Enantioselective Allylation

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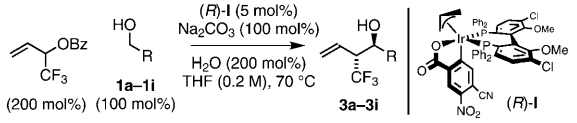
Iridium-Catalyzed *anti*-Diastereo- and Enantioselective Carbonyl (α-Trifluoromethyl)allylation from the Alcohol or Aldehyde Oxidation Level**

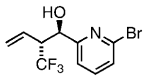
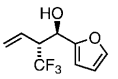
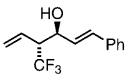
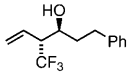
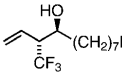
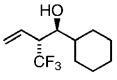
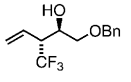
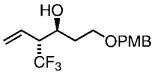
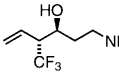
*Xin Gao, Yong Jian Zhang, and Michael J. Krische**

It is estimated that 20% of approved pharmaceutical agents and 30–40% of commercially available agrochemicals contain one or more fluorine atoms.[1a,b] Additionally, in 2006, 80% of the small-molecule drugs entering the market were estimated to contain one or more chiral centers.[1c,2] These facts underscore the importance of developing enantioselective methods for the preparation of organofluorine compounds.[3,4] Toward this end, highly enantioselective nucleophilic trifluoromethylations of aldehydes and ketones have been developed.[3a,e,4] Nucleophilic (α-trifluoromethyl)allylation might also serve to establish absolute stereochemistry at CF_3-bearing carbon centers.[5] Yet, despite persistent efforts aimed at the development of asymmetric carbonyl allylation protocols,[6] enantioselective carbonyl (α-trifluoromethyl)allylation remains an unmet challenge.[5,6] Here, under the conditions of C–C bond forming transfer hydrogenation,[7] we report the first examples of enantioselective carbonyl (α-trifluoromethyl)allylation: a process in which carbonyl addition occurs with equal facility from the alcohol or aldehyde oxidation level.

Our approach takes advantage of carbonyl allylation protocols recently developed in our laboratory, wherein primary alcohol dehydrogenation triggers reductive generation of allyliridium nucleophiles, enabling carbonyl allylation from the alcohol oxidation level.[7,8] In initial experiments, carbonyl (α-trifluoromethyl)allylation was attempted using the *ortho*-cyclometalated catalyst generated in situ from [{Ir(cod)Cl}$_2$] (cod = cyclooctadienyl), various 4-substituted 3-nitrobenzoic acids, BIPHEP (2,2′-bis(diphenylphosphino)-biphenyl), and α-trifluoromethyl allyl benzoate in THF (1M). However, C–C coupling products were not observed in reactions involving in situ catalyst generation. Rather, products of transesterification, the benzoates derived from alcohols **1**, were obtained. Eventually, it was found that transesterification is suppressed for reactions employing the isolated π-allyl iridium *C*,*O*-benzoate modified by BIPHEP and 4-cyano-3-nitrobenzoic acid in THF (0.2M). As observed in related (α-trimethylsilyl)allylations,[8k] the presence of water (200 mol%) improved conversion and suppressed byproduct formation, including formation of transesterification products. The stoichiometry of base (Na_2CO_3 or K_3PO_4) and water are adjusted such that the benzoic acid generated over the course of the reaction is neutralized, yet transesterification is suppressed. At this point, an assay of chiral ligands was undertaken and it was found that the iridium complex modified by (*R*)-Cl,MeO-BIPHEP, designated "(*R*)-**I**", provides the highest levels of enantiomeric enrichment. Thus, upon exposure of primary alcohols **1a**–**1i** to α-trifluoromethyl allyl benzoate (200 mol%) in the presence of (*R*)-**I**, Na_2CO_3 (100 mol%), and water (200 mol%) in THF (0.2M) at 70°C, the desired products of (α-trifluoromethyl)allylation **3a**–**3i** were generated in moderate to good yields with high levels *anti*-diastereo- and enantioselectivity (Table 1). Notably, in the presence of isopropyl alcohol, but under otherwise

Table 1: *anti*-Diastereo- and enantioselective carbonyl (α-trifluoromethyl)allylation from the alcohol oxidation level.[a]



1a, R = 6-Br-2-Pyr	**1b**, R = 2-Furyl	**1c**, R = CH=CHPh
1d, R = $(CH_2)_2$Ph	**1e**, R = $(CH_2)_7$Me	**1f**, R = *c*-C_6H_{11}
1g, R = CH_2OBn	**1h**, R = $(CH_2)_2$OBn	**1i**, R = $(CH_2)_2$NHBoc
		
60% yield, ≥20:1 d.r. 95% *ee*, **3a**[b]	70% yield, ≥20:1 d.r. 94% *ee*, **3b**	60% yield, ≥20:1 d.r. 87% *ee*, **3c**
		
61% yield, ≥20:1 d.r. 94% *ee*, **3d**	64% yield, ≥10:1 d.r. 92% *ee*, **3e**	77% yield, ≥20:1 d.r. 91% *ee*, **3f**[b]
		
57% yield, ≥20:1 d.r. 99% *ee*, **3g**	63% yield, 10:1 d.r. 94% *ee*, **3h**	73% yield, ≥20:1 d.r. 96% *ee*, **3i**[b]

[a] Yields are of isolated material. Diastereoselectivity was determined by 1H NMR analysis of crude reaction mixtures. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. See Supporting Information for further details. [b] K_3PO_4 (100 mol%), H_2O (500 mol%), THF (1.0M).

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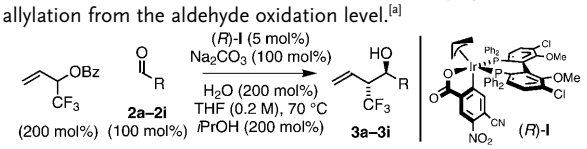
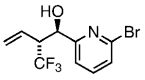
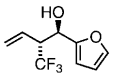
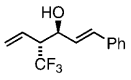
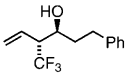
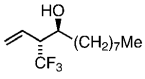
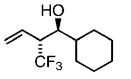
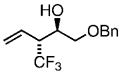
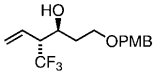
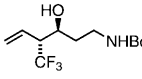
Table 2: *anti*-Diastereo- and enantioselective carbonyl (α-trifluoromethyl)allylation from the aldehyde oxidation level.[a]



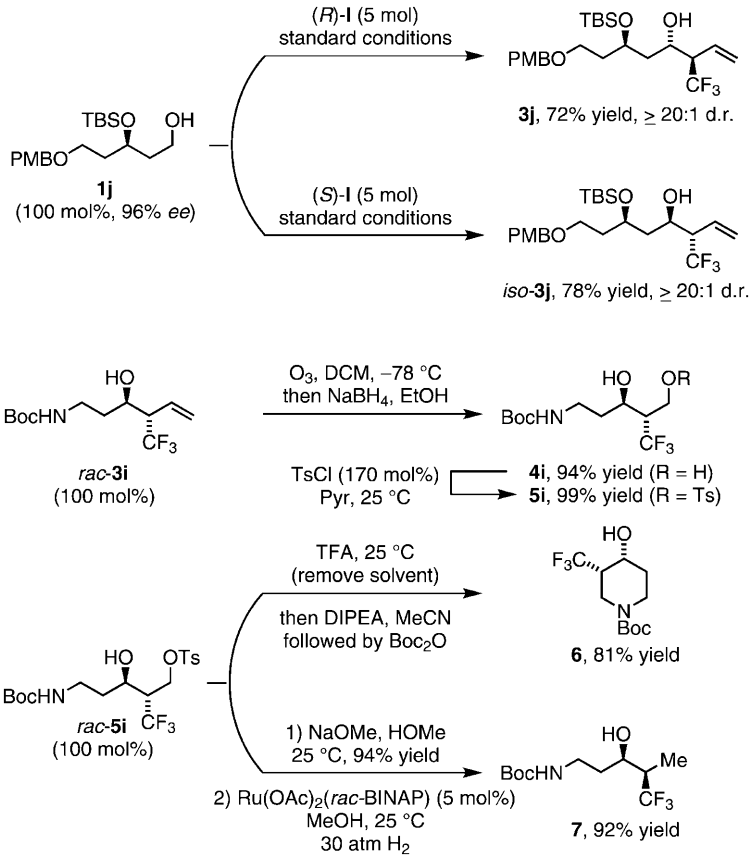
2a, R = 6-Br-2-Pyr	**2b**, R = 2-Furyl	**2c**, R = CH=CHPh
2d, R = $(CH_2)_2$Ph	**2e**, R = $(CH_2)_7$Me	**2f**, R = *c*-C_6H_{11}
2g, R = CH_2OBn	**2h**, R = $(CH_2)_2$OBn	**2i**, R = $(CH_2)_2$NHBoc
		
72% yield, ≥20:1 d.r. 95% *ee*, **3a**[b]	69% yield, ≥20:1 d.r. 95% *ee*, **3b**	67% yield, ≥20:1 d.r. 89% *ee*, **3c**
		
65% yield, ≥20:1 d.r. 94% *ee*, **3d**	69% yield, 10:1 d.r. 92% *ee*, **3e**	81% yield, ≥20:1 d.r. 93% *ee*, **3f**[b]
		
55% yield, ≥20:1 d.r. 99% *ee*, **3g**	67% yield, 10:1 d.r. 93% *ee*, **3h**	70% yield, ≥20:1 d.r. 97% *ee*, **3i**[b]

[a] As described for Table 1.

equivalent conditions, an identical set of adducts **3a**–**3i** are generated from aldehydes **2a**–**2i** with similar levels of relative and absolute stereocontrol (Table 2). Superstoichiometric loadings of α-trifluoromethyl allyl benzoate (200 mol%) are required to offset competing protonolysis of the transient allyliridium intermediate.

Exposure of optically enriched alcohol **1j** to standard conditions for *anti*-diastereo- and enantioselective (α-trifluoromethyl)allylation employing (*R*)-**I** as the precatalyst produces compound **3j** as a single stereoisomer, as determined by ^{1}H and ^{19}F NMR analysis. Similarly, using (*S*)-**I** as the precatalyst, alcohol **1j** is converted into the isomeric adduct *iso*-**3j** as a single stereoisomer, as determined by ^{1}H and ^{19}F NMR analysis. Using the catalyst modified by the achiral ligand, BIPHEP, compounds **3j** and *iso*-**3j** are produced in a 1:1.5 ratio, respectively. These data establish high levels of catalyst-directed stereoselectivity.[9] Exposure of compound **3i** to ozone followed by $NaBH_4$-mediated decomposition of the ozonide produces 1,3-diol **4i** in 94% yield of isolated product. The primary alcohol of diol **4i** was converted into the primary *p*-toluenesulfonate **5i** in 99% yield of isolated product. Conversion of *p*-toluenesulfonate **5i** into piperidine **6** was accomplished in analogy to an established procedure.[10] Alternatively, elimination of *p*-toluenesulfonate **5i** followed by hydrogenation of the resulting terminal olefin provides the *syn*-1,1,1-trifluoroisopropyl secondary alcohol **7** as a single diastereomer, as determined by ^{1}H and ^{19}F NMR analysis (Scheme 1).[11]

In summary, we report the first protocol for *anti*-diastereo- and enantioselective carbonyl (α-trifluoromethyl)allylation. Notably, asymmetric carbonyl addition is possible from the alcohol oxidation level, bypassing discrete alcohol oxidation and the use of stoichiometric organometallic reagents. Future studies will focus on the development of related C–C couplings of amines.



Scheme 1. Elaboration of carbonyl (α-trifluoromethyl)allylation products (as described for Table 1). TBS = *tert*-butylsilyl, PMB = *p*-methoxybenzyl, DIPEA = diisopropylethylamine.

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