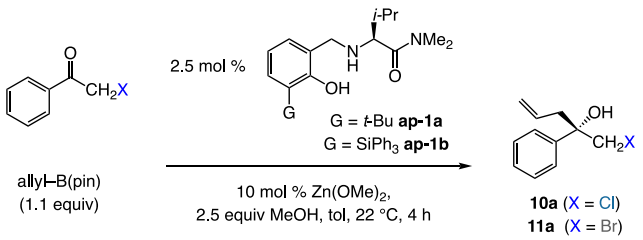
a. Electrostatic attraction at the cost of strongly unfavorable dipole
b. More steric pressure
Less favored?

XVII

a. No electrostatic attraction but much more favorable dipole
b. Less steric pressure
More favored?

Dipole minimization and steric effects more dominant: reversal of enantioselectivity (vs tri- and dihalomethyl ketones)

Table 2. Reversal of Enantioselectivity and Greater Influence of Steric Factors in Additions to Monochloromethyl and Monobromomethyl Ketones[a]



entry	X	aminophenol	yield (%)[b]	er[c]
1	Cl	**ap-1a**	83	81:19
2	Cl	**ap-1b**	96	97:3
3	Br	**ap-1a**	91	87:13
4	Br	**ap-1b**	98	98:2

[a]Reactions were run under an N_2 atmosphere. Conversions (>98% in all cases) were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). [b]Yields are for purified products (±5%). [c]Enantioselectivity was determined by HPLC analysis (±1%). See the Supporting Information for details.

values (Sterimol B_1 (L) values: phenyl, 1.71 (6.28); Cl_2HC, 1.65 (3.85); Br_2HC, 1.64 (4.04);[8] see below for further analysis).

Enantioselectivities increased at −40 °C, and **6a** and **7a** were isolated in 90:10 to 94:6 er (Scheme 9). Reactions with dihalomethyl ketones bearing an electron-deficient (e.g., **6c**, Scheme 9a; **7c**, Scheme 9b) or electron-donating aryl group (e.g., **7d**, Scheme 9b) or those with a heterocyclic moiety (e.g., **6d**, Scheme 9a, and **7f**, Scheme 9b) afforded the desired tertiary alcohols in up to 98% yield and 97.5:2.5 er. Control experiments indicate that the lower er for **7d** probably originates from an increase in competitive uncatalyzed addition, which in turn might be because of stronger association of the more electron rich carbonyl with allyl–B(pin). Addition of a 2-substituted allyl–B(pin) gave **6e** in 98% yield and 98:2 er (Scheme 9a).

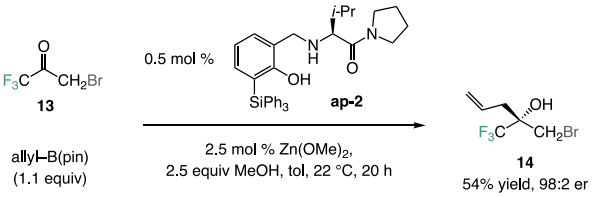
Like trichloromethyl ketones, reactions with alkyl-substituted substrates were efficient but less enantioselective (e.g., **7g**, Scheme 9b), which is in line with the aforementioned proposal vis-à-vis the diminished er for reactions of an alkyl-substituted trichloromethyl ketone (see Scheme 4). The factors described above notwithstanding, it seems that, with the competition between electrostatic attraction and dipolar minimization favoring the latter (i.e., **XIV** vs **XV**, Scheme 10), there would be little difference in the activation energies.

Direct synthesis of tertiary homoallylic alcohols with an adjacent dihalomethylene is a convenient way of synthesizing valuable but otherwise difficult to access compounds. For example, treatment of **6a** or **7a** (Scheme 11) with NaHMDS (3 h, 22 °C), probably affording epoxides **8a,b**,[20] was followed by the addition of $CeCl_3{\cdot}7H_2O$[21] (5 h, 50 °C). We thus isolated **9a,b** in 76% yield and 90:10 er and 58% yield and 93:7 er, respectively. The α-halo-γ,δ-unsaturated aldehydes were accordingly synthesized with exceptional enantiospecificity (es). Although there are catalytic methods for the enantioselective synthesis of such entities, which have been used to prepare bioactive compounds,[22] a protocol for the synthesis of a fully substituted variant is uncommon.[23]

2.3. Monochloromethyl and Monobromomethyl Ketones. In light of the enantioselectivity trends for additions to trihalomethyl versus dihalomethyl ketones, and the weaker impact of electrostatic factors in the latter, we wondered whether steric factors might play a greater role with monohalomethyl variants (Scheme 12). With a C–halogen bond anti to the C=O (**XVII** vs **XVI**, Scheme 12), electrostatic attraction can be countered by dipolar forces, which has two consequences: additions would occur on the *opposite* enantiotopic carbonyl face preferentially and steric factors would be more dominant. Experimental data indicate that this is the case (Table 2), as **10a** and **11a**, derived from addition to the *re* face, were obtained in 97:3 (96% yield) and 98:2 er (98% yield), respectively.[24] The central role of steric factors is underscored by the higher enantioselectivity with the more sizable **ap-1b** (vs **ap-1a**; Table 2).

After a mild basic workup (3.0 equiv of dbu, 30 min–3 h, 22 °C), various 2,2-substituted epoxides, including aryl-, heteroaryl-, alkynyl-, and alkyl-substituted variants, were isolated in 42–94% yield and 92:8 to >99:1 er (Scheme 13; lower yields due to product volatility).[25] Either a chloride or a bromide product may be used as the substrate for epoxide formation. It would be difficult to access this class of epoxides in high er by another protocol (catalytic or otherwise), whether it involves an olefin[26] or a ketone[27] substrate (i.e., due to chemoselectivity issues or sensitivity of α,β-unsaturated ketones). For the most part, enantioselectivities are consistent with the proposed stereochemical model presented in Scheme 12. However, at times, notably in the case of adamantyl-substituted **12o**, it is unclear why, despite the use of a more sterically hindered aminophenol, the enantioselectivity is lower than expected (89:11 and 92:8 er with **ap-2** and **ap-4**, respectively).

The epoxides derived from an electron-rich aryl ketone are unstable[28] and thus difficult to isolate and purify (Scheme 14). Unlike an epoxide derived from an ynone (e.g., **12n**, Scheme 13), we could not isolate that which is derived from an α-halogenated enone (**10e**, Scheme 14). Otherwise, all processes were efficient and highly enantioselective. Two additional points are worth mentioning. (1) Alkyl-substituted monohalomethyl products, which may be readily converted to



(1)

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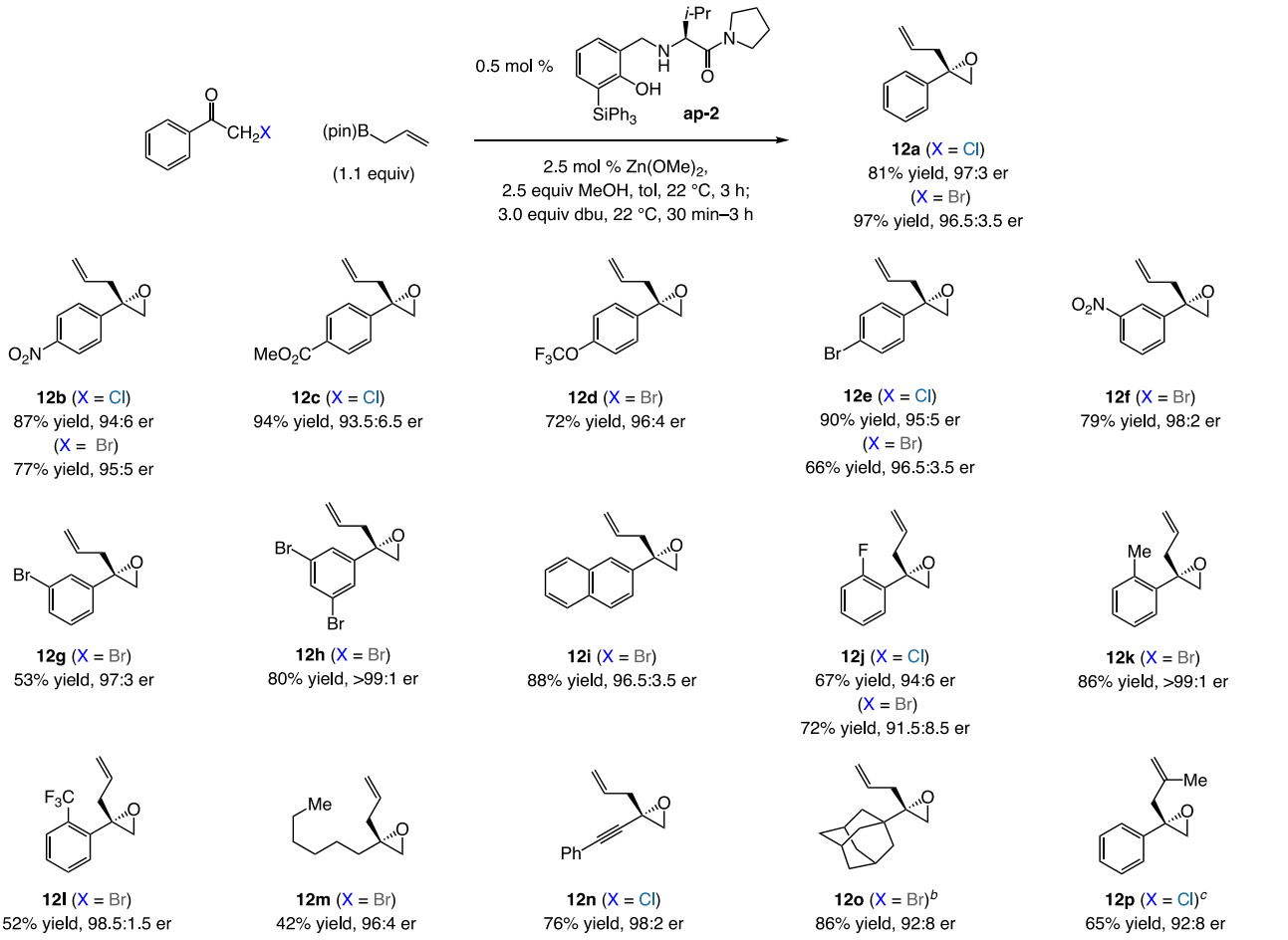
Scheme 13. Enantioselective Conversion of Monochloromethyl and Monobromomethyl Ketones to 2,2-Disubstituted Epoxides[a]



[a]Reactions were run under an N_2 atmosphere. Conversions (>98% in all cases) were determined by analysis of ^{1}H NMR spectra of unpurified mixtures (±2%). Yields are for purified products (±5%). Enantioselectivity was determined by HPLC analysis (±1%). All experiments were run at least in triplicate. [b]With **ap-4** (Scheme 17); 89:11 er with **ap-2**. [c]With 1.0 mol % **ap-2**. See the Supporting Information for details.

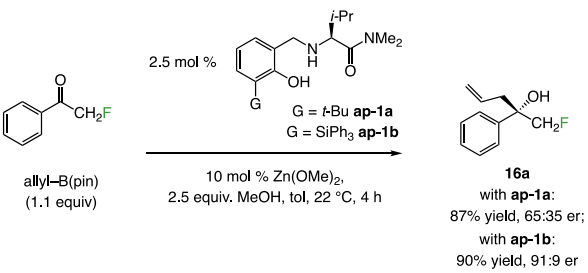
epoxides, can also be isolated in high yield (e.g., **11e**, Scheme 14). (2) Similar to the aforementioned reactions with a trichloromethyl ketone (see Scheme 2), there is substantial transformation without an aminophenol (e.g., ∼70% in the case of **12a** (X = Cl or Br)), and yet with only 0.5 mol % loading and within 3 h the catalytic process dominates.

The transformation with ketone **13** (eq 1), bearing a trifluoromethyl and a bromomethyl substituent, is noteworthy. The fact that **14** was generated in 98:2 er[21] suggests that, despite the involvement of **ap-2**, which probably places the bromomethyl moiety in the proximity of the catalyst's triphenylsilyl group, the transformation proceeds enantioselectively by the virtue of the electrostatic attraction between the trifluoromethyl group and ammonium ion imbedded within the catalyst structure.

The ease with which **12q** can be prepared highlights the utility of the approach (Scheme 15). This 2,2-disubstituted epoxide was recently prepared in three steps, in 53% yield and 96:4 er, from an allylic alcohol (including operations that require −25 to −78 °C) for an enantioselective synthesis of boscartin F.[29] By a single-vessel operation, 1 g of the readily accessible α-bromoketone was converted to **11f** and then **12q** (0.76 g; >98% conversion, >98% yield, and 94.5:5.5 er). We prepared enoate **15** in 74% yield and 94.5:5.5 er by catalytic cross-metathesis between **11f** and benzyl acrylate.

2.4. Monofluoromethyl and Difluoromethyl Ketones.

The dominance of steric factors in reactions of monochloromethyl and monobromomethyl ketones implies that, with an appropriate catalyst, the corresponding fluoro-substituted products might be synthesized in high er. In view of the importance of monofluoromethyl and difluoromethyl groups in medicine,[30] we chose to pursue this objective. In the event, whereas we obtained **16a** in 87% yield and 65:35 er with *t*-Bu-substituted **ap-1a** (eq 2), with Ph_3Si-substituted **ap-1b**, the tertiary alcohol was isolated in 90% yield and 91:9 er. There was 40−50% conversion without an aminophenol present.



(2)

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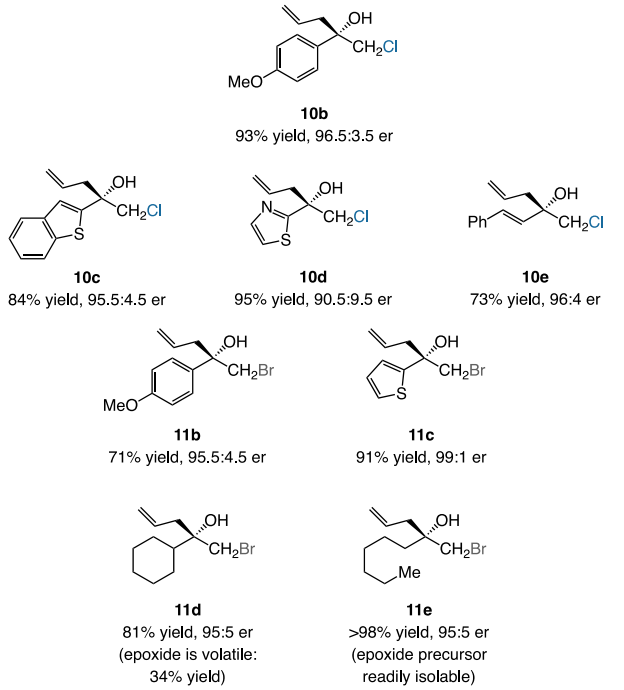
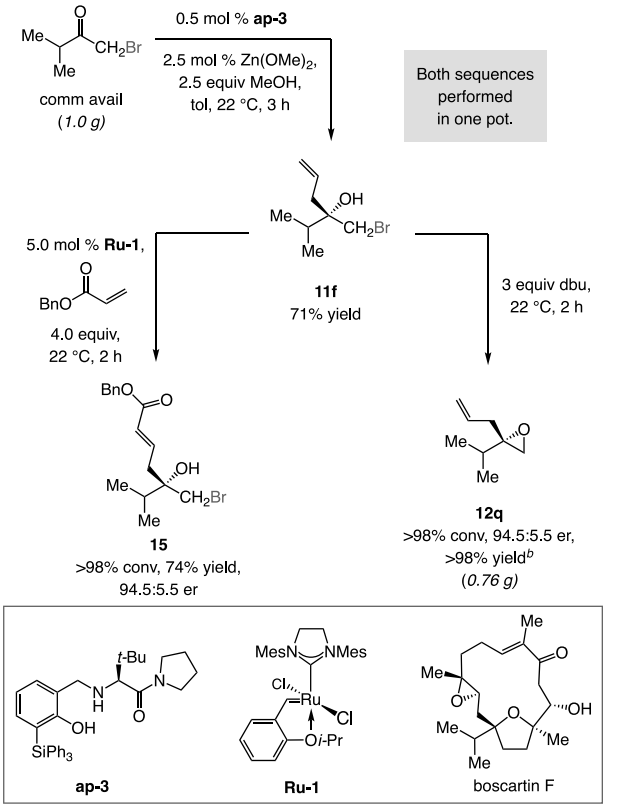
Scheme 14. Monochloromethyl and Monobromomethyl Tertiary Alcohol Products[a]



[a]Reactions were run under an N_2 atmosphere, under the same conditions as in Scheme 12 but without basic workup. Conversions were >98% in all cases and were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields are of purified products (±5%). Enantioselectivity was determined by HPLC analysis (±1%). All experiments were run in duplicate or more. See the Supporting Information for details.

Scheme 15. Representative Functionalizations[a]



[a]Reactions were run under an N_2 atmosphere. Conversions (>98% in all cases) were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields are of purified products (±5%). Enantioselectivity was determined by HPLC analysis (±1%). All experiments were run at least in triplicate. [b]Owing to product volatility, the yield was determined by analysis of the ^{1}H NMR spectra. See the Supporting Information for details.

Optimization studies led us to identify conditions for the preparation of **16a** in 92.5:7.5 er (Scheme 16). Other aryl ketones (**16b**–**e**), including one with a hindered *o*-tolyl group (**16e**), were converted to tertiary alcohols in 82–96% yield and 88.5:11.5–98:2 er. The 95:5 er for 2-thienyl-substituted **16f** was a surprise, as it is in contrast to lower values (vs 3-thienyl derivatives) associated with reactions of trifluoromethyl ketones (see Scheme 1a); a rationale for this finding is provided below.

On a related front, we have previously shown that additions to difluoromethyl ketones proceed with low er.[5] This is likely because the conformations that represent minimal dipole–dipole repulsion between the C=O and C–F bonds do not allow for electrostatic attraction between the difluoromethyl and ammonium moieties. The question here was to what extent might we improve er by exploiting steric factors. Screening studies indicated that **ap-4** (Scheme 17), bearing a much larger trinaphthylsilyl moiety (vs *t*-Bu), is optimal, reflecting the more challenging differentiation between the enantiotopic faces of a difluoromethyl ketone (vs monofluoromethyl) (Sterimol B_1 (*L*) values: Ph, 1.71 (6.28); FH_2C, 1.52 (3.31); F_2HC, 1.63 (3.29)). For instance, **17a** was obtained in 71% and 80% yield and 76:24 and 85.5:14.5 er with **ap-3** and **ap-4**, respectively. Also revealing is that, as with monofluoromethyl product **16f** (Scheme 16), 2-thienyl-substituted **17c** was obtained in 96:4 er, which is far more enantioselective in comparison to 3-thienyl variant **17d** (79:21 er). It bears emphasizing that this trend is *opposite* to that found for trichloromethyl-, dichloromethyl-, or dibromomethyl-substituted derivatives.

A possible reason for **16f** and **17c** being formed in *higher* er (in stark contrast to trihalomethyl derivatives) is that electrostatic attraction is weaker with a difluoromethyl group (vs a CF_3) and, as a result, steric factors are more dominant. It follows that for the sterically less hindered mode of addition (**XVIII**, Scheme 18) electrostatic attraction can serve a supporting role. In the case of a 3-thienyl substituent, the latter type of interaction is not feasible (**XIX**), and the enantioselectivity should be lower. This model is supported by the exceptionally high er for the Boc-protected[31] indole **17e** (>99:1 er) and the fact that the major enantiomer derived from the trifluoromethyl analogue is the alternative enantiomer (see Scheme 1). It should also be noted that these selectivity patterns point to the significance of electrostatic attraction between a trihalomethyl and an ammonium group. The inherent steric bias can thus be overcome, as supported by the much lower er when a smaller aminophenol was used (e.g., **17a** in 58:42 vs 85.5:14.5 er with **ap-1a** and **ap-4**, respectively).

Halogen-substituted tertiary alcohols connected to a triazole ring, an amide bond isostere,[32] are another important set of compounds. These haloacetyl substituted triazoles indeed are central features of several biaoactive entities,[33] an example being leukotriene biosynthesis inhibitor (Scheme 19a).[34] The only relevant published case entails the reaction of organo-

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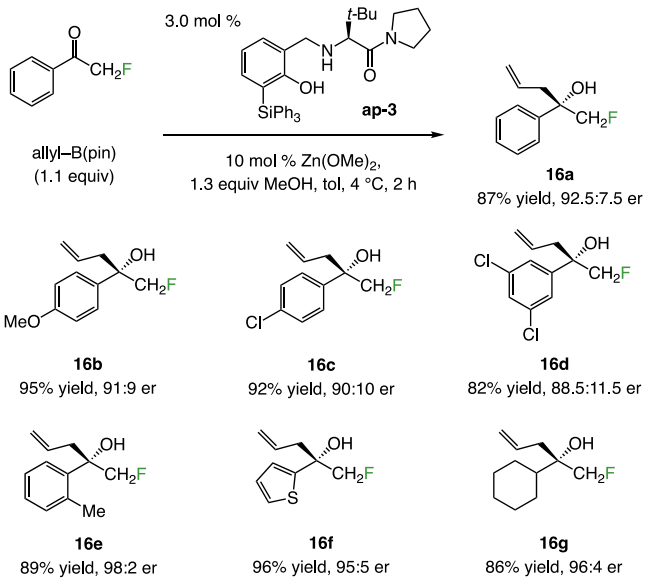
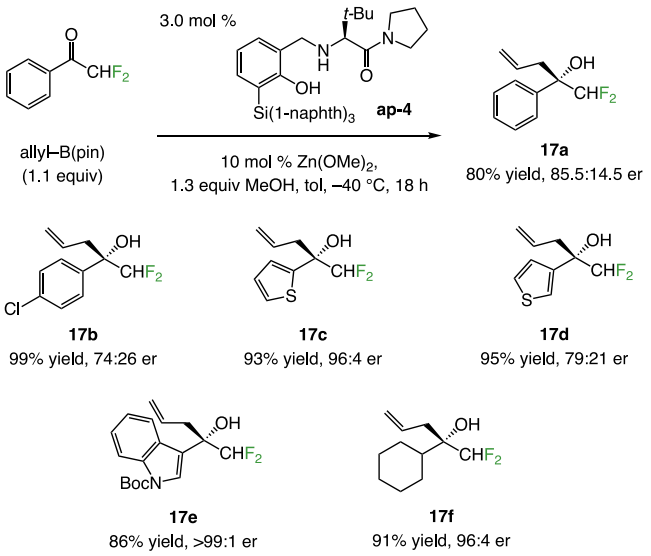
Scheme 16. Additions to Monofluoromethyl Ketones[a]



[a]Reactions were run under an N_2 atmosphere. Conversions (>98% in all cases) were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields are for purified products (±5%). Enantioselectivity was determined by HPLC analysis (±1%). Experiments were run at least in triplicate. See the Supporting Information for details.

Scheme 17. Additions to Difluoromethyl Ketones[a]

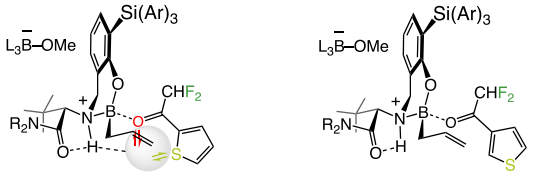


[a]Reactions were run under an N_2 atmosphere. Conversions (>98% in all cases) were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields are for purified products (±5%). Enantioselectivity was determined by HPLC analysis (±1%). Experiments were run at least in triplicate. See the Supporting Information for details.

aluminum reagents (non-enantioselective) with a trifluoromethyl or trichloromethyl ketone precursor of the antiseizure medication Banzel.[35]

We first studied allyl additions to ketones **18** and **19**, which are structurally related to Banzel (Scheme 19b). To our surprise, however, enantioselectivity was minimal (**20** and **21** in 56.5:43.5 and 52:48 er). We attributed this to competitive H

Scheme 18. When and Why Steric or Electronic Factors Dominate



bonding between the triazole moiety and the ammonium proton within the catalyst. Accordingly, we expected that the reactions with a monohalomethyl or a dihalomethyl ketone would be more enantioselective. Unexpectedly, there was only a slight improvement (e.g., **22** → **23**, 69.5:30.5 er). Subsequent control studies showed that this is largely a consequence of exceptionally facile non-catalytic addition to the electronically more activated and less hindered carbonyl unit (≥74% conversion, same conditions but no aminophenol).

We therefore developed a catalytic one-pot strategy, entailing initial allyl addition to an ynone followed by triazole ring[36] formation (Scheme 19c). Treatment of **24** or **27** to allyl–B(pin) addition conditions (with 3.0 mol % aminophenol) and subjection of the mixture to 20 mol % $CuSO_4 \cdot 2H_2O$, benzyl azide **25**, and 40 mol % L-ascorbic acid (2.0 equiv K_2CO_3, 1/1 MeOH/H_2O, 22 °C, 12 h) afforded **26** and **28** in 86% and 89% yield and ≥99:1 er.[37] This approach is suitable for enantioselective late-stage incorporation of a fluoro-substituted tertiary alcohol moiety within a complex molecule.

3. CONCLUSIONS

These investigations shed new light on several key, but scarcely explored, properties of tri-, di-, and monochloromethyl and tri-, di-, and monobromomethyl, as well as di- and monofluoromethyl, moieties. We show how differences in polarizability, the ability of a halogen atom to establish electrostatic association with an ammonium group, and variations in size and the length and polarity of the corresponding C–halogen bond can strongly impact reactivity and/or enantioselectivity.

Along the way, we have developed the first broadly applicable catalytic and enantioselective strategies for conversion of a wide range of halomethyl ketones to the corresponding tertiary homoallylic alcohols. The method can be used to transform many trihalomethyl (halogen = Cl or Br), dihalomethyl (halogen = F, Cl, or Br), and monohalomethyl (halogen = F, Cl, or Br) ketones. Our studies reveal that, whereas electrostatic interaction between a trihalomethyl, a dichloromethyl, or a dibromomethyl group and a catalyst's ammonium moiety is the overriding factor (Scheme 20), with monochloromethyl, monobromomethyl, difluoromethyl, and monofluoromethyl substituents steric effects take control, leading to products generated from addition to the opposite carbonyl enantiotopic face. In these latter cases, steric differentiation is maximized by utilizing an aminophenol that contains a sizable silyl substituent (e.g., $SiPh_3$ in **ap-1b**).

Another outcome of the above studies is that direct and practical routes have been made available for the synthesis of a number of desirable derivatives, such as α-halo-aldehydes and 2,2-disubstituted epoxides, many of which are difficult to

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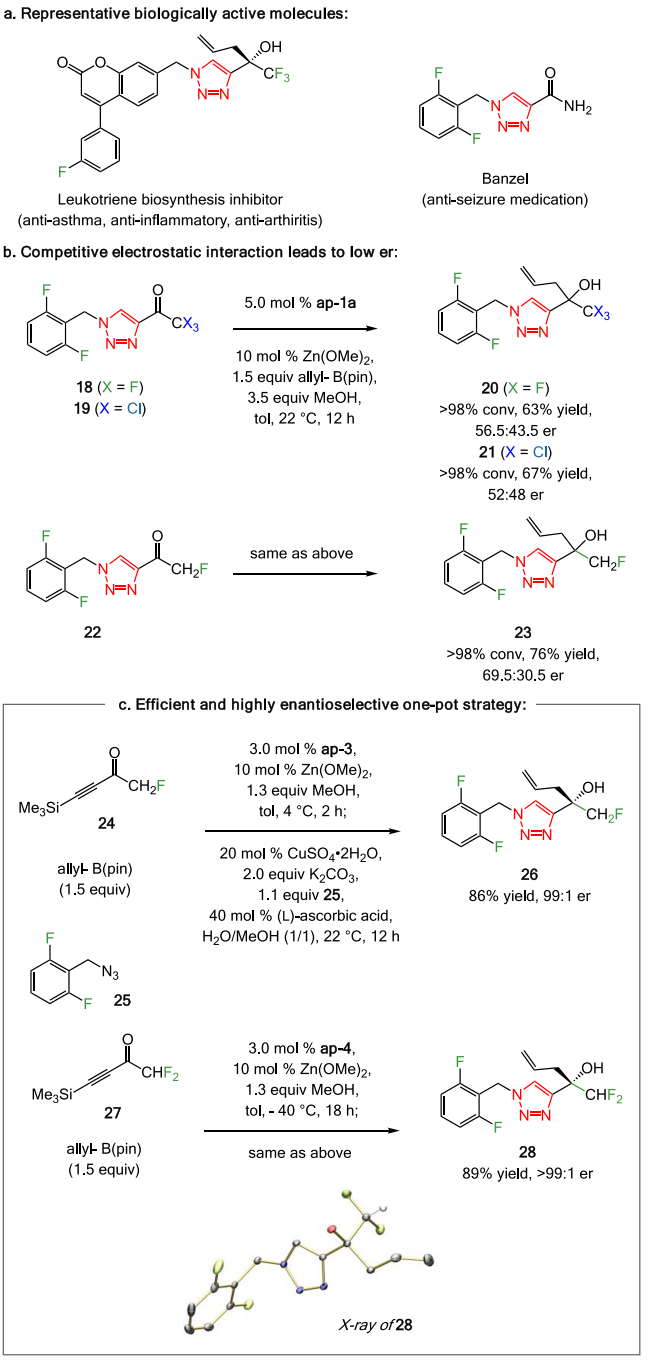
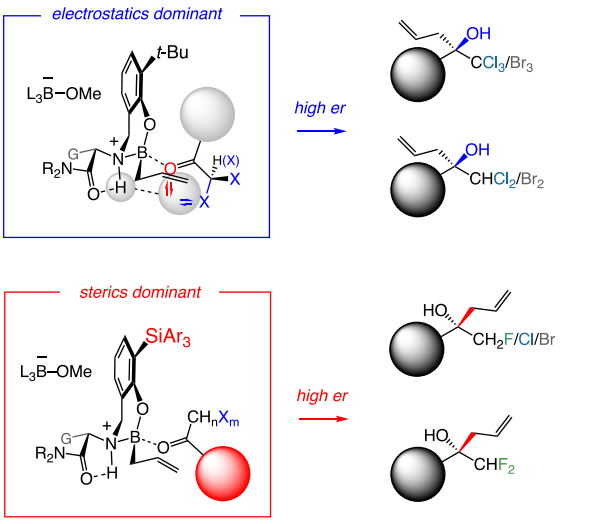
Scheme 19. Triazole-Containing Products[a]



[a]Reactions were carried out under an N_2 atm. Conversions were >98% in all cases and were determined by analysis of ^{19}F NMR spectra of unpurified product mixtures (±2%). Yields are for purified products (±5%). Enantioselectivity was determined by HPLC analysis (±1%). All experiments were run in duplicate or more. See the Supporting Information for details.

access otherwise. The versatility of the approach is further underscored by a concise transformation of 1 g of a commercially available ketone to ca. 0.7 g of an enantiomerically enriched epoxide, formerly used to prepare boscartin F. We show that triazole-substituted tertiary alcohols bearing a monofluoromethyl or a difluoromethyl moiety, features relevant to drug development, can be synthesized through the present strategy.

Scheme 20. Electrostatic versus Steric Effects, Depending on the Halomethyl Substituent



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b08443.

Experimental details for all reactions and analytic details for all products (PDF)
Crystallographic data (CIF)
Crystallographic data (CIF)
Crystallographic data (CIF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

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