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Enantioselective Formation of CF_3-Bearing All-Carbon Quaternary Stereocenters via C−H Functionalization of Methanol: Iridium Catalyzed Allene Hydrohydroxymethylation

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Supporting Information

ABSTRACT: Using an iridium catalyst modified by PhanePhos, CF_3-allenes react with methanol to form branched products of hydrohydroxymethylation as single regioisomers with excellent levels of enantiomeric enrichment. This hydrogen autotransfer process enables catalytic enantioselective formation of acyclic CF_3-bearing all-carbon quaternary stereocenters in the absence of stoichiometric metals or byproducts.

The catalytic enantioselective formation of all-carbon quaternary stereocenters remains a formidable challenge in chemical synthesis.[1−3] In this context, the enantioselective formation of acyclic CF_3-bearing all-carbon quaternary centers is especially daunting.[4−7] As established in seminal work by Shibata,[4a] methods capable of delivering this motif are restricted to conjugate additions of *β*,*β*-disubstituted enones[4a,b,e,g,h] or nitroolefins[4c,d,f,i−k] and two isolated reports of asymmetric allyl[5a] and propargyl[5b] substitution. In connection with ongoing studies of alcohol mediated C−C coupling via hydrogen autotransfer,[8] we recently developed catalytic enantioselective methods for the formation of acyclic all-carbon quaternary stereocenters that utilize vinyl epoxides[3a,b,d] and 1,3-dienes[3c] as pronucleophiles. Attempts to adapt this technology to the formation of acyclic CF_3-bearing stereocenters via ruthenium catalyzed CF_3-allene-paraformaldehyde reductive coupling mediated by 2-propanol failed to deliver highly enantiomerically enriched adducts.[9]

The unique efficacy of iridium(I)-PhanePhos[10] complexes in recently developed methanol mediated hydrohydroxymethylations of 2-substituted-1,3-dienes,[3c] along with the availability of improved protocols for the preparation of CF_3-allenes,[11] motivated our continued efforts toward this elusive bond formation. Here, expanding upon the use of methanol as a C1-feedstock in metal catalyzed C−C coupling,[12−14] we report that iridium-PhanePhos complexes promote the methanol-mediated hydrohydroxymethylation of CF_3-allenes to form highly enantiomerically enriched adducts with complete branched-regioselectivity (Scheme 1). Thus, catalytic enantioselective formation of acyclic CF_3-bearing all-carbon quaternary stereocenters is achieved in the absence of stoichiometric metals or byproducts.

Given the singular effectiveness of iridium(I)-PhanePhos in asymmetric diene hydrohydroxymethylation,[3c] these conditions were applied to the coupling of methanol with 1,1-disubstituted CF_3-allenes **1a**−**1o**. Although the desired coupling products **2a**−**2o** were generated with complete branched regioselectivity, the reaction was highly substrate dependent with significant variation in isolated yield and enantioselectivity. Furthermore, all other chiral ligands that were evaluated failed to deliver products of C−C coupling. These circumstances led us to explore the influence of alternate reaction parameters. As illustrated in the optimization of the methanol-mediated hydrohydroxymethylation of CF_3-allene **1i** to form **2i**, several interesting trends emerged (Table 1). For CF_3-allene **1i** and other allenes bearing electron deficient aryl moieties, changing the precatalyst from $[Ir(cod)Cl]_2$ to Ir(cod)(acac) resulted in higher levels of enantiomeric enrichment, but with lower conversion (Table 1, entries 1 and 2). A modest increase in reaction temperature improved the isolated yield of **2i** without compromising enantioselectivity (Table 1, entry 3). The addition of water (500 mol %) increased enantioselectivity, but led to competing transfer hydrogenation of **1i** (Table 1, entry 4). Tetrabutylammonium iodide (TBAI) (10 mol %) suppresses competing transfer hydrogenation and increases enantioselectivity to a small extent (Table 1, entry 5). Using water (500 mol %) and TBAI (10 mol %) in concert, the neopentyl alcohol **2i** could be obtained in 81% yield and 90% ee (Table 1, entry 6). Exchanging acetone for ethyl acetate as solvent improved enantioselectivity but diminished yield (Table 1, entry 7).

Taking into account the aforesaid influence of the indicated reaction parameters, the conversion of 1,1-disubstituted CF_3-allenes **1a**−**1o** to neopentyl alcohols **2a**−**2o** was explored (Table 2). Two general sets of conditions emerged. In the coupling of CF_3-allenes **1a**−**1f** and **1k**, which incorporate electron rich, electron neutral or slightly electron deficient aryl moieties, use of

Scheme 1. Catalytic Enantioselective Formation of Acyclic CF_3-Bearing All-Carbon Quaternary Stereocenters

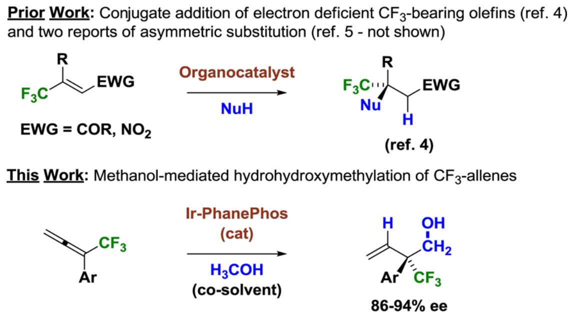

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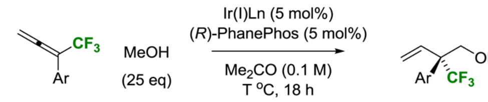
Table 1. Influence of Various Reaction Parameters in the Optimization of the Enantioselective Iridium-Catalyzed C−C Coupling of CF_3-Allene 1i with Methanol To Form Alcohol 2i[a]



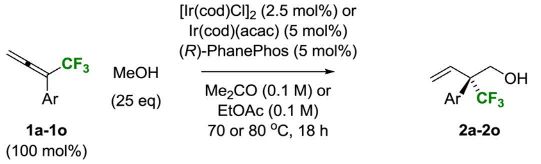
1i, Ar = 3-NO_2-Ph (100 mol%)

2i

entry	Ir(I)Ln	additive (mol %)	T (°C)	yield (%)	ee (%)
1	$[Ir(cod)Cl]_2$		70	56	64
2	Ir(cod)(acac)		70	14	79
3	Ir(cod)(acac)		80	79	79
4	Ir(cod)(acac)	H_2O (500 mol %)	80	56	89
5	Ir(cod)(acac)	TBAI (10 mol %)	80	79	84
6	Ir(cod)(acac)	H_2O/TBAI	80	81	90
7[b]	Ir(cod)(acac)	H_2O/TBAI	80	72	94

[a]Yields of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. [b]EtOAc solvent.

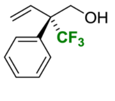
Table 2. Enantioselective Iridium-Catalyzed Coupling of Methanol with CF_3-Allenes 1a−1o To Form Higher Alcohols 2a−2o[a]



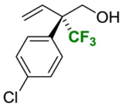
1a-1o (100 mol%)

2a-2o

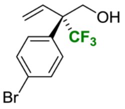
1a, Ar = Ph	**1b**, Ar = 4-Cl-Ph	**1c**, Ar = 4-Br-Ph
1d, Ar = 4-MeO-Ph	**1e**, Ar = 3-MeO-Ph	**1f**, Ar = 5-benzodioxole
1g, Ar = 4-CO_2Me-Ph	**1h**, Ar = 4-CF_3-Ph	**1i**, Ar = 3-NO_2-Ph
1j, Ar = 3,5-F_2-Ph	**1k**, Ar = 5-(2-MeO-Pyr)	**1l**, Ar = 5-indanone
1m, Ar = 4-CF_3S-Ph	**1n**, Ar = 3-NO_2-4-MeO-Ph	**1o**, Ar = 3,5-Cl_2-Ph



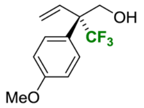
2a, 76% Yield, 87% ee[b]
95% Yield, 90% ee[b,d]



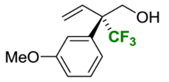
2b, 77% Yield, 86% ee[b]
62% Yield, 90% ee[b,f]
(X-ray)



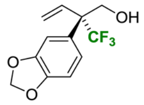
2c, 79% Yield, 87% ee[b]
60% Yield, 91% ee[b,f]



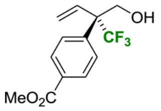
2d, 90% Yield, 89% ee[b]
93% Yield, 90% ee[b,d]



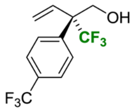
2e, 84% Yield, 90% ee[b]



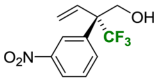
2f, 79% Yield, 90% ee[b,d]
(X-ray)



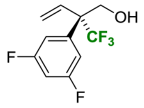
2g, 59% Yield, 92% ee[c,e]



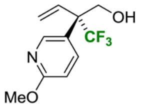
2h, 64% Yield, 90% ee[c,e]



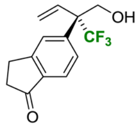
2i, 72% Yield, 94% ee[c,f]



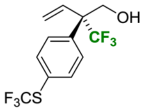
2j, 69% Yield, 91% ee[c,e]



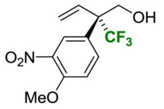
2k, 80% Yield, 84% ee[b]
71% Yield, 89% ee[b,f]



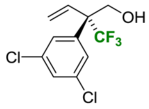
2l, 81% Yield, 89% ee[c,e]
59% Yield, 92% ee[c,f]



2m, 58% Yield, 91% ee[c,f]



2n, 73% Yield, 94% ee[c,f]



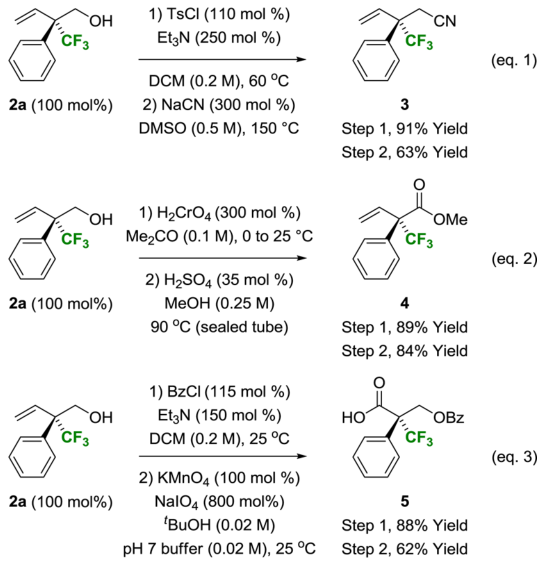
2o, 57% Yield, 90% ee[c,f]

[a]Yields of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. [b]$[Ir(cod)Cl]_2$, 70 °C, Me_2CO. [c]Ir(cod)(acac), TBAI (10 mol %), 80 °C, EtOAc. [d]TBAI (10 mol %). [e]H_2O (200 mol %). [f]H_2O (500 mol %). See Supporting Information for further experimental details.

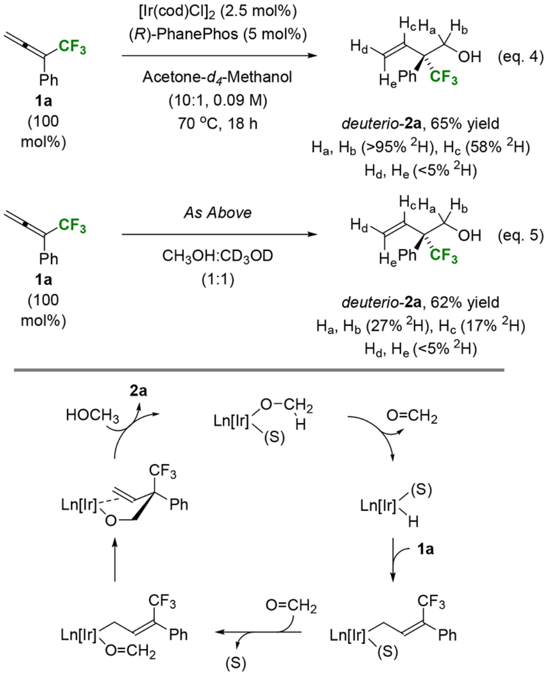
the iridium catalyst derived from $[Ir(cod)Cl]_2$ and (*R*)-PhanePhos in acetone solvent at 70 °C was optimal. For CF_3-allenes bearing highly electron deficient aryl moieties, the precatalyst Ir(cod)(acac) in ethyl acetate solvent at 80 °C was preferred. Under both sets of conditions, TBAI and H_2O were frequently required to enhance enantioselectivity. By tailoring reaction conditions in this manner, alcohols **2a**−**2o** with CF_3-bearing all-carbon quaternary stereocenters could be formed with uniformly high levels of enantioselectivity and as single regioisomers. Alkyl substituted CF_3-allenes engage in efficient methanol-mediated hydrohydroxymethylation, but enantioselectivities were lower (<50% ee). The absolute stereochemical assignment of adducts **2a**−**2o** is based on single crystal X-ray diffraction analysis of **2b** and **2f**. Attempted use of higher alcohols led to regio- and enantioselective transfer hydrogenation of the internal allene π-bond (ca. 40% ee).

To demonstrate how adducts **2a**−**2o** can be used in chemical synthesis, alcohol **2a** was subjected to a series of functional group manipulations. Conversion of alcohol **2a** to the corresponding *p*-toluenesulfonate followed by exposure to sodium cyanide in DMSO at 150 °C provided the nitrile **3**, representing a remarkable example of an S_N2 reaction at a highly congested neopentyl center (eq 1). Jones oxidation of alcohol **2a** followed by Fischer esterification provides the β,γ-unsaturated methyl ester **4** (eq 2). Finally, conversion of alcohol **2a** to the benzoate followed by oxidative cleavage[15] of the vinyl moiety delivers the chiral α-stereogenic carboxylic acid **5** (eq 3).

As exemplified in methanol-mediated transfer hydrogenations of C−C π-bonds,[16] the reversible and highly endothermic nature of methanol dehydrogenation ($\Delta H_{(MeOH)}$ = +20 kcal/mol vs $\Delta H_{(EtOH)}$ = +16 kcal/mol)[17] can be overcome by linking dehydrogenation to an exothermic process. Methanol dehydrogenation also poses a significant challenge in the hydrohydroxymethylation of π-unsaturated reactants and invariably represents the rate-limiting step.[3c,14] However, as the present allene-methanol C−C couplings involve formation of a highly congested CF_3-bearing all-carbon quaternary stereocenter, it was unclear whether methanol dehydrogenation or carbonyl addition would be rate-limiting. To gain further insight into the catalytic mechanism, CF_3-allene **1a** was subjected to d_4-methanol under otherwise standard conditions (Scheme 2, eq 4). The product, *deuterio*-**2a**, completely retains deuterium at the carbinol position (H_a, H_b = >95% ^2H), suggesting *deuterio*-**2a** is kinetically inert with respect to dehydrogenation due to coordination of the homoallylic olefin to iridium, blocking the adjacent coordination site required for β-hydride elimination. Although deuterium is not incorporated at the vinylic terminus of *deuterio*-**2a** (H_d, H_e = <5% ^2H), a significant quantity of deuterium appears at the internal vinylic position (H_c = 58% ^2H). Unlike related diene-methanol C−C couplings,[3c] this data suggests the hydrometalation event is a completely regioselective process. Incomplete incorporation of deuterium at the internal vinylic



Scheme 2. General Catalytic Mechanism and Deuterium Labelling Studies[a]



[a]Yields of material isolated by silica gel chromatography. The extent deuterium incorporation was determined by HRMS and ^1H and ^2H NMR analysis. See Supporting Information for further experimental details. Haptomeric equilibria and equilibria involving alkoxy-bridged dimers are not depicted.

position may be due to adventitious water.[17,18] In a related competition kinetics experiment, CF_3-allene **1a** was exposed to equimolar quantities of methanol and d_4-methanol under otherwise standard conditions (Scheme 2, eq 5). Deuterium incorporation at the carbinol methylene (H_a, H_b = 27% ^2H) of the product *deuterio*-**2a** constitutes a normal primary kinetic isotope effect ($k_H/k_D \approx 3.0$) consistent with turnover-limiting methanol dehydrogenation. The influence of the precatalyst and additives (TBAI, H_2O) on enantioselectivity suggest the counterion (and water) are present during the enantiodetermining carbonyl addition event. To accommodate this observation, we propose that carbonyl addition occurs from an allyliridium(III) intermediate (Scheme 2, bottom).

To summarize, CF_3-bearing all-carbon quaternary stereocenters are exceptionally difficult to prepare in enantiomerically enriched form, with existing protocols for their construction largely restricted to conjugate additions to β,β-disubstituted CF_3-enones and nitroolefins.[4] Here, we demonstrate that iridium complexes modified by PhanePhos catalyze the methanol-mediated hydrohydroxymethylation of CF_3-allenes to generate this structural motif in a completely regioselective and highly enantioselective fashion in the absence of stoichiometric metals or byproducts. Future studies will focus on the development of related C−C bond forming transfer hydrogenations for the conversion of abundant feedstocks to value-added products.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b04374.

> Experimental procedures and spectral data; HPLC traces corresponding to racemic and enantiomerically enriched samples (PDF)
> X-ray diffraction data for **2b** (CIF)
> X-ray diffraction data for **2f** (CIF)

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Notes

The authors declare no competing financial interest.

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