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Catalytic enantioselective addition of organoboron reagents to fluoroketones controlled by electrostatic interactions

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Abstract

Organofluorine compounds are central to modern chemistry, and broadly applicable transformations that generate them efficiently and enantioselectively are in much demand. Here we introduce efficient catalytic methods for additions of allyl and allenyl organoboron reagents to fluorine-substituted ketones. These reactions are facilitated by readily and inexpensively available catalysts and deliver versatile and otherwise difficult-to-access tertiary homoallylic alcohols in up to 98% yield and >99:1 enantiomeric ratio. Utility is highlighted by a concise enantioselective approach to synthesis of anti-parasitic drug Bravecto™ (presently sold as the racemate). Different forms of ammonium-organofluorine interactions play a key role in controlling enantioselectivity. The greater understanding of various non-bonding interactions afforded by these studies should facilitate future development of transformations involving fluoro-organic entities.

The properties of an organic molecule can be altered significantly when a C–H is replaced with a C–F unit; this is largely because there is a strong electron density shift toward the bond's halogen terminus[1]. Fluoro-organic entities have indeed had a palpable impact on the discovery of new therapeutics[2], agrochemicals[3] and materials[4]. Similarly impacted have been efforts in catalyst development[5,6] (see the Supplementary Information for extended bibliography). For instance, strategically positioned fluorine atoms in chiral N-heterocyclic carbenes influence and alter catalyst electronegativity and/or cause repulsive electronic interaction in enantioselective C–C bond-forming processes[7,8]. Alternatively, largely due to $\sigma_{C–H} \rightarrow \sigma^*_{C–F}$ hyperconjugation (*gauche* effect)[9], a fluorinated site may engender structural rigidity with a catalyst framework to promote high enantioselectivity and/or help reveal the identity of the reactive conformers[10,11,12].

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Author Contributions. K.L. and D. L. S. developed the catalytic enantioselective transformations and analyzed the results regarding various interactions; K. L. carried out the experiments in Fig. 5.; S. T. made the initial observations. DFT calculations were designed and performed by S.T., F. H., and F. W. v. d. M. D. W. R. developed the silyl-substituted catalyst. A. H. H. designed and directed the investigations and composed the manuscript with revisions provided by the other authors.

Our interest in organofluorine non-bonding interactions arose from studies of catalytic enantioselective additions of organoboron compounds to fluoroketones (Fig. 1a). These transformations would afford trifluoromethyl-substituted tertiary alcohols that may be converted to molecules of interest such as anti-parasitic compound Bravecto™ (or fluralaner)[13], the anti-inflammatory agent BI 653048[14] or their analogues. Although catalytic enantioselective allyl additions to ketones are known [15] and reactions with trifluoromethyl-substituted α-ketoesters have been disclosed[15] (see the Supplementary Information for bibliography), there is only one reported case of a catalytic allyl addition to a fluoro-substituted ketone: Reaction of tetraallyltin with 2,2,2-trifluoroacetophenone may be catalysed by 30 mol % of an indium salt and 60 mol % of a chiral ligand, affording, after three days, the tertiary alcohol in 70% yield and 86.5:13.5 enantiomeric ratio (e.r.)[16]. Two other transformations have been performed with superstoichiometric amounts of the chiral ligand and costly allyl-indium species[17,18]. Selectivity has never exceeded 90:10 e.r., probably because the insufficient size difference between the carbonyl substituents; a trifluoromethyl unit, sans electronic effects, occupies a similar volume as an ethyl or an *iso*-propyl group[19] (cf. **2b**, Fig. 1a), rendering enantiotopic face differentiation non-trivial. Unlike α-ketoesters transition state organization through intramolecularly chelated intermediates[15] is not feasible. Enhanced electrophilicity of fluorinated ketones makes achieving high enantioselectivity still more challenging, since uncatalysed pathways are especially competitive, as reflected in the need for relatively large amounts of chiral promoters in the aforementioned studies. There are no cases of allyl additions to sterically or electronically modified aryl-trifluoromethyl ketones or the corresponding alkenyl- or alkyl-substituted derivatives, and there is just one reported case of a reaction with a heterocyclic trifluoromethyl ketone (73:27 e.r. with an allyl-indium reagent)[17]. We are not aware of any reports of catalytic enantioselective allenyl addition to ketones (except isatins[20]), the products from which may be subjected to site- and/or stereoselective procedures.[21]

We aimed to utilize the recently introduced chiral catalysts that are generated in situ from a simple aminophenol molecule (e.g., **1a**, Fig. 1b) and shown to promote additions of unsaturated organoboron reagents to phosphinoylimines,[20] *tert*-butoxycarbonyl (Boc-) imines[21] or isatins[20]. A protonated amine within the catalyst's structure is key to high efficiency and enantioselectivity[20], allowing substrates with a second Lewis basic site to react with high stereoselectivity (other than interaction with the catalyst's boron center). Association of the additional Lewis basic unit with the imbedded proton signals a preference for addition to one of the C=N or C=O bond enantiotopic faces. Reactions of simpler ketones (e.g., **2a**,**b**) are therefore far less enantioselective; again, based purely on steric factors, mode of addition **I** (Fig. 1b) can only be slightly preferred (vs. one with a pseudo-axial phenyl group).

We wondered whether electrostatic attraction and/or hydrogen-bonding involving a catalyst's ammonium moiety and a substrate's C–F bond(s) might lead to enhanced enantioselectivity. If so, in addition to providing valuable synthesis methods, the associated investigations could shed light on how a positively charged species might associate with an organofluorine molecule. Other compelling questions that could then be addressed: How would the presence of a neighboring carbonyl unit, itself a markedly polar group, impact the

ammonium-F–C association? What would be the influence of the different substituents at the carbon center that holds a fluorine atom (e.g., a CF_2H unit)? Can fluorine atoms that are more distal alter enantioselectivity? Other than the aforementioned studies[10,11], we are aware of only two cases in connection to epoxidation[22] and hydrogenation reactions[23] (neither is highly selective) where the possibility of ammonium-F–C attraction in a catalytic enantioselective process has been mentioned but without any further detailed investigation.

There has been much spectroscopic and/or computational scrutiny and debate about the nature of interactions of organofluorine compounds with other molecules[9,24,25,26,27] (see the Supplementary Information for extended bibliography). Hydrogen-bonding with a suitably situated proton donor is supported by computational[28] and experimental findings[24,29]. There is general agreement that, as pointed out long ago by Pauling [30] and utilized in recent development of catalytic reactions[31,32], fluoride ions are effective H-bonding acceptors. There is nevertheless evidence[2,33] that, because of fluorine's exceptional electronegativity and low polarizability, a C–F bond may not participate in strong hydrogen-bonding[34]; fluorocarbons are after all more hydrophobic than even hydrocarbons. Disposition of the proton of an H–X unit (X = N or O) toward a fluorine atom, at times attributed to hydrogen-bonding, might instead be at least partly due to hyperconjugative stabilization[25] or minimization of electron–electron repulsion[35]. Still, with a relatively robust binding support[36] and proper alignment of a C–F and an H–X bond in place (covalent component; X = N or O; optimally, ~180° to achieve $n_F \rightarrow \sigma^*_{H-X}$ overlap), hydrogen-bonding affinities seem to be influential. A relevant case is the enantioselective cyanide addition to di- and trifluoromethyl ketoimines promoted by chiral thiourea catalysts[37], where a near-linear N–H···F interaction and a C=N···H–N association are likely operative. Another notable affinity mode, referred to as ion-dipole attraction[1,2], entails an electrostatic contact between a C–F unit and a charged moiety (e.g., an ammonium proton).

Results

Preliminary DFT calculations

The possibility of ammonium-trifluoromethyl attraction found initial support in DFT calculations (see the Supplementary Information for details). To gain insight regarding non-bonding ammonium-trifluoromethyl attraction with minimal interference by steric factors, we focused on 1,1,1-trifluoroacetone. We established that catalyst-substrate complex formation requires approximately 3−5 kcal/mol, and that among **IIa**–**Va** (R = Me; Fig. 1c) mode of reaction **IVa** is the most favorable (vs. **IIa** by 2.6 and 3.3 kcal/mol with M06-2X and ωB97XD, respectively). Although the calculated distance of 4.10 Å between the ammonium proton and the nearby fluorine atom precludes hydrogen-bonding in **IVa**, significant electrostatic attraction would be feasible (see the Supplementary Information for details). That is, the ammonium proton may alleviate the inherent electron–electron repulsion within the trifluoromethyl ketone substrate arising from the non-bonding electrons of the carbonyl oxygen and a proximal fluorine atom. What is more, the repulsive interaction between the non-bonding electrons of aryloxy and carbonyl oxygens in **IIa** is minimized in **IVa** (Fig. 1c). The shorter O···O distance in **IIa** (2.40 Å vs. 2.50 Å in **IVa**) is because of weaker attractive interaction between the carbonyl oxygen and the ammonium proton (2.80

Å in **IIa** vs. 2.58 Å in **IVa**). Mode of addition **Va** (R = Me), leading to the minor enantiomer, is likely less preferred (vs. **IVa**; e.g., by 3.0 and 3.7 kcal/mol with M06-2X and ωB97XD, respectively) due to enhanced electronic repulsion between the aryloxy and a fluorine atom of the pseudo-axially disposed trifluoromethyl group; this would be despite the favorable chair conformation permitting electrostatic attraction between the carbonyl oxygen and the ammonium proton. With the corresponding (trifluoromethyl)phenyl ketone (R = Ph), DFT calculations indicated less energy difference between **IIb** and **IVb** probably because of steric interactions, but the trends favoring **IVb** persisted (e.g., vs. **IIb** by 1.5 and 2.8 kcal/mol with M06-2X and ωB97XD, respectively). These calculated values represent the ability of electrostatic attractive forces to override steric repulsion between the axial phenyl group and the bulk of the catalyst in **IVb**.

Highly enantioselective allyl additions to trifluoromethylketones

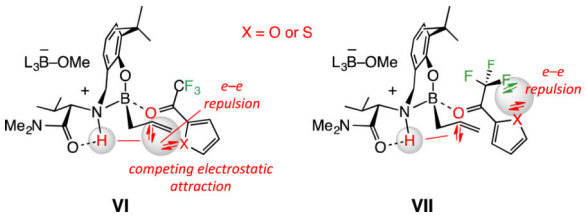
To obtain preliminary experimental evidence, we treated trifluoromethylphenyl ketone **3a** (Fig. 2a) with 1.1 equivalents of allyl–B(pin) with 2.5 mol % **1a**, 10 mol % NaO*t*-Bu and MeOH; **4a** was isolated in 93% yield and 96:4 e.r. (4 h, 4 °C). There was 45% conversion to **4a** without the aminophenol. Heating diminished e.r. (e.g., 92.5:7.5 e.r. at 60 °C), and lower temperatures reduced efficiency (e.g., 56% conv. at −15 °C, 96:4 e.r.). With organic amine 1,8-diazabicyclo[5.4.0]undec-7-ene, C–C bond formation was similarly efficient but less selective (88% yield, 90:10 e.r.), indicating that transition metal impurities in NaO*t*-Bu are not involved. Thus, consistent with the model in Fig. 1c (favoring **IVb**), enantioselectivity with trifluoromethylketone **3a** is substantially higher and the opposite isomer is favored compared to when acetophenone is used (**2a**, Fig. 1b). The change in e.r. is unlikely to arise from the larger trifluoromethyl unit (vs. methyl)[38], as then only a decrease (e.g., additions to **2a**,**b** in Fig. 1b) – but not a reversal and not to higher levels – of enantioselectivity would be observed (further analysis below).

Steric factors and enantioselectivity

Transformations affording *ortho*-substituted **4b**,**c** are less selective (Fig. 2b). DFT studies pointed to stronger steric hindrance caused by the substrate's aryl group being near the catalyst's phenol moiety (cf. **IVc**); to minimize repulsion, the aryl unit moves out of conjugation with the carbonyl group (O=C–C–C dihedral angle of ~55° in **IVc** vs. ~32° in **IVb**, Fig. 2a), raising the energy of the associated transition structure. Depending on the density functional employed, **IIc** (M06-2X) or **IVc** (ωB97XD) emerged as favorable. Since neither **IIc** nor **IVc** is free of additional steric strain, the energetic preference compared to **Vc** would be minimized (1.4 or 1.8 kcal/mol with M06-2X and ωB97XD, respectively). To probe if any relief of repulsion induced by the catalyst's *tert*-butyl group causes higher selectivity, we examined reactions of fluoro-ketones **3a-c** with aminophenol **1b** (*tert*-butyl replaced by H), but e.r. was reduced (**4a-c**, Fig. 2a,b). We attribute this to a more competitive background reaction and diminished efficiency of the catalytic reaction (lower conversion). The same substrate modification (i.e., the presence of a larger aryl unit) led to higher enantioselectivity with the methyl ketones (e.g., 6.5:93.5 e.r. for 2-naphthyl methyl ketone vs. 72:28 e.r. for the trifluoromethyl analogue), further underlining the distinct mechanistic features of reactions with fluorinated ketones.

Scope of enantioselective allyl additions

Many polyfluoroalkyl-substituted ketones can be used (Table 1, Table 3). Electronic attributes of the aryl substituent do not strongly influence selectivity, indicating that differential Lewis basicity of carbonyl non-bonding electrons is not important [39] (non-bonding carbonyl electrons that are *anti* to the CF_3 group can have considerable hyperconjugative interaction with C–CF_3 σ* orbital). Otherwise, due to diminished Lewis basicity difference between carbonyl lone pairs, formation of **4g**,**h** (entries 4–5) containing electron-withdrawing aryl groups would be less stereoselective than that of **4a** or **4e**. The changes in enantioselectivity for 2- and 3-furyl-substituted products **4j**,**k** (90:10 vs. 98:2 e.r.; entries 7–8) as well as the S-containing heterocycles **4l**,**m** (84.5:15.5 vs. 96.5:3.5 e.r.; entries 9–10) are noteworthy. Electrostatic attraction arising from electronic repulsion between the non-bonding electrons of the carbonyl oxygen and the heterocyclic O or S atom, while weaker than with a trifluoromethyl unit, may lower e.r. with **4j** and **4l** via complex **VI**. Furan and thiophene are weakly polarized (molecular μ = 0.7 and 0.5 Debye, respectively[40,41]), orienting a C–O or a C–S (bond μ = 0.7 and 0.9 Debye[42], respectively) and a C=O group (bond μ = 2.3 Debye[42]) in a *syn*-periplanar manner should cost relatively little in dipole–dipole destabilization. There is inherent e-e repulsion within such substrates (regardless of the conformation) that can be alleviated in **VI** by the ammonium proton (vs. **VII**). The factors responsible for furyl products



4j and **4k** being formed in e.r. higher than their corresponding thienyl analogues (vs. **4l** and **4m**, respectively) are multi-faceted, but the consistent trend in selectivity, depending on the position of the heteroatom within each substrate class, is meaningful (more examples below). Additions to substrates with an alkyl substituent (**4n-o**; entries 11–12, Table 1, Table 3), or those containing longer chain perfluoroalkyl units (**4p-q**; entries 13–14) gave the desired tertiary alcohols in 85–95% yield and 88:12–97.5:2.5 e.r. Reactions with C2-substituted allylboron reagents were efficient and stereoselective (**5a,b**; entries 15–16).

Enantioselective allenyl additions

Subjection of **3a** to 1.0 mol % **1a** and commercially available allenylboronic acid pinacol ester (Fig. 3a) afforded **6a** in 93:7 e.r. [<2% homopropargyl alcohol: >98% net α addition ("double-γ" mechanism[20]]. Without **1a**, there was 80% conversion to *rac*-**6a**, pointg to high chiral catalyst efficiency. With acetophenone (**2a**) a nearly equal mixture of enantiomers was formed (32% conv., 44:56 e.r., <2% homopropargyl alcohol).

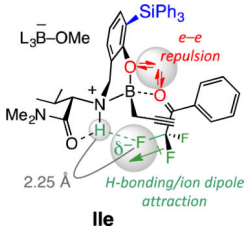
Better catalyst for allenyl additions

DFT studies pointed to distinct variances between allyl and allenyl additions. In **IVb**, **Vb**, **IVd** and **Vd** (Fig. 3b), regardless of whether there is an attractive interaction, the catalyst-ketone complex seems less tightly held in propargylboron intermediates **IVd-Vd** (vs. **IVb-**

Vb). The distance between the ammonium proton and the closest fluorine atom in **IVd** was calculated to be longer than in **IVb** (4.23 vs. 4.10 Å, respectively). Similarly, the pseudo-axially disposed trifluoromethyl group is situated further away from the *tert*-butyl group in complex **Vb** versus **Vd** (2.42 vs. 2.34 Å). Hence, the ammonium-F–C attraction that favors **IVb** and the steric reinforcement provided by the sizeable catalyst moiety, which steers the reaction away from **Vb**, seems weaker in the allenyl additions. This might originate from the structural adjustment needed for achieving proper overlap between the carbonyl and the propargylboron group (vs. an allylboron; see the Supplementary Information for further analysis). With the less hindered **1b**, **6c** was generated in 93:7 e.r., identical to when **1a** was used, emphasizing the diminished effectiveness with which the *tert*-butyl moiety provides "steric reinforcement" and the contribution by the ammonium-organofluorine attractive forces.

The above considerations implied that a modified catalyst with a farther-reaching steric influence than a *tert*-butyl group could be beneficial to enantioselectivity of the allenyl additions. In the higher energy **Vb** or **Vd** the CF_3 group is closer to the sizeable catalyst substituent (vs. aryl in **IVb** or **IVd**), and, unlike the symmetric trifluoromethyl, steric repulsion with an aromatic plane can be eased by the C–aryl bond rotation. These expectations were experimentally verified (Fig. 3a). With triphenylsilyl-substituted aminophenol **1c**, tertiary alcohols **6a-c** were obtained with higher enantioselectivity. Accordingly, steric factors imposed by the catalyst's silyl group better buttress the structural organization provided by electrostatic attraction. Lending further credence, in the corresponding allyl additions, where a *tert*-butyl unit can exert sufficient influence on the more tightly held catalyst-substrate assembly, use of silyl-substituted **1c** typically led to less significant e.r. improvement (e.g., 85:15 vs. 83:17 with **1a** for **4b** and 87:13 vs. 92:8 for **4c**).

DFT calculations indicated that in the case of the silyl-substituted catalyst mode of addition **IIe** is competitive perhaps because with the more sizeable substituent, steric factors gain in significance (e.g., between Ph and $SiPh_3$ when **2a** is used). A separation of 2.25 Å computed for the distance between the ammonium proton and the F atom in **IIe** suggests that H-bonding/ion–dipole attraction between the ammonium and the CF_3 group is now feasible (the shortest reported value is ~2.2 Å (X-ray crystallography)[1]. Moreover, the relative orientation of the C–F and the N–H bond (~129° in **IIe**) should allow for some degree of H-bonding (i.e., C–F···H–N interaction with partial covalent character[34]), which benefits from the involvement of a positively charged donor group ("ionic H-bonding"[43]). A representative set of



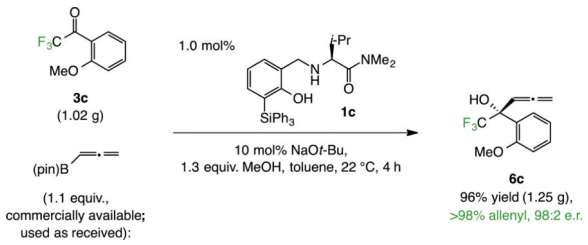
IIe

DFT calculations with model systems support this possibility (see the Supplementary Information). Contribution by H-bonding is also consistent with a quantum theory atoms-in-

molecule (QTAIM)-derived bond critical point (BCP) wherein the electron density is 0.018 electrons•bohr^{-3}; this value is, not surprisingly, lower than calculated for a phosphinoyl imine for which the electron density value is $\rho = 0.048$ electrons•bohr^{-3} ($0.005 < \rho < 0.5$ electrons•bohr^{-3} suggest hydrogen-bonds of varying strength[44]).

Scope of enantioselective allenyl additions

Allenyl additions can be performed with polyfluoroalkyl ketones containing electronically diverse aryl or heteroaryl groups (Table 2, Table 4). 2- Furyl and 2-thienyl-substituted products **6g,i** (entries 4 and 6) were again less enantioselective than 3-furyl and 3-thienyl variants **6h,j** (94.5:5.5 and 91.5:8.5 vs. 98:2 and >99:1 e.r., respectively; entries 5 and 7). Ethers[33] (a C–O bond is much less polarizable than a carbonyl group) and sulfides[45] (sulfur has "soft"/diffused electron density) are not effective H-bond acceptors, but electrostatic attraction involving the ammonium group can be operative here too (cf. **VI**). Substrates with an alkenyl (**6k**; entry 8) or an alkyl substituent (**6l-m**; entries 9–10) are suitable. As with the allyl additions, transformations are simple to perform and amenable to gram-scale procedures; the reaction in Eq. 1 was carried out with unpurified reagents and without rigorous exclusion of air or moisture.



(1)

Reactions with difluoro- and monofluoroalkyl ketones

In a trifluoroketone, electron repulsion between non-bonding electrons of the carbonyl group and the adjacent fluorine atom cannot be relieved by rotation of the CF_3 group. With a mono- or difluoroalkyl group, on the other hand, such repulsive interactions can be avoided and dipole–dipole interactions may be minimized when the C=O and C–F bonds are in an *anti* orientation. Electrostatic attraction with ammonium moiety and enantioselectivity may consequently be reduced; *anti*-periplanar monofluoroacetone is indeed estimated to be ~2.2 kcal/mol lower in energy than its *syn*-coplanar conformer[46]. Another factor is the number of fluorine atoms that are attached to the carbon centre. Apropos, computational/spectroscopic studies indicate the order of CH_2F>CHF_2>CF_3 regarding the strength of ion–dipole association[47], but the possibility of intervention by an opposing interaction is absent in such systems.

To probe the interplay of different electrostatic forces, we investigated additions to 2-fluoro- and 2,2-difluoroacetophenone. Unlike trifluoromethyl-substituted **4a**, tertiary homoallylic alcohols **7** and **8** were generated with low enantioselectivity (65:35 and 58:42 vs. 96:4 e.r.; Fig. 4a). The precipitous drop in e.r. may be attributed to a competitive pathway via a

complex such as **Vf** (vs. **IVf**, Fig. 4a) with opposing C–F and C=O dipoles. Carbonyl chelation to the boron atom leads to a net increase in electron density of the donor atom (Lewis base activation of Lewis acids[48]; see the Supplementary Information for additional references), causing an enhancement in the C=O bond dipole. Attractive forces involving a CH_2F or a CHF_2 moiety therefore cannot overcome the conflicting dipolar effects induced by the adjacent carbonyl group. Homoallylic alcohol **9** (Fig. 4a) was formed in higher e.r. (79:21) in comparison to monofluoromethyl- (**7**) or difluoromethyl-substituted (**8**) derivatives because reaction through **Vg** brings with it more electronic and steric repulsion (vs. **IVg**, Fig. 4a). The higher e.r. (94:6) for bicyclic tertiary alcohol **10** therefore makes sense: here, alternative transition structures leading to diminution of repulsive dipolar interactions are no longer relevant. Equally illuminating is the difference in the enantiomeric purity with which difluoro-homoallylic alcohols **9** and **10** are generated (79:21 vs. 94:6 e.r.); this demonstrates that selectivity changes for differentially fluorinated substrates arise from electrostatic attractive forces and not in size differences caused by the fluorine (vs. H) atoms or as a result of stronger donation of a carbonyl oxygen electron lone pair into the σ*C–C bond[38]. The superior e.r. for 2,2,2-trifluoromethyl-substituted **4a**, compared to 2,2-difluoroethyl-containing **9** (96:4 vs. 79:21 e.r.) wherein a fluorine atom is replaced by a larger methyl, supports the contribution to enantioselectivity by non-bonding affinities. If steric effects were dominant, either the ketone with the larger moiety would be formed in higher e.r. (i.e., **9** vs. **4a**) or substrates with a more distinctive size difference between their aryl and alkyl groups would be more enantioselective (e.g., **7** vs. **9**). It is mostly because of ammonium-organofluorine affinities that, compared to *iso*-propyl ketone **2b** (Fig. 1b), product **4a**, containing a similarly sized substituent (CF_3 vs. *i*-Pr), is generated with higher and opposite selectivity sense (96:4 vs. 34:66 e.r.).

Additions to fluoroaryl ketones

Transformations involving fluoroaryl methyl ketones expand the method's scope and provide additional insight (Fig. 4b). Allyl addition to *ortho*-fluoroacetophenone afforded tertiary alcohol **12** with low e.r. (59:41 vs. 68:32 e.r. for **2a**). This is because the carbonyl group and the C–F bond likely adopt an *anti*-periplanar orientation to avoid dipolar and electron–electron repulsion [cf. **11a** vs. **11b**, Fig. 4b; calculated energy difference (ΔG) = 2.4 kcal/mol; **11a**: μ = 4.7 Debye, **11b**: μ = 3.0 Debye]. Natural charges and natural bond orbital (NBO) calculations indicate that the energy of the non-bonding electrons on the carbonyl oxygen are raised by 0.09 eV (= 2.1 kcal/mol); the heteroatomic charge is smaller in value in **11a** as the electronic repulsion is alleviated by means of electron flow towards the carbonyl carbon, contributing to the lower stability of conformer **11a**. In the formation of **12**, the determinant steric factors and the resulting enantioselectivity are thus nearly the same as when acetophenone is converted to **4a**.

The major enantioselectivity increase for the 2,6-difluoroacetophenone reaction, on the other hand, was less expected (**13** in 93.5:6.5 e.r., Fig. 4b). Under identical conditions but with 2,6-dichlorophenylacetophenone, there was <2% conversion, indicating that the chlorine atoms are sufficiently large to shut down addition. That is, the two fluorine atoms are not sizeable enough to lower reaction rate (van der Waals radius: 1.47 Å vs. 1.74 Å for Cl[27]) and yet they enhance the effective volume of the aryl unit to induce substantial enantioselectivity

enhancement. DFT calculations indicate that complex **IVh** is favored over **Vh**, (by 1.1 and 1.6 kcal/mol with M06-2X and ωB97XD, respectively). The distance of 3.18 Å between the ammonium proton and the nearby fluorine atom in **IVh**, renders H-bonding unlikely but electrostatic attraction remains feasible. Further, **Vh** contains a significantly tilted aryl moiety as a result of steric repulsion with the catalyst's phenol and/or *tert*-butyl unit (∠O=C–C–C = 48°). It is for analogous reasons (cf. **9**) that pentafluorophenyl tertiary alcohols **14** and **15** can be accessed in 95.5:4.5 and 96:4 e.r., respectively (Fig. 4b). Addition to octafluoroacetophenone proceeds with minimal selectivity (**16** in 59:41 e.r.; 59% yield; <2% conv. without **1a**) because ammonium-fluorine interactions are countered by steric forces involving the pentafluorophenyl moiety and the catalyst's *tert*-butyl unit (as with the formation of *ortho*-substituted products **4b**,**c** in Fig. 2b). The basis for the differences in selectivity in the formation of **12**–**16** is the strong C–F bond polarization.

Synthesis of Bravecto™

To demonstrate utility, we devised an enantioselective route to fluralaner, which is marketed in the racemic form as Bravecto™ (Merck); the targeted enantiomer has been shown to possess superior activity[13]. Subjection of commercially available 3,5-dichlorophenyl-2,2,2-trifluoromethyl ketone **3r** to allyl–B(pin) and 2.5 mol % adamantyl-substituted aminophenol **1d**, 10 mol % $Zn(OMe)_2$ and 1.3 equivalents of MeOH in 3:1 pentane:toluene gave tertiary alcohol **4r** (97% yield, 95:5 e.r.) Enantioselectivity was slightly lower in pure toluene (93.5:6.5 e.r.) or when **1a** and NaO*t*-Bu were used (92:8 e.r.). Aminophenol **1d** was accessed from a purchasable aryl aldehyde. The modified conditions for enantioselective synthesis of **4r** highlight the ease with which the catalyst structure and/or the conditions can be implemented for improving reaction outcomes. β-Hydroxy ketone **18** was obtained via aldehyde **17** (CCDC deposition number 1471454) after three straightforward operations in 56% overall yield (Fig. 5). Isoxazoline **19**, previously converted to fluralaner[49], was then generated in 40% overall yield (three steps).

Conclusions

The newly developed catalytic methods allow efficient access to an assortment of versatile homoallyl and allenyl compounds that contain a trifluoromethyl-substituted tertiary alcohol in high enantiomeric purity. These protocols can facilitate increasing the pharmacokinetic properties of a drug candidate by “substitution” of a functional group to a trifluoromethyl unit[50] (e.g., proton of a secondary or methyl unit of a tertiary alcohol). The knowledge gained regarding the influence of different modes of non-bonding interactions between an ammonium group and an organofluorine compound should prove valuable in future efforts toward the design of other efficient and stereoselective transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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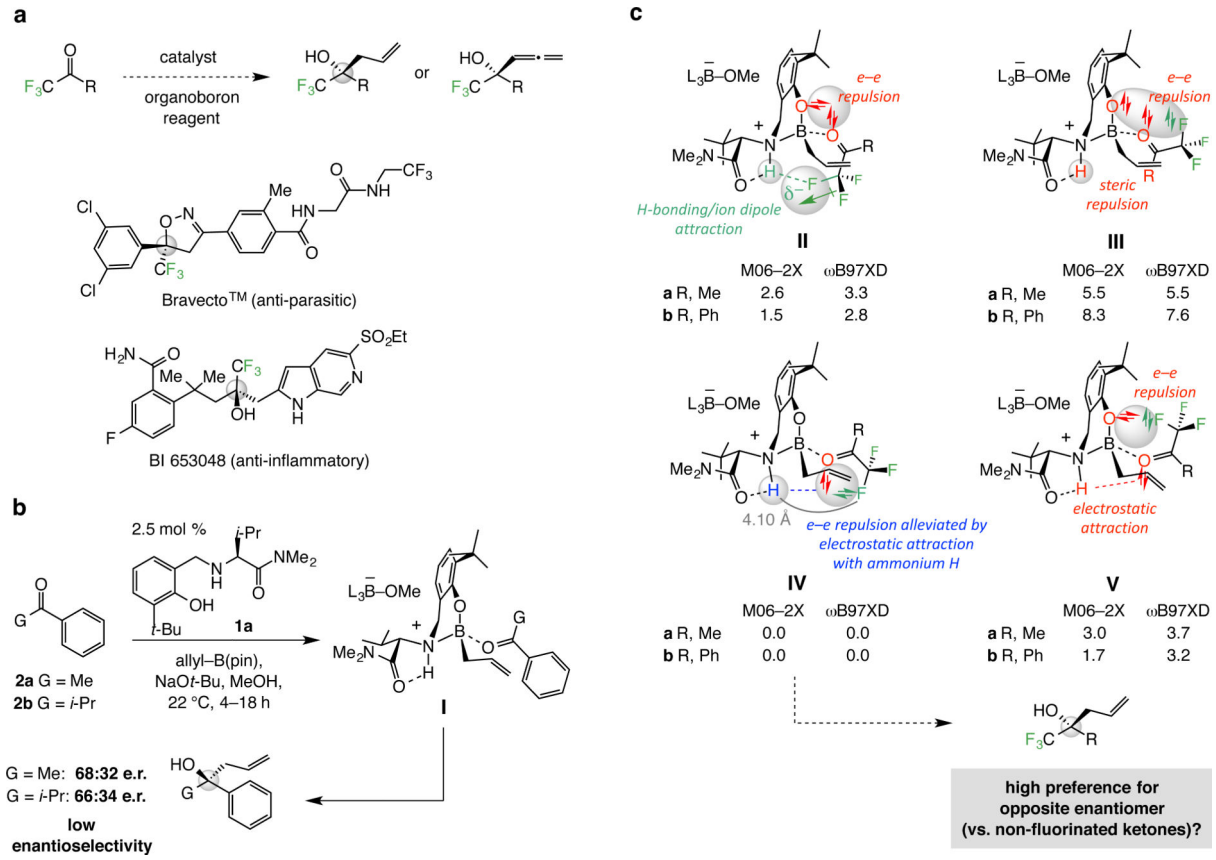


Figure 1. Ammonium-organofluorine affinity in enantioselective organoboron addition to trifluoromethylketones

a, Effective catalytic methods for additions of allyl or allenyl units to fluorinated ketones may allow for facile synthesis of biologically active molecules and drugs such as fluralaner and BI 653048. **b,** Catalytic enantioselective additions of unsaturated organoboron compounds proceed with minimal enantioselectivity (unlike phosphinoyl imines or isatins). **c,** DFT calculations at the M06-2X or ωB97XD/6-311++G(2df,2pd)//M06-2X/6-31G(d,p)$_{toluene(PCM)}$ level suggest that higher enantiomeric ratio (e.r.) might be achievable with trifluoromethylketones because of a combination of different attractive and/or repulsive electrostatic forces involving a fluorine atom. Free energy values for transition states are in kcal/mol relative to the most favorable alternative. Abbreviations: G or R, a functional group; pin, pinacolato; L, ligand.

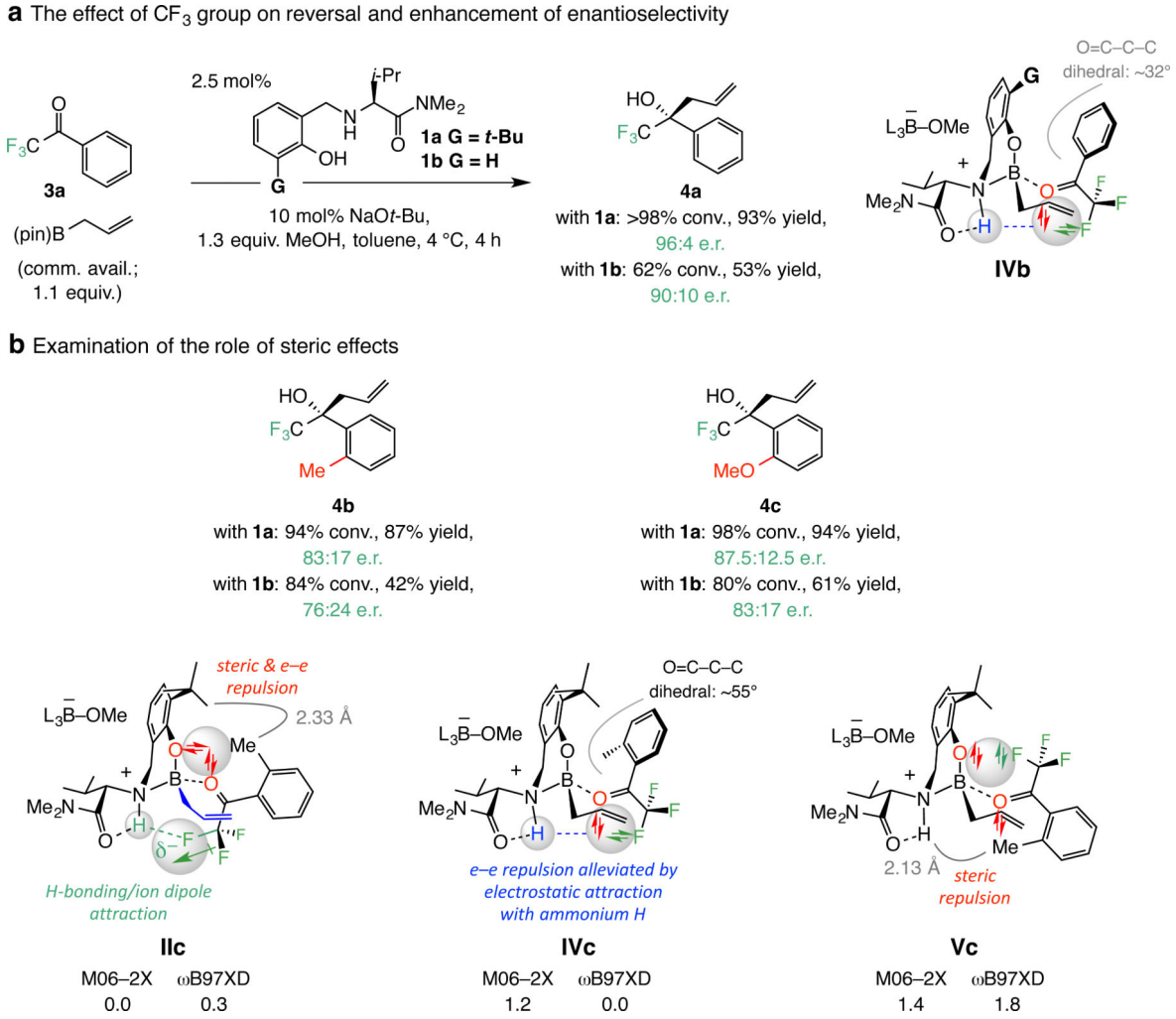


Figure 2. Catalytic enantioselective allyl additions to trifluoromethylphenyl ketones

a, Reaction with **3a** proceeds with substantially higher enantioselectivity compared to its non-fluorinated analogue (**2a**). Reactions with substrates that contain an ortho-substituted aryl group are less enantioselective and remain so when the modified aminophenol **1b** is used. **b,** Selectivity differences in reactions with **1a,b** illustrate the possible role of steric factors. DFT calculations were carried out at the M06-2X or ωB97XD/6-311++G(2df,2pd)// M06-2X/6-31G(d,p)$_{\text{toluene(PCM)}}$ level; free energy values are provided in kcal/mol relative to the most favorable transition state. (See the Supplementary Information for details.)

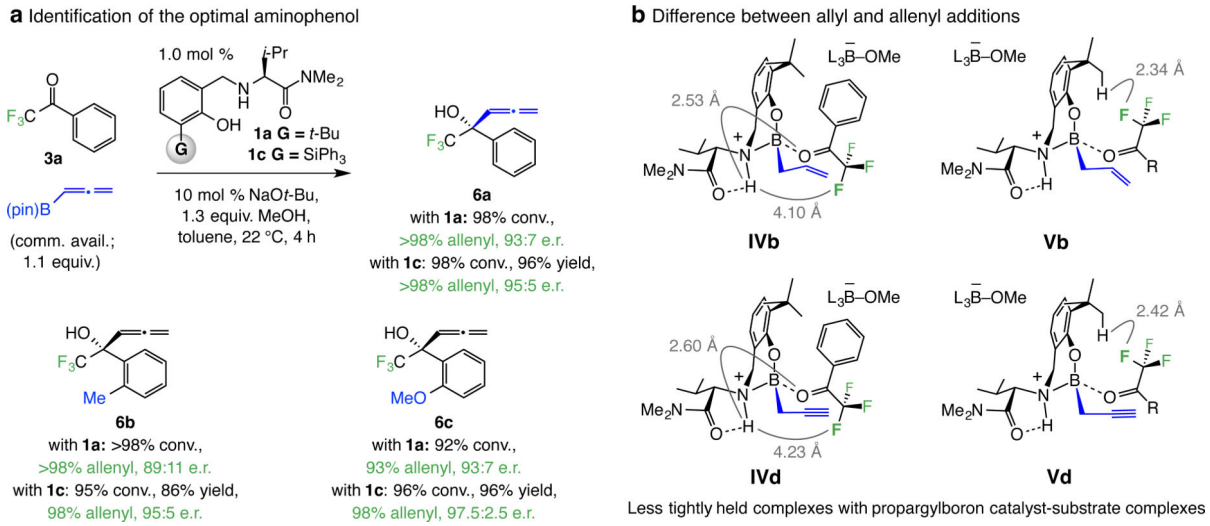


Figure 3. Catalytic enantioselective allenyl additions to trifluoromethylphenyl ketones

a, The boron-based catalyst derived from triphenylsilyl-substituted aminophenol **1c** proves to be superior for additions of allenyl units to trifluoromethylphenyl ketones (vs. **1a**). **b,** Analysis of subtle differences in the structures of catalyst-ketone complexes for allyl versus allenyl addition reactions points to a comparatively distal positioning of the substrate molecule in the latter set of transformation. Accordingly, use of triphenylsilyl-substituted aminophenol **1c**, which extends the reach of the chiral catalyst, was found to generate improved enantioselectivities. DFT calculations were carried out at M06-2X or ωB97XD/6-311++G(2df,2pd)//M06-2X/6-31G(d,p)$_{\text{toluene(PCM)}}$ level. (See the Supplementary Information for details.)

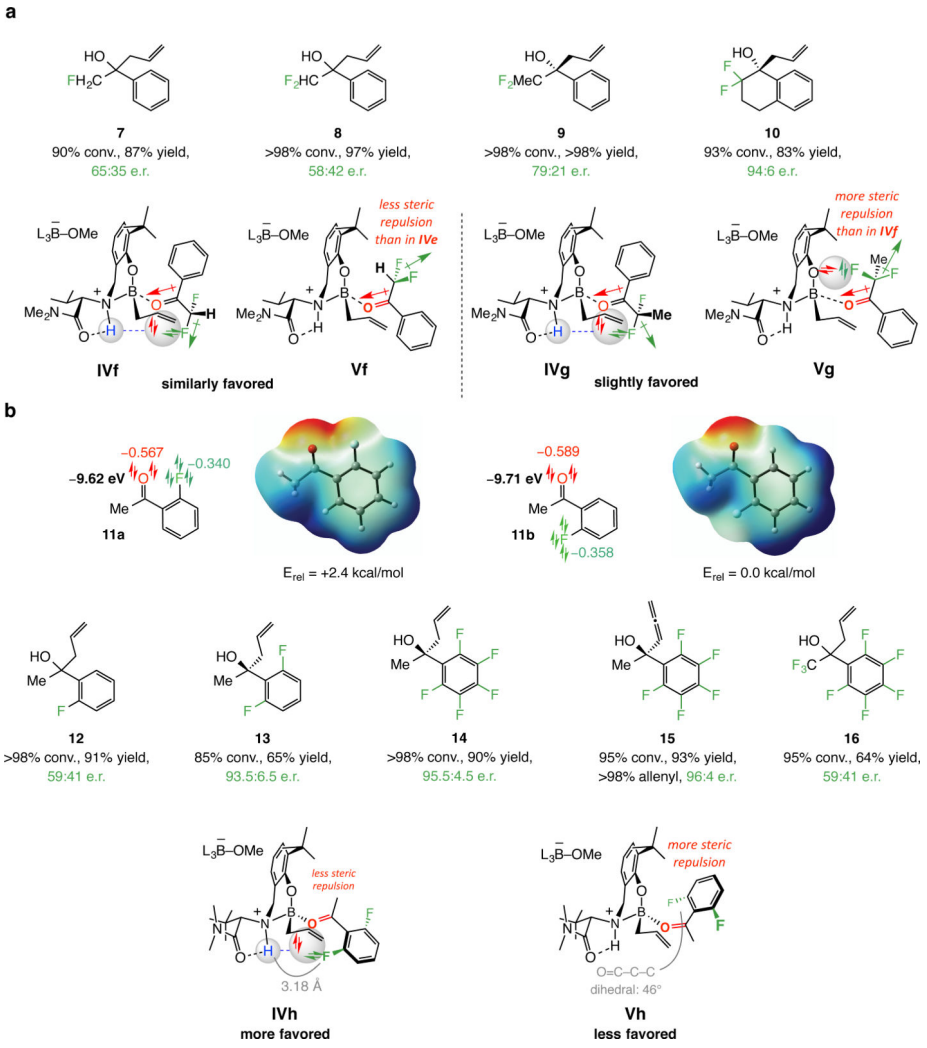


Figure 4. Dependence of enantioselectivity on the number and positioning of the fluorine atoms in a ketone substrate

a, The number of fluorine atoms, the identity of the other units on the fluoro-substituted alkyl substituent of a ketone substrate as well as its conformational flexibility determine the degree to which dipolar forces can disrupt electrostatic attraction and therefore influence enantioselectivity. **b,** In the case of additions to ketones that carry a fluoro-substituted aryl unit, the number of fluorine atoms has a strong impact on the feasibility of ammonium-F–C non-bonding interaction and thus exerts a strong influence on the observed enantiomeric ratios. Reactions were performed under N_2 with **1a**, except for allenyl product **15**, for which **1c** was used. Conversions were measured by analysis of 376 MHz ^{19}F NMR spectra of unpurified mixtures vs. internal standard of trifluorotoluene or fluorobenzene; the variance of values estimated to be <±2%. Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantiomeric ratios were determined by HPLC analysis (±2%). See the Supplementary Information for experimental details and spectroscopic analyses.

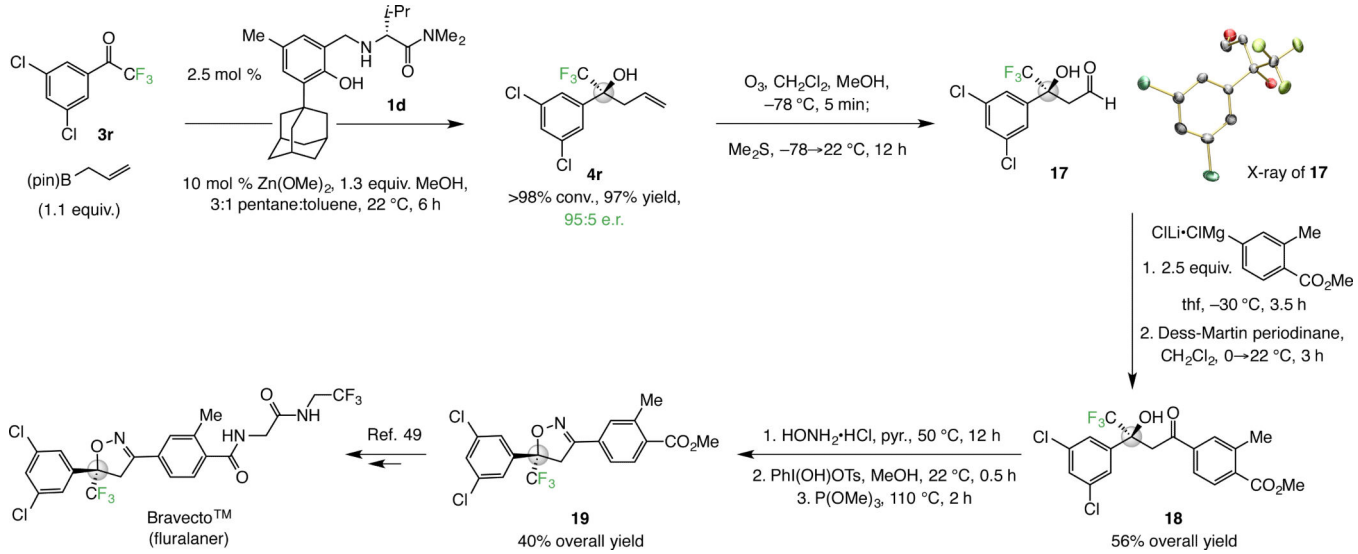
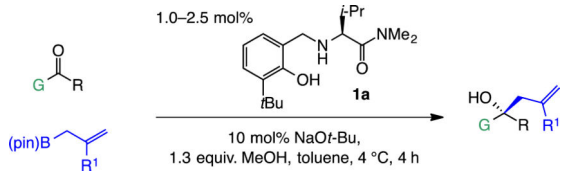


Figure 5. Enantioselective synthesis of anti-parasitic drug Bravecto™

The precursor to anti-parasitic agent, currently marketed as Bravecto™, isoxazoline **19**, can be prepared efficiently and in high enantiomeric purity through a pathway that features the enantioselective allyl addition to commercially available 3,5-dichlorophenyl-2,2,2-trifluoromethyl ketone **3r**. The key allyl addition delivers the highest e.r. value (95:5) with 10 mol % $Zn(OMe)_2$ as the base and the boron-based complex that is derived from adamantyl-substituted aminophenol **1d**. The resulting tertiary homoallylic alcohol **4r** is then converted to β-hydroxy ketone **18**, the product that would be expected from a ketone aldol addition to **3r** in 56% overall yield.

Table 1

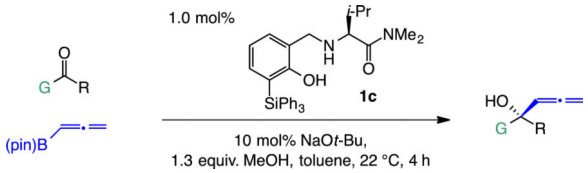
Catalytic enantioselective allyl additions to fluoroketones.



Entry	G; R; R^1	1a (mol%)	Product	Conv. (%)*; Yield (%)†	e.r.††
1	CF_3; 3-MeC_6H_4; H	2.5	**4d**	>98; 94	92.5:7.5
2	CF_3; 4-$Me_2NC_6H_4$; H	2.5	**4e**	>98; 98;	93.5:6.5
3	CF_3; 4-BrC_6H_4; H	1.0	**4f**	>98; 94	96:4
4	CF_3; 4-$F_3CC_6H_4$; H	2.5	**4g**	>98; 91	93.5:6.5
5	CF_3; 2-(Boc)pyrrole; H	2.5	**4h**	>98: 71	>99:1
6	CF_3; HC=C(H)Ph; H	2.5	**4i**	>98; 94	96.5:3.5
7	CF_3; 2-furyl; H	2.5	**4j**	98; 77	90:10
8	CF_3; 3-futyl; H	5.0	**4k**	>98; 88	98:2
9	CF_3; 2-thlenyl; H	2.5	**4l**	98; 71	84.5:15.5
10	CF_3; 3-thienyl; H	2.5	**4m**	>98; 98	96.5:3.5
11	CF_3; CH_2Ph; H	2.5	**4n**	95; 95	94:6
12	CF_3; cyclohexyl; H	2.5	**4o**	95; 88	88:12
13	C_2F_5; Ph; H	1.0	**4p**	>98; 85	96:4
14	C_3F_7; Ph; H	1.0	**4q**	>98; 89	96.5:3.5
15	CF_3; Ph; Me	2.5	**5a**	>98; 85	97.5:2.5
16	CF_3; Ph; CI	2.5	**5b**	>98; 96	96.5:3.5

Table 2

Catalytic enantioselective allenyl additions to fluoroketones.



Entry	G; R	Product	Conv. (%)*; Yield (%)†	Allenyl: Propargyl**	e.r.††
1	CF_3; 4-FC_6H_4	**6d**	95; 87	>98:2	97.5:2.5
2	CF_3; 4-$Me_2NC_6H_4$	**6e**	93; 91	>98:2	96.5:3.5
3	CF_3; 4-$F_3CC_6H_4$	**6f**	>98; 97	>98:2	96.5:3.5
4	CF_3; 2-furyl	**6g**	>98; 93	>98:2	94.5:5.5
5	CF_3; 3-furyl	**6h**	>98; 91	>98:2	98:2
6	CF_3; 2-thienyl	**6i**	97; 92	>98:2	91.5:8.5
7	CF_3; 3-thienyl	**6i**	97; 88	>98:2	>99:1
8	CF_3; HC=C(H)Ph	**6k**	98; 93	>98:2	95:5
9	CF_3; CH_2Ph	**6l**	96; 96	>98:2	94.5:5.5
10	CF_3; cyclohexyl	**6m**	>98; 85	>98:2	94:6
11	C_2F_5; Ph; H	**6n**	95; 89	>98:2	97:3

Table 3

Catalytic enantioselective allyl additions to fluoroketones.

Entry	G; R^1; R^2	1a (mol %)	Product	Conv. (%)*; Yield (%)†	e.r.††
1	CF_3; 3-MeC_6H_4; H	2.5	**4d**	>98; 94	92.5:7.5
2	CF_3; 4-$Me_2NC_6H_4$; H	2.5	**4e**	>98; 98	93.5:6.5
3	CF_3; 4-BrC_6H_4; H	1.0	**4f**	>98; 94	96:4
4	CF_3; 4-$F_3CC_6H_4$; H	2.5	**4g**	>98; 91	93.5:6.5
5	CF_3; 3-(Boc)pyrrole; H	2.5	**4h**	>98; 71	>99:1
6	CF_3; HC=C(H)Ph; H	2.5	**4i**	>98; 94	96.5:3.5
7	CF_3; 2-furyl; H	2.5	**4j**	98; 77	90:10
8	CF_3; 3-furyl; H	5.0	**4k**	>98; 88	98:2
9	CF_3; 2-thienyl; H	2.5	**4l**	98; 71	84.5:15.5
10	CF_3; 3-thienyl; H	2.5	**4m**	>98; 98	96.5:3.5
11	CF3; $CH_2C_6H_5$; H	2.5	**4n**	95; 95	94:6
12	CF_3; Cyclohexyl; H	2.5	**4o**	95; 88	88:12
13	C_2F_5; C_6H_5; H	1.0	**4p**	>98; 85	96:4
14	C_3F_7; C_6H_5; H	1.0	**4q**	>98; 89	96.5:3.5
15	CF_3; C_6H_5; Me	2.5	**5a**	>98; 85	97.5:2.5
16	CF_3; C_6H_5; Cl	2.5	**5b**	>98; 96	96.5:3.5

Reactions were carried out under the same conditions used for **4a,** except that **4k** required 7 hours and reactions for **4j,** and **5a,b** were performed at 22 °C.

*Conversion to the desired product as measured by analysis of 376 MHz ^{19}F NMR spectra of unpurified mixtures vs. an internal standard of trifluorotoluene; variance of values is estimated to be ±±2%.

†Yield of isolated product (±5%). The differences between conversion and yield (i.e., when **1b** was used) are largely due to difficulties in separation of the recovered substrate and products.

††Enantiomeric ratios determined by GC or HPLC analysis (±±2%). (See the Supplementary Information for details.)

Table 4

Catalytic enantioselective allenyl additions to fluoroketones.

Entry	G; R	Product	Conv. (%)*; Yield (%)†	Allenyl: Propargyl**	e.r.††
1	CF_3; 4-FC_6H_4	**6d**	95; 87	>98:2	97.5:2.5
2	CF_3; 4-$Me_2NC_6H_4$	**6e**	93; 91	>98:2	96.5:3.5
3	CF_3; 4-$F_3CC_6H_4$	**6f**	>98; 97	>98:2	96.5:3.5
4	CF_3; 2-furyl	**6g**	>98; 93	>98:2	94.5:5.5
5	CF_3; 3-furyl	**6h**	>98; 91	>98:2	98:2
6	CF_3; 2-thienyl	**6i**	97; 92	>98:2	91.5:8.5
7	CF_3; 2-thienyl	**6j**	97; 88	>98:2	>99:1
8	CF_3; HC=C(H)Ph	**6k**	98; 93	>98:2	95:5
9	CF_3; $CH_2C_6H_5$	**6l**	96; 96	>98:2	94.5:5.5
10	CF_3; Cyclohexyl	**6m**	>98; 85	>98:2	94:6
11	C_2F_5; C_6H_5	**6n**	95; 89	>98:2	97:3

Reactions carried out in toluene under under N_2.

*Conversion to the desired product as measured by analysis of 376 MHz ^{19}F NMR spectra of unpurified mixtures vs. an internal standard of trifluorotoluene; the variance of values is estimated to be ±±2%.

**Determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures

†Yield of isolated product after purification and represent an average of at least three runs; the variance of values is estimated to be ±±5%.

††Enantiomeric ratios were determined by HPLC analysis; the variance of values is estimated to be ±±2%. (See the Supplementary Information for details.)