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Catalytic enantioselective alkenylation and phenylation of trifluoromethyl ketones

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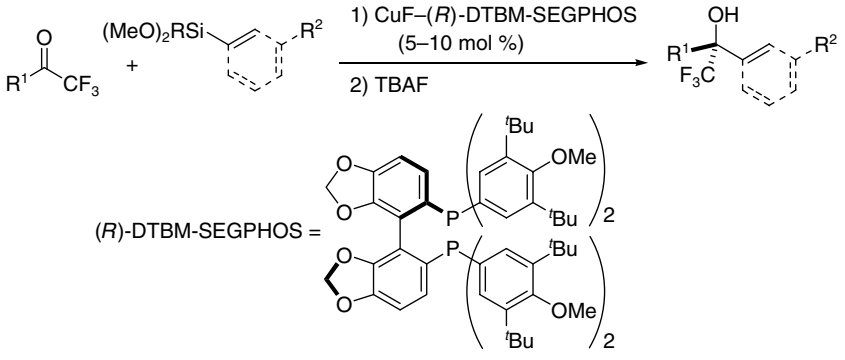
Abstract—Catalytic enantioselective alkenylation and phenylation of trifluoromethyl ketones are described. High enantioselectivity (up to 84% ee) was produced in an alkenylation of aryl trifluoromethyl ketones using a CuF–DTBM-SEGPHOS complex as the catalyst (5–10 mol %) and alkenylsilanes as the nucleophile. This is the first example of catalytic enantioselective alkenylation of trifluoromethyl ketones. The products are versatile chiral building blocks, which contain a trifluoromethyl-substituted tertiary alcohol moiety.

Due to their unique properties, fluorinated compounds are attracting growing interest in medicinal chemistry and material sciences.[1] Catalytic asymmetric synthesis of fluorine-containing molecules, however, has only recently begun to be explored.[2–4] In this letter, we describe a Cu(I)-catalyzed enantioselective alkenylation and phenylation of trifluoromethyl ketones that produces enantiomerically enriched tertiary alcohols containing a trifluoromethyl substituent (Scheme 1). To access this potentially important class of compounds, asymmetric trifluoromethylation of ketones is an alternative strategy. Although there are many racemic catalytic trifluoromethylation methods,[5] only two asymmetric versions of this reaction type have been reported.[6] Those reactions, however, produced only moderate enantioselectivity (6–64% ee), except for one special substrate. Furthermore, catalytic enantioselective addition of organozinc reagents—one of the most intensively studied catalytic enantioselective reactions[7]—has not been applied to trifluoromethyl ketones as a substrate.[8] Therefore, there are no reports of synthetically useful catalytic carbon–carbon bond-forming reaction to access enantiomerically enriched trifluoromethyl-substituted tertiary alcohols to date, except that substrates are highly activated trifluoropyruvate derivatives.[9] In this letter, we report the first example of catalytic enantioselective alkenylation of simple trifluoromethyl ketones. The same conditions are also applicable to phenylation and alkynylation.



Scheme 1.

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We recently reported an enantioselective alkenylation and arylation using a CuF-chiral bisphosphine (DTBM-SEGPHOS as the optimized chiral ligand) complex as the catalyst, and alkenylsilanes, alkenylboronates, phenylsilane, and arylboronates as the nucleophiles.[10] Enantiomerically enriched secondary allylic alcohols and diarylmethanols can be synthesized from a range of aldehydes using air- and moisture-stable silicon- or boron-based sp^2-hybridized carbon nucleophiles. Mechanistically, the reaction proceeds through an organocopper species generated via transmetalation from silicon or boron to copper. Although the reaction did not proceed at all when simple ketones were used as the substrate, activated ketones such as α-ketoesters afforded the products in high enantioselectivity. We expected that trifluoromethyl ketones would be reactive under the catalytic enantioselective alkenylation reaction conditions due to the strong electron-withdrawing characteristic of the trifluoromethyl group.

When previously optimized reaction conditions were applied to trifluoromethyl ketone **1d** using 10 mol % of chiral CuF catalyst (generated reductively in situ from 10 mol % of $CuF_2{\cdot}2H_2O$ and 20 mol % of DTBM-SEGPHOS) and vinyltrimethoxysilane (**2a**) as a nucleophile in toluene solvent, the vinylation product **3d** was obtained in only 12% yield (18 h, 76% ee: Table 1, entry 1). Over 80% of the starting ketone was recovered unchanged. To improve the product yield, we used vinyldimethoxymethylsilane (**2b**) as a nucleophile. Due to the difference in electronic character, **2b** should be more active in generating vinylcopper through transmetalation than **2a** when the corresponding silicates are generated.[11] Using **2b** as the nucleophile, the desired product was produced in quantitative yield with 83% ee (entry 2). A reaction using vinylboronate (**2c**) produced less satisfactory yield, even in the presence of tetrabutylammonium difluorotriphenylsilicate (TBAT: 15 mol %) as an additive (entry 3).[10b] In this case, however, enantioselectivity was comparable to the reaction using **2b**.

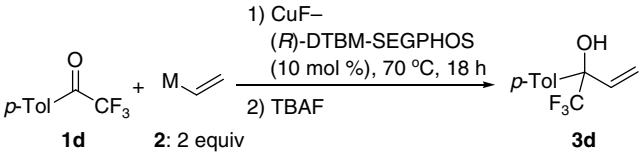
The optimized conditions were then applied to various trifluoromethyl ketones and nucleophiles (Table 2). High enantioselectivity was consistently produced from aromatic trifluoromethyl ketones using 5 or 10 mol % of catalyst (entries 1–4). A nucleophile containing a longer alkenyl chain (**2d**), which was readily prepared from **2a** and the corresponding alkene via Grubbs cross-metathesis,[12] afforded the products with high enantioselectivity (entries 5 and 6). Although the enantioselectivity was more moderate, the same reaction conditions were applicable to catalytic phenylation reactions using dimethoxydiphenylsilane (**2e**), which produced enantiomerically enriched trifluoromethyl-substituted diaryl methanols (**4**: entries 7 and 8).[13,14]

Tertiary alcohols produced in the current study in an enantiomerically enriched form are themselves interesting chiral building blocks for pharmaceuticals and agrochemicals. Additionally, these compounds are versatile because many variations of olefin transformation are possible. For example, trifluoromethyl-substituted hydroxy carboxylic acid **5**, an important component of Mosher's acid,[15] was synthesized from **3a** via ozonolysis and perchlorite oxidation in 87% yield (Scheme 2, Eq. 1). Tertiary allylic alcohol **3a** is also a precursor of β-hydroxy carboxylic acid derivative **6**, which is a representative aldol product between trifluoromethyl ketones and an acetate-derived enolate, via Rh-catalyzed hydroboration[16] followed by oxidation (Scheme 2, Eq. 2). Compound **6** was previously synthesized through diastereoselective reaction using a chiral enolate, but the diastereoselectivity was not satisfactory.[17]

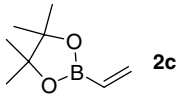
As a preliminary extension, we found that this catalysis can be applied to a catalytic enantioselective alkynylation of trifluoromethyl ketones (Scheme 3).[18] As far as we notice, this is the first example of catalytic enantioselective alkynylation of trifluoromethyl ketones.

In conclusion, we developed a catalytic enantioselective alkenylation, phenylation, and alkynylation of trifluoromethyl ketones using a CuF–DTBM-SEGPHOS complex. Air-stable alkenylsilanes, phenylsilane, and alkynylsilane can be used as nucleophiles. The method allowed for an entry to the catalytic enantioselective synthesis of chiral trifluoromethyl-substituted tertiary alcohols. Further improvement of the enantioselectivity and substrate scope is ongoing.[19]

Table 1. Nucleophile screening in catalytic enantioselective vinylation of trifluoroacetophenone (**1d**)

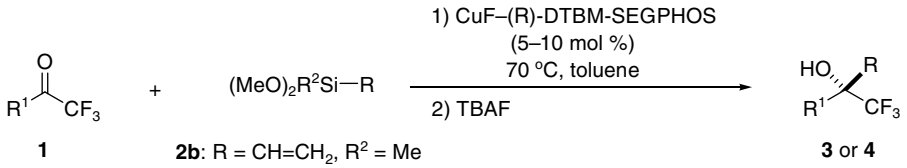


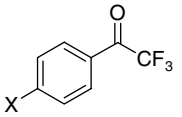
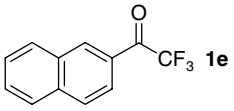
1d **2**: 2 equiv **3d**

Entry	**2**	**3d**
1	$(MeO)_3Si$ **2a**	12%, 76% ee
2	$(MeO)_2MeSi$ **2b**	100%, 83% ee
3[a]	 **2c**	26%, 82% ee

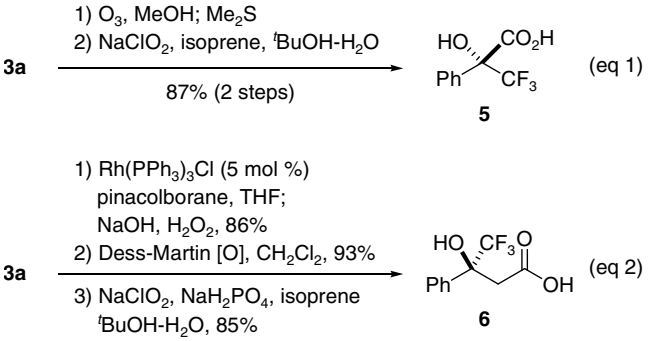
[a] The reaction was conducted in the presence of TBAT (15 mol %).

Table 2. Scope and limitations of Cu-catalyzed enantioselective alkenylation and phenylation of trifluoromethyl ketones

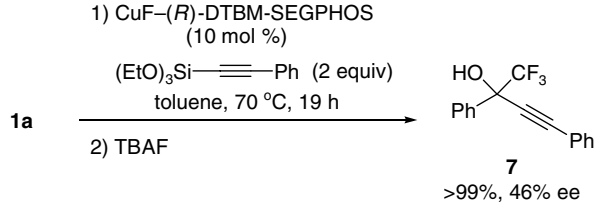


Entry	Substrate		Catalyst (mol %)	Nucleophile	Product	Time (h)	Yield[a] (%)	ee[b] (%)
1		**1a**: X = H	5	**2b**	**3a**	39	100	84[c]
2		**1b**: X = Cl	10	**2b**	**3b**	43	77	84
3		**1c**: X = Br	10	**2b**	**3c**	41	92	82
4		**1d**: X = Me	10	**2b**	**3d**	18	100	83
5	**1a**		10	**2d**	**3e**	17	75	80
6	**1d**		10	**2d**	**3f**	45	75	80
7	**1d**		10	**2e**	**4a**	10	80	67
8	 **1e**		10	**2e**	**4b**	37	91	49

[a] Isolated yield.
[b] Determined by chiral HPLC or GC.
[c] Absolute configuration was determined as shown.



Scheme 2. Conversion to synthetically useful trifluoromethyl-substituted tertiary alcohols.



Scheme 3. Catalytic enantioselective alkynylation of trifluoromethyl ketone.

General procedure: A MeOH solution (0.6 mL) of $CuF_2 \cdot 2H_2O$ (1.4 mg, 0.01 mmol) and (*R*)-DTBM-SEGPHOS (23.6 mg, 0.02 mmol) was refluxed under Ar for 2 h. After removal of the solvent under vacuum, the residue was azeotropically dried through co-evaporation with toluene twice. The resulting CuF–phosphine complex was dissolved in toluene (0.2 mL), and ketone **1a** (28 μL, 0.2 mmol) and nucleophile **2b** (60 μL, 0.4 mmol) were added at room temperature. The reaction was performed at 70 °C for 39 h. TBAF (1 M in THF, 0.25 mL) was added after cooling to room temperature. H_2O was added, and products were extracted with AcOEt. The combined organic layers were washed with brine, and dried over Na_2SO_4. Filtration, evaporation of the solvent, and purification through SiO_2 (AcOEt/hexane = 1/15) afforded **3a** in quantitative yield. Enantiomeric excess of **3a** was determined by chiral HPLC (DAICEL CHIRALPAK AS-H, ^{i}PrOH/hexane = 1/50, $t_R = 8.4$ min (minor) and 9.1 min (major)). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.74$ (s, 1H), 5.56 (d, $J = 10.7$ Hz, 1H), 5.62 (d, $J = 16.8$ Hz, 1H), 6.44 (dd, $J = 10.7$ Hz, 16.8 Hz, 1H), 7.4 (m, 3H), 7.6 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$): $\delta = -79.7$ (s); ^{13}C NMR (125 MHz, $CDCl_3$): 77.2 (q, $J = 29$ Hz), 118.4, 124.6 (q, $J = 286.1$ Hz), 126.6, 128.3, 128.7, 135.6, 137.0.

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