Published in final edited form as:

J Am Chem Soc. 2017 June 21; 139(24): 8114–8117. doi:10.1021/jacs.7b04374.

Enantioselective Formation of CF₃-Bearing All-Carbon Quaternary Stereocenters via C-H Functionalization of Methanol: Iridium Catalyzed Allene Hydrohydroxymethylation

Michael Holmes, Khoa D. Nguyen, Leyah A. Schwartz, Tom Luong, and Michael J. Krische*

University of Texas at Austin, Department of Chemistry, Austin, TX 78712, USA

Abstract

Using an iridium catalyst modified by PhanePhos, CF₃-allenes react with methanol to form branched products of hydrohydroxymethylation as single regioisomers with excellent levels of enantiomeric enrichment. This hydrogen auto-transfer process enables catalytic enantioselective formation of acyclic CF₃-bearing all-carbon quaternary stereocenters in the absence of stoichiometric metals or byproducts.

Graphical abstract

The catalytic enantioselective formation of all-carbon quaternary stereocenters remains a formidable challenge in chemical synthesis.^{1,2,3} In this context, the enantioselective formation of *acyclic CF₃-bearing* all-carbon quaternary centers is especially daunting.^{4,5,6,7} 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,j,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 auto-transfer,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 CF₃-bearing stereocenters *via*

Corresponding Author: mkrische@mail.utexas.edu.

ORCID

Michael J. Krische: 0000-0001-8418-9709

Supporting Information **Available:** Experimental procedures and spectral data. HPLC traces corresponding to racemic and enantiomerically enriched samples. Single crystal X-ray diffraction data for **2b** and **2f**. This material is available free of charge *via* the internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.

ruthenium catalyzed CF₃-allene-paraformaldehyde reductive coupling mediated by 2-propanol failed to deliver highly enantiomerically enriched adducts.⁹

The unique efficacy of iridium(I)-PhanePhos¹⁰ 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 CF₃-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,^{12,13,14} we report that iridium-PhanePhos complexes promote the methanol-mediated hydrohydroxymethylation of CF₃-allenes to form highly enantiomerically enriched adducts with complete branched-regioselectivity. Thus, catalytic enantioselective formation of acyclic CF₃-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 CF₃-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 CF₃-allene **1i** to form **2i**, several interesting trends emerged (Table 1). For CF₃-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 CF₃-allenes **1a–1o** to neopentyl alcohols **2a–2o** was explored (Table 2). Two general sets of conditions emerged. In the coupling of CF₃-allenes **1a–1f** and **1k**, which incorporate electron rich, electron neutral or slightly electron deficient aryl moieties, use of the iridium catalyst derived from [Ir(cod)Cl]₂ and (*R*)-PhanePhos in acetone solvent at 70 °C was optimal. For CF₃-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 H₂O were frequently required to enhance enantioselectivity. By tailoring reaction conditions in this manner, alcohols **2a–2o** with CF₃-bearing all-carbon quaternary stereocenters could be formed with uniformly high levels of enantioselectivity and as single regioisomers. Alkyl substituted CF₃-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 cleavage¹⁵ 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 ($H_{(MeOH)} = +20$ kcal/mol vs $H_{(EtOH)} = +16$ 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 CF₃-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, CF₃-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. While 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 position may be due to adventitious water.¹⁷ In a related competition kinetics experiment, CF₃-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 ($kH/kD \approx 3.0$) consistent with turnover-limiting methanol dehydrogenation. The influence of the precatalyst and additives (TBAI, H₂O) 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, CF₃-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 CF₃-enones and nitroolefins.⁴ Here, we demonstrate that iridium complexes modified by PhanePhos catalyze the methanol-mediated hydrohydroxymethylation of CF₃-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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Robert A. Welch Foundation (F-0038) and the NIH-NIGMS (RO1-GM069445) are acknowledged for partial support of this research.

References

1. For selected reviews on the enantioselective formation of all-carbon quaternary centers, see: Fuji K. Chem. Rev. 1993; 93:2037. Corey EJ, Guzman-Perez A. Angew. Chem. Int. Ed. 1998; 37:388. Bella M, Gasperi T. Synthesis. 2009;1583. Shimizu M. Angew. Chem. Int. Ed. 2011; 50:5998. Hong AY, Stoltz BM. Eur. J. Org. Chem. 2013;2745. Minko Y, Marek I. Chem. Comm. 2014;12597. [PubMed: 25054432] Marek I, Minko Y, Pasco M, Mejuch T, Gilboa N, Chechik H, Das JP. J. Am. Chem. Soc. 2014; 136:2682. [PubMed: 24512113] Quasdorf KW, Overman LE. Nature. 2014; 516:181. [PubMed: 25503231] Liu Y, Han S-J, Liu W-B, Stoltz BM. Acc. Chem. Res. 2015; 48:740. [PubMed: 25715056] Zeng X-P, Cao Z-Y, Wang Y-H, Zhou F, Zhou J. Chem. Rev. 2016; 116:7330. [PubMed: 27251100]
2. For recent examples of the catalytic enantioselective formation of acyclic all-carbon quaternary centers, see: Dabrowski JA, Gao F, Hoveyda AH. J. Am. Chem. Soc. 2011; 133:4778. [PubMed: 21384918] Zhang P, Le H, Kyne RE, Morken JP. J. Am. Chem. Soc. 2011; 133:9716. [PubMed: 21648464] Jung B, Hoveyda AH. J. Am. Chem. Soc. 2012; 134:1490. [PubMed: 22214185] Gao L, Kang BC, Ryu DH. J. Am. Chem. Soc. 2013; 135:14556. [PubMed: 24032757] Liu W-B, Reeves CM, Stoltz BM. J. Am. Chem. Soc. 2013; 135:17298. [PubMed: 24160327] Mei T-S, Patel HH, Sigman MS. Nature. 2014; 508:340. [PubMed: 24717439] Zhang C, Santiago CB, Crawford JM, Sigman MS. J. Am. Chem. Soc. 2015; 137:15668. [PubMed: 26624236] Zhou Q, Cobb KM, Tan T, Watson MP. J. Am. Chem. Soc. 2016; 138:12057. [PubMed: 27610831] Patel HH, Sigman MS. J. Am. Chem. Soc. 2016; 138:14226. [PubMed: 27768842]
3. For catalytic enantioselective formation of acyclic all-carbon quaternary centers via C-C bond forming transfer hydrogenation, see: Feng J, Garza VJ, Krische MJ. J. Am. Chem. Soc. 2014; 136:8911. [PubMed: 24915473] Feng J, Noack F, Krische MJ. J. Am. Chem. Soc. 2016; 138:12364. [PubMed: 27632643] Nguyen KD, Herkommer D, Krische MJ. J. Am. Chem. Soc. 2016; 138:14210. [PubMed: 27762549] Guo Y-A, Lee W, Krische MJ. Chem. Eur. J. 2017; 23:2557. [PubMed: 28039892]
4. For catalytic enantioselective conjugate addition to form acyclic CF₃-bearing quaternary stereocenters, see: Kawai H, Okusu S, Tokunaga E, Sato H, Shiro M, Shibata N. Angew. Chem. Int. Ed. 2012; 51:4959. Kawai H, Yuan Z, Kitayama T, Tokunaga E, Shibata N. Angew. Chem. Int. Ed. 2013; 52:5575. Gao J-R, Wu H, Xiang B, Yu W-B, Han L, Jia Y-X. J. Am. Chem. Soc. 2013; 135:2983. [PubMed: 23409797] Chen Q, Wang G, Jiang X, Xu Z, Lin L, Wang R. Org. Lett. 2014; 16:1394. [PubMed: 24568696] Kwiatkowski P, Cholewiak A, Kasztelan A. Org. Lett. 2014; 16:5930. [PubMed: 25390507] Ma C-H, Kang T-R, He L, Liu Q-Z. Eur. J. Org. Chem. 2014;3981. Sanz-Marco A, Blay G, Vila C, Pedro JR. Org. Lett. 2016; 18:3538. [PubMed: 27417872] Zhu Y, Dong Z, Cheng X, Zhong X, Liu X, Lin Li, Shen Z, Yang P, Li Y, Wang H, Yan W, Wang K, Wang R. Org. Lett. 2016; 18:3546. [PubMed: 27390924] Lai X, Zha G, Liu W, Xu Y, Sun P, Xia T, Shen Y. Synlett. 2016; 27:1983. Hou X, Ma H, Zhang Z, Xie L, Qin Z, Fu B. Chem. Commun. 2016;1470. Hao X-Q, Wang C, Liu S-L, Wang X, Wang L, Gong J-F, Song M-P. Org. Chem. Front. 2017; 4:308.

5. (a) Kimura M, Yamazaki T, Kitazume T, Kubota T. *Org. Lett.* 2004; 6:4651. [PubMed: 15575652]
(b) Tsuchida K, Senda Y, Nakajima K, Nishi-bayashi Y. *Angew. Chem. Int. Ed.* 2016; 55:9728.
6. For selected reviews on methods for the preparation of organofluorine compounds, see: Ma J-A, Cahard D. *Chem. Rev.* 2004; 104:6119. [PubMed: 15584697] Brunet VA, O'Hagan D. *Angew. Chem. Int. Ed.* 2008; 47:1179. Bobbio C, Gouverneur V. *Org. Biomol. Chem.* 2006; 4:2065. [PubMed: 16729117] Audouard C, Ma J-A, Cahard D. *Adv. Org. Synth.* 2006; 2:431. Ma J-A, Cahard D. *Chem. Rev.* 2008; 108:PR1–PR43. [PubMed: 18798358] Cao L-L, Gao BL, Ma S-T, Liu Z-P. *Curr. Org. Chem.* 2010; 14:888. Kang YK, Kim DY. *Curr. Org. Chem.* 2010; 14:917. Cahard D, Xu X, Couve-Bonnaire S, Pannecoucke X. *Chem. Soc. Rev.* 2010; 39:558. [PubMed: 20111780] Nie J, Guo H-C, Cahard D, Ma J-A. *Chem. Rev.* 2011; 111:455. [PubMed: 21117644] Furuya T, Kamlet AS, Ritter T. *Nature.* 2011; 473:470. [PubMed: 21614074] Besset T, Schneider C, Cahard D. *Angew. Chem. Int. Ed.* 2012; 51:5048. Studer A. *Angew. Chem. Int. Ed.* 2012; 51:8950. Chen P, Liu G. *Synthesis.* 2013; 45:2919. Liang T, Neumann CN, Ritter T. *Angew. Chem. Int. Ed.* 2013; 52:8214. Barata-Vallejo S, Lantano B, Postigo A. *Chem. Eur. J.* 2014; 20:16806. [PubMed: 25335765] Camp-bell MG, Ritter T. *Chem. Rev.* 2015; 115:612. [PubMed: 25474722] Xu X-H, Matsuzaki K, Shibata N. *Chem. Rev.* 2015; 115:731. [PubMed: 25121343] Yang X, Wu T, Phipps RJ, Toste FD. *Chem. Rev.* 2015; 115:826. [PubMed: 25337896] Alonso C, Martinez de Marigorta E, Rubiales G, Palacios F. *Chem. Rev.* 2015; 115:1847. [PubMed: 25635524]
7. For examples of the catalytic enantioselective formation of cyclic CF₃-bearing quaternary stereocenters, see: Denton JR, Sukumaran D, Davies HML. *Org. Lett.* 2007; 9:2625. [PubMed: 17552531] Deng Q-H, Wadepohl H, Gade LH. *J. Am. Chem. Soc.* 2012; 134:10769. [PubMed: 22693950] Wo niak L, Murphy JJ, Melchiorre P. *J. Am. Chem. Soc.* 2015; 137:5678. [PubMed: 25901659] Zhang Z-M, Xu B, Xu S, Wu H-H, Zhang J. *Angew. Chem. Int. Ed.* 2016; 55:6324.
8. For selected reviews on C-C bond forming transfer hydrogenation, see: Ketcham JM, Shin I, Montgomery TP, Krische MJ. *Angew. Chem., Int. Ed.* 2014; 53:9142. Feng J, Kasun ZA, Krische MJ. *J. Am. Chem. Soc.* 2016; 138:5467. [PubMed: 27113543]
9. Sam B, Montgomery TP, Krische MJ. *Org. Lett.* 2013; 15:3790. [PubMed: 23841678]
10. Pye PJ, Rossen K, Reamer RA, Tsou NN, Volante RP, Reider PJ. *J. Am. Chem. Soc.* 1997; 119:6207.
11. For synthesis of CF₃-bearing allenes, see: Ambler BR, Peddi S, Altman RA. *Org. Lett.* 2015; 17:2506. [PubMed: 25910053] Boreux A, Lonca GH, Riant O, Gagosz F. *Org. Lett.* 2016; 18:5162. [PubMed: 27668446]
12. For a review on the use of methanol and paraformaldehyde as C1-feedstocks in metal catalyzed C-C coupling, see: Sam B, Breit B, Krische MJ. *Angew. Chem. Int. Ed.* 2015; 54:3267.
13. For selected examples of the use of methanol as a methyl donor in catalytic C-C coupling, see: Chan LKM, Poole DL, Shen D, Healy MP, Donohoe TJ. *Angew. Chem. Int. Ed.* 2014; 53:761. Ogawa S, Obora Y. *Chem. Comm.* 2014:2491. [PubMed: 24458143] Li Y, Li H, Junge H, Beller M. *Chem. Comm.* 2014:14991. [PubMed: 25327955] Shen D, Poole DL, Shotton CC, Kornahrens AF, Healy MP, Donohoe TJ. *Angew. Chem. Int. Ed.* 2015; 54:1642. Quan X, Kerdphon S, Andersson PG. *Chem. Eur. J.* 2015; 21:3576. [PubMed: 25589169]
14. Moran J, Preetz A, Mesch RA, Krische MJ. *Nature Chem.* 2011; 3:287. [PubMed: 21430686]
15. Lemieux RU, von Rudloff E. *Can. J. Chem.* 1955; 33:1701.
16. For methanol-mediated transfer hydrogenation catalyzed by iridium, see: Yamagata T, Iseki A, Tani K. *Chem. Lett.* 1997; 26:1215. Tani K, Iseki A, Yamagata T. *Chem. Commun.* 1999:1821.
17. (a) Qian M, Liauw MA, Emig G. *Appl. Catal. A. Gen.* 2003; 238:211. (b) Lin W-H, Chang H-F. *Catal. Today.* 2004; 97:181.
18. Ruthenium hydrides engage in H-D exchange with water: Tse SKS, Xue P, Lin Z, Jia G. *Adv. Synth. Catal.* 2010; 352:1512.

Prior Work: Conjugate addition of electron deficient CF₃-bearing olefins (ref. 4) and two reports of asymmetric substitution (ref. 5 - not shown)

This Work: Methanol-mediated hydrohydroxymethylation of CF₃-allenes

Scheme 1.

Catalytic enantioselective formation of acyclic CF₃-bearing all-carbon quaternary stereocenters.

Scheme 2.

General catalytic mechanism and deuterium labelling studies.^a

^aYields 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.

Influence of various reaction parameters in the optimization of the enantioselective iridium-catalyzed C-C coupling of CF₃-allene **1i** with methanol to form alcohol **2i**.^a

1i, Ar = 3-NO₂-Ph (100 mol%)

Entry	Ir(III)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 ₂ O (500 mol%)	80	56	89
5	Ir(cod)(acac)	TBAI (10 mol%)	80	79	84
6	Ir(cod)(acac)	H ₂ O/TBAI	80	81	90
7^b	Ir(cod)(acac)	H₂O/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 CF₃-allenes **1a–1o** to form higher alcohols **2a–2o**.^a

1a , Ar = Ph 1d , Ar = 4-MeO-Ph 1g , Ar = 4-CO ₂ Me-Ph 1j , Ar = 3,5-F ₂ -Ph 1m , Ar = 4-CF ₃ S-Ph	1b , Ar = 4-Cl-Ph 1e , Ar = 3-MeO-Ph 1h , Ar = 4-CF ₃ -Ph 1k , Ar = 5-(2-MeO-Pyr) 1n , Ar = 3-NO ₂ -4-MeO-Ph	1c , Ar = 4-Br-Ph 1f , Ar = 5-benzodioxole 1i , Ar = 3-NO ₂ -Ph 1l , Ar = 5-indanone 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}

^aYields of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis.

^b[Ir(cod)Cl]₂, 70 °C, Me₂CO;

^cIr(cod)(acac), TBAI (10 mol%), 80 °C, EtOAc;

^dTBAI (10 mol%);

^eH₂O (200 mol%);

^fH₂O (500 mol%). See Supporting Information for further experimental details.