A Journal of the Gesellschaft Deutscher Chemiker

Angewandte

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International Edition

Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201703844
Angew. Chem. 10.1002/ange.201703844

Link to VoR: http://dx.doi.org/10.1002/anie.201703844
http://dx.doi.org/10.1002/ange.201703844

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10.1002/anie.201703844

Electronically Activated Organoboron Catalysts for Enantioselective Propargyl Addition to Trifluoromethyl Ketones

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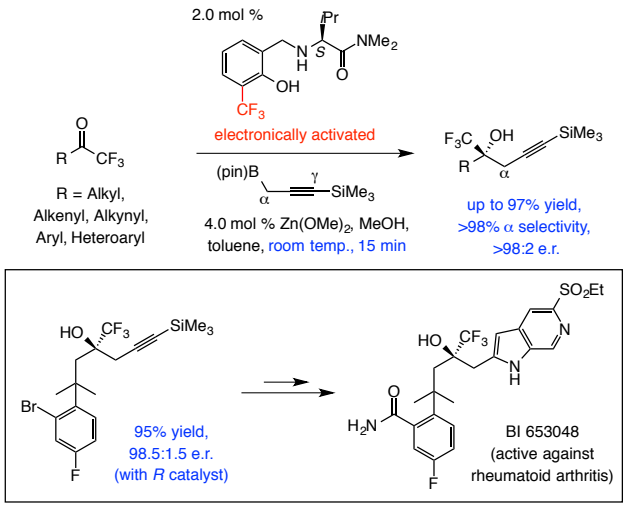
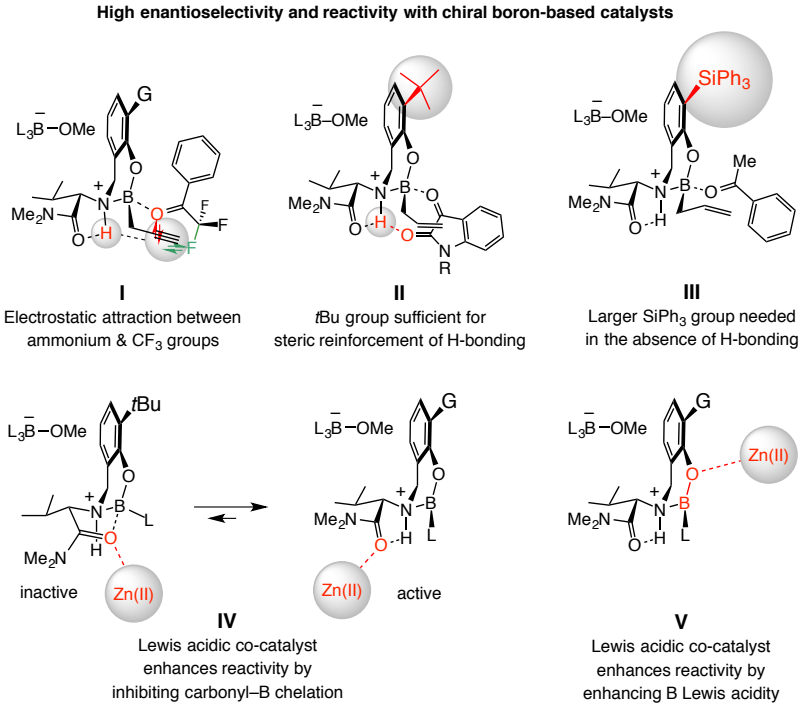
Abstract: *A broadly applicable, practical, scalable, efficient and highly α- and enantioselective method for addition of a silyl-protected propargyl moiety to trifluoromethyl ketones has been developed. Reactions, promoted by 2.0 mol % of a catalyst that is derived in situ from a readily accessible aminophenol compound at ambient temperature, were complete after only 15 minutes at room temperature. The desired tertiary alcohols were isolated in up to 97% yield and 98.5:1.5 enantiomeric ratio. Alkyl-, alkenyl-, alkynyl-, aryl- or heteroaryl-substituted trifluoromethyl ketones can be used. Utility is highlighted by application to a transformation that is relevant to enantioselective synthesis of BI 653048, a compound active against rheumatoid arthritis.*



Organic molecules that contain a trifluoromethyl unit often possess desirable properties,[1] and efficient and reliable methods for their enantioselective synthesis are needed.[2] Catalytic enantioselective additions to trifluoromethyl ketones is an attractive way to synthesize trifluoromethyl-substituted tertiary alcohols,[3,4] but developing such transformations is hardly straightforward.[5] One issue is the high electrophilicity of trifluoromethyl ketones and rapid competitive non-catalyzed/non-enantioselective background reactions. Another problem is the smaller size difference between a trifluoromethyl group and the other carbonyl substituent (more so than methyl ketones), rendering enantiotopic face differentiation based on steric factors less tenable. As part of a program designed to address these general issues, we have developed an ammonium containing boron-based chiral catalyst capable of promoting enantioselective additions of allyl– and allenyl–boron compounds to trifluoromethyl ketones.[6] High enantioselectivity in these reactions arises from transition state organization induced through electrostatic attraction (**I**, Scheme 1).

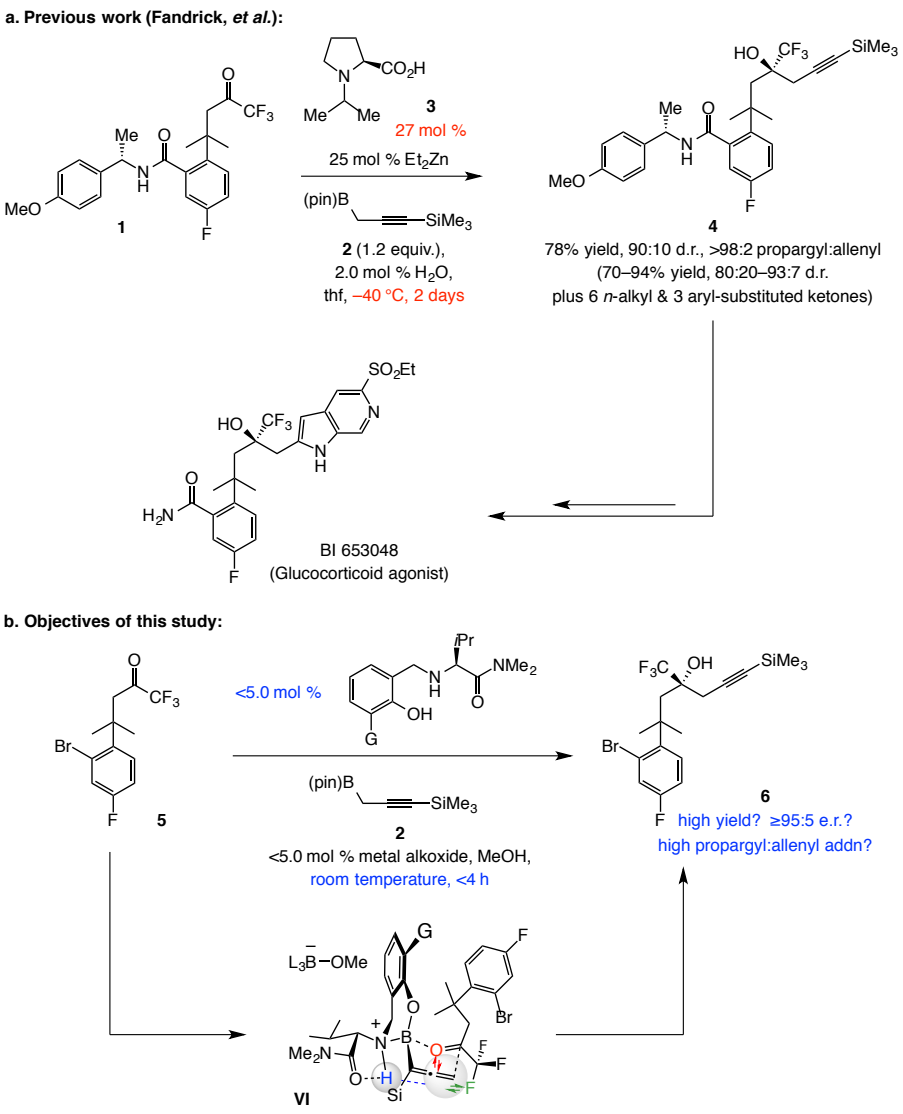
A range of aminophenol-based catalysts can be synthesized easily. For instance, as supported by mechanistic investigations and computational studies,[7] H-bonding interactions lead to enantioselective organoboron additions to phosphinoylimines, isatins (e.g., **II**, Scheme 1) and Boc-protected aldimines.[8] In the additions to ketones, where there is just one point of catalyst-substrate contact (i.e., no electrostatic attraction with the ammonium group), high e.r. arises from a more sizeable triphenylsilyl moiety in the catalyst (**III**), which helps prevent the larger ketone substituent to orient pseudo-axially.[9] With $Zn(OMe)_2$ as the co-catalyst, reactivity can be enhanced and/or alternative pathways made available.[10] We have proposed that, among other factors, chelation of the Lewis acid to phenoxy

oxygen (**V**) destabilizes an inactive form of the chiral catalyst, increasing boron center Lewis acidity and accelerating 1,3-borotropic shift so that it occurs prior to the addition step (i.e., net γ vs. α selectivity).[10]



Scheme 1. Readily modifiable small-molecule chiral aminophenol-derived catalysts allow for mechanism-based optimization of reaction efficiency and/or enantioselectivity.

The present studies were inspired by the complications associated with enantioselective synthesis of glucocorticoid agonist BI 653048, developed for the treatment of rheumatoid arthritis (Scheme 2a).[11e, 12] Towards this end, Fandrick *et al.* have reported what is, as far as we know, the only available method for catalytic enantioselective propargyl group addition to trifluoromethyl ketones.[12] Homopropargyl alcohol **4** was synthesized by reaction of ketone **1** with silyl-protected propargyl–B(pin) compound **2**[13,14] promoted by a catalyst generated *in situ* from 27 mol % *N-iso*-propyl-L-proline (**3**) and 25 mol % Et_2Zn (Scheme 2a). After two days at –40 °C, tertiary alcohol **4** was isolated in 78% yield, 90:10 diastereomeric ratio and >98:2



Scheme 2. A problem in catalytic enantioselective synthesis and the objectives of this study.

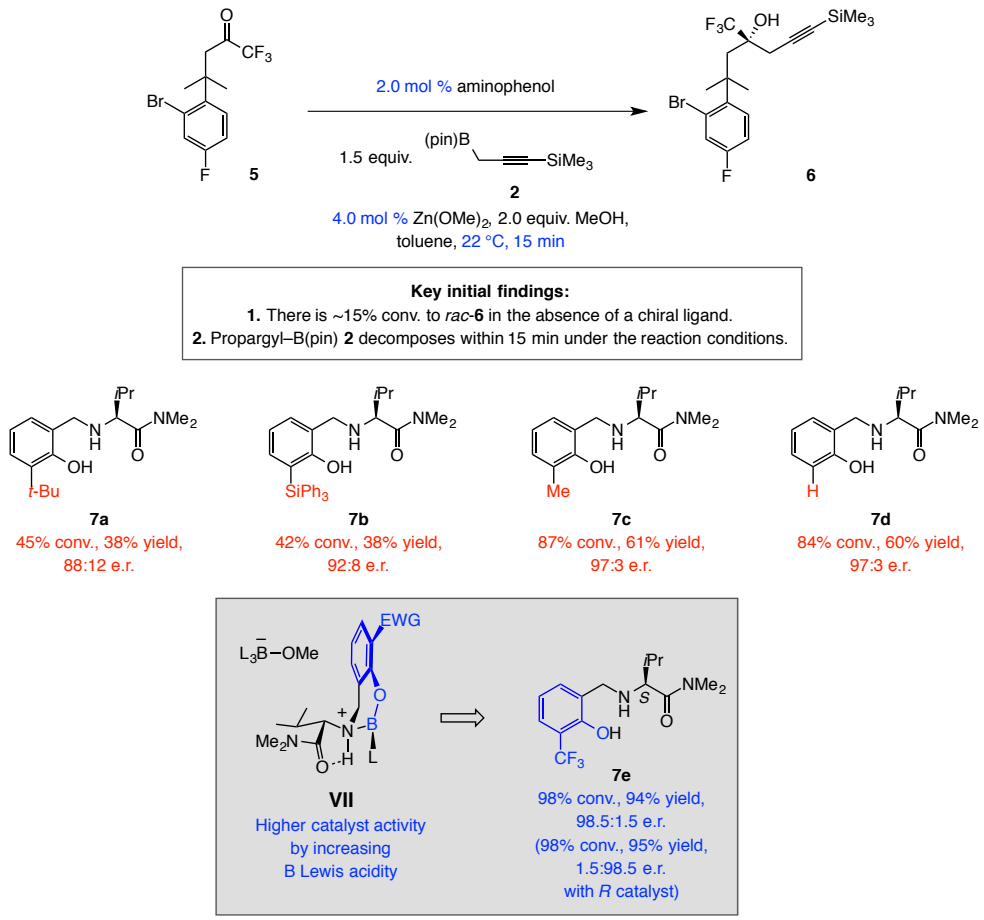
propargyl:allenyl selectivity. We wondered if with an appropriate aminophenol-based organoboron catalyst, products such as **6** (Scheme 2b; precursor to BI 653048),[12] might be synthesized more efficiently (e.g., <4 h), with higher enantioselectively (e.g., ≥95:5 e.r.), at room temperature (vs. –40 °C), and with lower catalyst loading (e.g., <5.0 vs. 25 mol %). It has been demonstrated that the silyl-alkyne moiety, in its protected or unmasked form, can be converted to several desirable derivatives, including those not easily accessible by modification of the corresponding homoallylic alcohols.[13c, 15]

Another aim was therefore to develop a method that would be applicable to an assortment of trifluoromethyl ketones.

Preliminary studies were performed with ketone **5**, which may be used to access BI 653048. Control experiments showed ~15% conversion in the absence of a chiral organoboron catalyst (conv. to **6**, Scheme 3). We were also met with a more significant challenge: silyl-protected propargyl–B(pin) **2** undergoes complete proto-deboration within 15 minutes at 22 °C (Scheme 3; >98% by ^{1}H NMR analysis).[16] A catalyst would have to be identified for bringing the transformation to completion within the same brief length of time.

There was appreciable enantioselectivity (88:12 e.r.) with 2.0 mol % **7a**, but the yield was low (38% yield; Scheme 3). Selectivity improved to 92:8 e.r. with triphenylsilyl-substituted **7b**, but there was little change in efficiency. Based on the reasoning that a smaller aryloxy group might better accommodate the large alkyl moiety of **5** (see complex **VI**, Scheme 2), reactions with **7c** and **7d** were probed; efficiency did improve (87% and 84% conv., 61% and 60% yield, respectively) and there was a boost in e.r. (97:3). We attributed the enantioselectivity increase to the ability of the smaller catalyst to compete more effectively with the non-catalytic pathway. There was complete α selectivity in all cases (i.e., >98:2 propargyl:allenyl addition).

The key question then was whether further catalyst activation could be achieved electronically, as represented in **VII**. We wondered if, while bulkier than **7c** and **7d**, an aminophenol ligand containing an electron-withdrawing substituent on its aryloxide unit (e.g., vs. Me in **7c**) could provide appropriate rate enhancement without adversely impacting e.r. We prepared trifluoromethyl-substituted aminophenol ligand

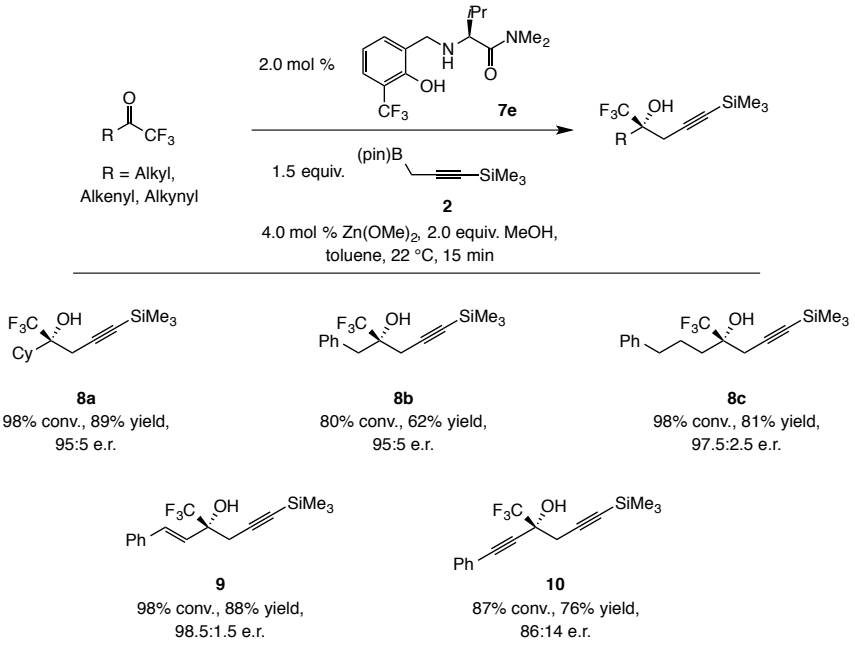


Scheme 3. Identification of an optimal catalyst for enantioselective synthesis of homopropargyl alcohol **6**. Conversion (±2%) determined by analysis of the ^{19}F NMR spectra of unpurified product mixtures (trifluoro-toluene as reference); >98% α selectivity in all cases. E.r. (±1%) was determined by HPLC analysis. See the Supporting Information for details. Abbreviation: EWG = electron-withdrawing group; L = methoxy or silyl-allenyl group.

7e (from commercially available 3-trifluoromethyl salicylaldehyde) according to the logic that a trifluoromethyl differs slightly from a methyl group (similar in size to an Et unit[17]). Indeed, after 15 minutes at room temperature with 2.0 mol % **7e**, **6** was isolated in 94% yield, >98% α selectivity and 98.5:1.5 e.r. Electronic activation of the catalyst not only led to considerable increase in efficiency, it resulted in some enhancement in e.r. as well. To obtain the enantiomer for synthesis of the biologically active enantiomer of BI 653048,[11e,12] we used the aminophenol ligand derived from D-valine and obtained *ent*-**6** in nearly the same yield and e.r. (Scheme 3).[18] The aryl bromide moiety in **6** was readily converted to the

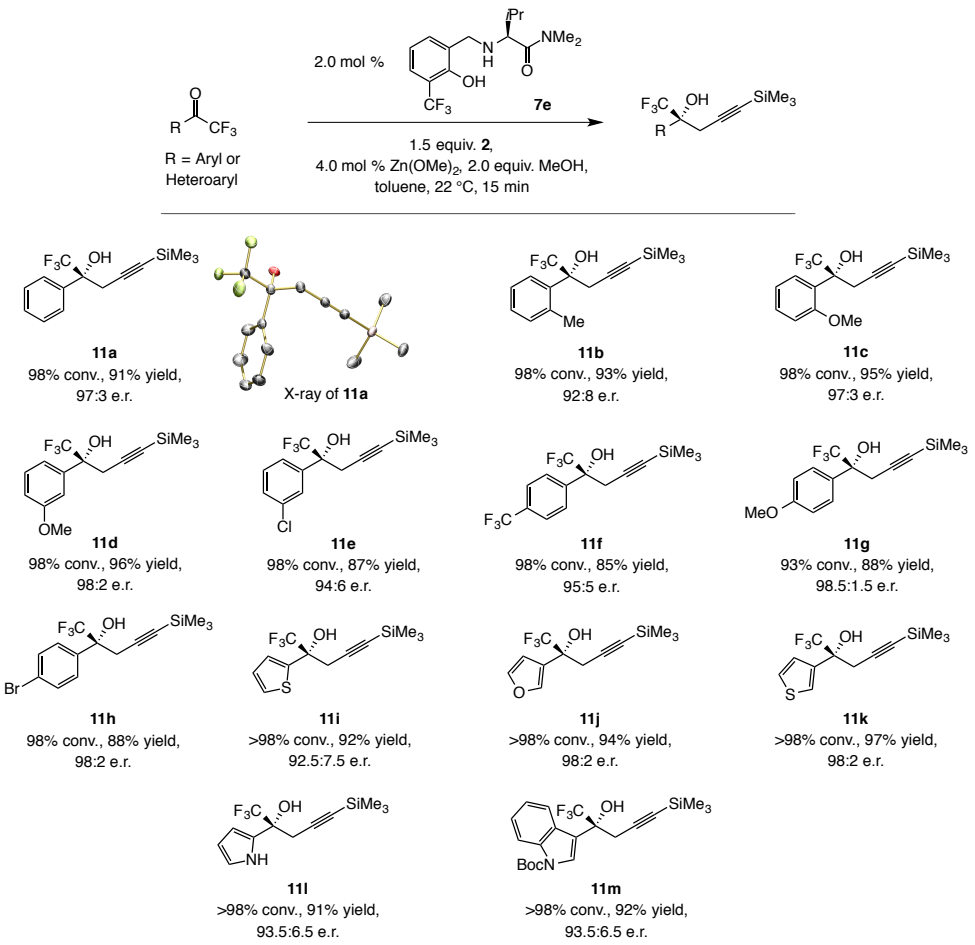
corresponding carboxylic acid, ready for use for synthesis of the target molecule, by a one-pot procedure (*i*PrMgCl•LiCl, –78–22 °C, 2 h; CO_2, 22 °C, 6 h; 89% yield).[16]

Yields and enantioselectivities were high for the additions to ketones with smaller alkyl substituents (vs. the moiety in **5**), for which enantiotopic differentiation is more challenging; only one moderately selective example was previously disclosed (80:20 e.r.).[12] Tertiary alcohols **8a-c**, derived from additions to a ketone with an α-branched, β-branched or an *n*-alkyl substituent, respectively, were isolated in 62–89% yield and 95:5–97.5:2.5 e.r. Formation of enyne **9** was similarly efficient and enantioselective (88% yield, 98.5:1.5 e.r.). Diyne **10** was obtained in lower enantiomeric purity (76% yield, 86:14 e.r.) perhaps because of the increased steric repulsion between the catalyst's CF_3 group and the conformationally less mobile phenylacetylene moiety (see **VI**, Scheme 2). There was no improvement in enantioselectivity at higher catalyst loading.



Scheme 4. Additions to alkyl-, alkenyl- and alkynyl-substituted trifluoromethyl ketones. Conversion (±2%) determined by analysis of the ^{19}F NMR spectra of unpurified product mixtures (trifluoro-toluene as reference); >98% α selectivity in all cases. E.r. (±1%) determined by HPLC analysis. See the Supporting Information for details.

Aryl- and heteroaryl-substituted trifluoromethyl ketones were similarly suitable (Scheme 5), despite background processes being more competitive (~30–60% conv. without **7e**). Reactions of trifluoromethyl-substituted ketones with an aromatic moiety that contains either an electron-withdrawing or –donating group proceeded to >90% conversion within 15 minutes, affording **11a-m** in 85–97% yield and 92:8–98.5:1.5 e.r.[16] As indicated by efficient preparation of pyrrole-substituted **11l**, protection of basic amines was not required.

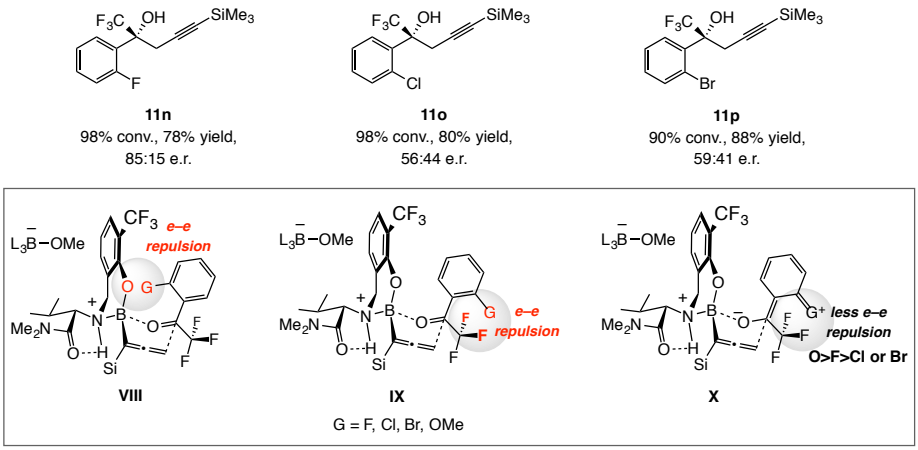


Scheme 5. Additions to aryl- and heteroaryl-substituted ketones. Conversion (±2%) determined by analysis of the ^{19}F NMR spectra of unpurified product mixtures (trifluoro-toluene as reference); >98% α selectivity in all cases. E.r. (±1%) determined by HPLC analysis. See the Supporting Information for details.

Nonetheless, *o*-fluorophenyl substituted alcohol **11n** (86:14 e.r.) and most notably *o*-chloro- and *o*-bromophenyl derivatives **11o** and **11p** (56:44 e.r.) were formed in markedly lower e.r. This

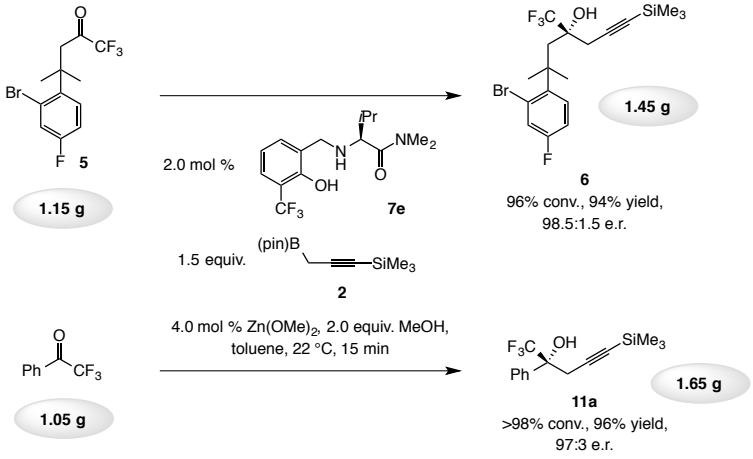
was surprising for two reasons: 1) Compounds **11b** and **11c** (Scheme 5), derived from additions to the related *o*-tolyl- and *o*--methoxy-substituted ketones, were generated with considerably higher e.r. (92:8 and 97:3, respectively). 2) Allyl–B(pin) additions to methyl ketones bearing the same *o*-halo-substituted aryl groups were much more enantioselective with the same class of catalysts (93:7–99:1 e.r.).[9]

The above data suggest that steric repulsion between an *ortho* substituent and the catalyst structure can cause diminution in enantioselectivity (e.g., **11a-c**, Scheme 5); this explains why e.r. is more favorable (85:15 vs. 59:41) with a smaller fluorine atom and a shorter C–F bond in **11n** compared to a bromine atom and a longer C–Br bond in **11p**. Electronic factors probably play a role as well. In what we suggest as the preferred mode of addition (**VIII**, Scheme 6) there would be some degree of electron–electron repulsion between the non-bonding electrons of the halogen atom and the catalyst's phenolic oxygen. Unlike a methyl ketone, the alternative conformer **IX** cannot offer relief as a result repulsive interactions with the substrate's trifluoromethyl group. Consequently, competitive pathways become more vaiable and enantioselectivity suffers. *o*-Methoxyphenyl- and *o*-fluorophenyl-substituted **11c** and **11n** can be generated in higher e.r. because of the better overlap involving period two elements and the resulting resonance stabilization that can reduce electron–electron repulsion (see **X**, Scheme 6).[19] The above trends underscore key electrostatic interactions that impact enantioselectivity and are particular to trifluoromethyl ketones.



Scheme 6. The unusual trends in enantioselectivity in propargyl group additions to *o*-halophenyl-substituted trifluoromethyl ketones. Conversion (±2%) determined by analysis of the ^{19}F NMR spectra of the unpurified product mixtures; >98% α selectivity in all cases. E.r. (±1%) was determined by HPLC analysis. See the Supporting Information for details.

In summary, we have developed the first broadly applicable method for efficient and enantioselective addition of a propargyl group to trifluoromethyl ketones. The chiral ligand and the organoboron reagent can be prepared in gram quantities from commercially available materials. Reactions may be conveniently performed at 22 °C, are complete in just 15 minutes with 2.0 mol % catalyst and can be performed on gram scale, as the examples in Scheme 7 show.



Scheme 7. Gram scale. Conversion (±2%) determined by analysis of the ^{19}F NMR spectra of the unpurified product mixtures; >98% α selectivity in all cases. E.r. (±1%) was determined by HPLC analysis. See the Supporting Information for details.

Development of additional enantioselective processes catalyzed by small-molecule organoboron chiral catalysts is in progress.

Acknowledgements. Financial support was provided by the NIH (GM-57212). We are grateful to KyungA Lee and Farid W. van der Mei for helpful discussions.

Keywords: catalysis, enantioselective synthesis, homopropargylic alcohols, propargyl groups, trifluoromethyl group

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[16] See the Supporting Information for details. Protodeboration probably occurs through formation of the derived methoxy borate followed by the rupture of C–B(pin) bond by the proton counter-ion.

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[18] Consistent with a previous report (see ref. [6]) additions to mono- and difluoromethylphenyl ketone were considerably less enantioselective (with **7e** under conditions shown in Scheme 3: 95% conv., 76% yield, >98:2 propargyl:allenyl, 50:50 e.r. and >98% conv., 94% yield, >98:2 propargyl:allenyl, 86:14 e.r., respectively). See the Supporting Information for details.

[19] It is unlikely that the enantioselectivity profile for *o*-halophenyl-substituted trifluoromethyl ketones (**11n-p**) is due to differences in rates of competitive un-catalyzed background additions (i.e., less in the case of the more enantioselective *o*-fluorophenyl substrate). In fact, control experiments point to the opposite trend: 61%, 40% and 29% conversion was observed for **11n-p**, respectively, under the same conditions but in the absence of 2.0 mol % **7e**.