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Ruthenium Catalyzed Reductive Coupling of Paraformaldehyde to Trifluoromethyl Allenes: CF_3-Bearing All-Carbon Quaternary Centers

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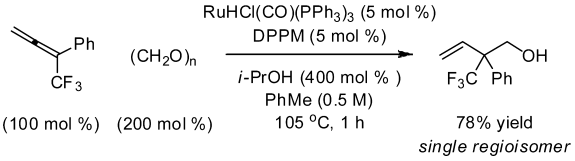
ABSTRACT



Trifluoromethyl substituted allenes engage in ruthenium catalyzed reductive couplings with paraformaldehyde to form products of hydrohydroxymethylation as single regioisomers. This method enables generation of CF_3-bearing all-carbon quaternary stereocenters.

Alkene hydroformylation can be performed in an efficient and regioselective manner and represents the largest volume application of homogeneous metal catalysis.[1] Although significant progress toward the hydroformylation of other π-unsaturated reactants has been made (dienes,[2] alkynes,[3] allenes[4]), incomplete regioselectivities and "over-hydroformylation" to form dialdehyde products is often problematic. Alcohol mediated reductive couplings[5] of paraformaldehyde to allenes,[6a] alkynes,[6c] and dienes,[6b,d] which form related products of hydrohydroxymethylation, provide an alternative to hydroformylation wherein alternate regioisomers are efficiently partitioned through the use of ruthenium and nickel catalysts.[6b−d] To advance this emergent technology further, a study of the reductive coupling of CF_3-substituted allenes to paraformaldehyde was undertaken.[6a] Here, we report a ruthenium catalyzed reductive coupling of paraformaldehyde to CF_3-substituted allenes that displays complete levels of branched regioselectivity, thus delivering all-carbon quaternary stereocenters bearing CF_3 groups.[7−9]

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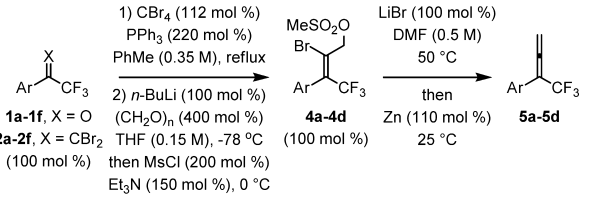
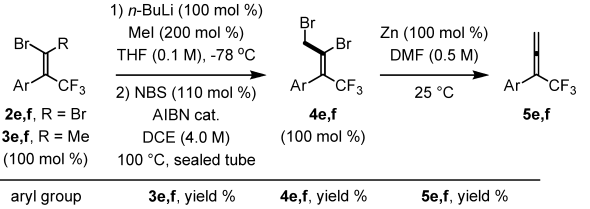
Scheme 1. Synthesis of CF_3-Substituted Allenes **5a**–**5f**[a]



aryl group	**2a-2f**, yield %	**4a-4d**, yield %	**5a-5d**, yield %
1a, Ar = Ph	**2a**, 81	**4a**, 49	**5a**, 78
1b, Ar = *m*-$MeOC_6H_5$	**2b**, 82	**4b**, 37	**5b**, 86
1c, Ar = *p*-$MeOC_6H_5$	**2c**, 91	**4c**, 48	**5c**, 72
1d, Ar = 2-napthyl	**2d**, 84	**4d**, 38	**5d**, 77
1e, Ar = 3,5-$Cl_2C_6H_4$	**2e**, 82		
1f, Ar = *p*-ClC_6H_5	**2f**, 84		

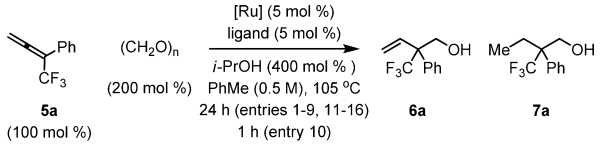


aryl group	**3e,f**, yield %	**4e,f**, yield %	**5e,f**, yield %
1e, Ar = 3,5-$Cl_2C_6H_4$	**3e**, 73	**4e**, 56	**5e**, 56
1f, Ar = *p*-ClC_6H_5	**3f**, 81	**4f**, 43	**5f**, 84

[a] Yields are of material isolated by silica gel chromatography or distillation. See Supporting Information for further details.

Our study required a method for the synthesis of 1-aryl-1-trifluoromethylallenes. Although syntheses involving propargyl substitution using CF_3 nucleophiles are reported,[10] these methods do not permit formation of 1-aryl-1-trifluoromethylallenes. Syntheses involving introduction of the CF_3 group at an early stage have been reported, but do not employ readily accessible starting materials and are not step-economic.[11] Classical strategies for allene synthesis, such as the Doering–LaFlamme method,[12] were unsuccessful. Hence, an effective protocol for the synthesis of 1-aryl-1-trifluoromethylallenes was developed (Scheme 1). Corey–Fuchs olefination of the aryl trifluoromethyl ketones **1a**–**1f**[13] delivers the corresponding methylene dibromides **2a**–**2f**. Lithiation[14] of the resulting methylene dibromides **2a**–**d** followed by treatment with paraformaldehyde and quenching with methanesulfonyl chloride delivers the allylic sulfonates **4a**–**4d**, which appear as single geometrical isomers. The allylic sulfonates **4a**–**4d** were converted to the corresponding allylic bromides *in situ* and then exposed to zinc dust[15] to form allenes **5a**–**5d** in good isolated yields. The vinyllithium species derived from methylene dibromides **2e**,**f** did not react efficiently with paraformaldehyde, but could be methylated in good yield to form adducts **3e**,**f** as single geometrical isomers. Allylic bromination, which occurs

Table 1. Selected Optimization Experiments in the Ruthenium Catalyzed Reductive Coupling of CF_3-Substituted Allene **5a** and Paraformaldehyde[a]



entry	[Ru]	ligand	yield %	**6a:7a**
1	$RuBr(CO)_3(B^3\text{-}C_3H_5)$	*t*-$BuPPh_2$[b]	12	20:1
2	$RuH_2(CO)(PPh_3)_3$	–	18	>20:1
3	$RuHCl(CO)(PPh_3)_3$	–	37	12:1
4	$RuTFA_2(CO)(PPh_3)_2$	–	41	13:1
5	$RuTFA_2(CO)(PPh_3)_2$	DPPF	40	1:4
6	$RuHCl(CO)(PPh_3)_3$	DPPF	68	12:1
7	$RuHCl(CO)(PPh_3)_3$	DiPPF	37	>20:1
8	$RuHCl(CO)(PPh_3)_3$	DtBPF	58	>20:1
9	$RuHCl(CO)(PPh_3)_3$	DPPM	74	20:1
10	**$RuHCl(CO)(PPh_3)_3$**	**DPPM**	**78**	**20:1**
11	$RuHCl(CO)(PPh_3)_3$	DPPE	70	9:1
12	$RuHCl(CO)(PPh_3)_3$	DPPP	35	3:1
13	$RuHCl(CO)(PPh_3)_3$	DPPB	70	1:4
14	$RuHCl(CO)(PPh_3)_3$	DCyPM	68	10:1
15	$RuHCl(CO)(PPh_3)_3$	DCyPE	67	17:1
16	$RuHCl(CO)(PPh_3)_3$	BINAP	31	10:1

[a] Yields are of material isolated by silica gel chromatography. Ratios of **6**:**7** were determined by ^{19}F NMR analyses of crude reaction mixtures. DCyPM = 1,1-bis(dicyclohexylphosphino)methane, DCyPE = 1,1-bis(dicyclohexylphosphino)ethane. See Supporting Information for ligand definitions and experimental details. [b] *t*-$BuPPh_2$ (15 mol %).

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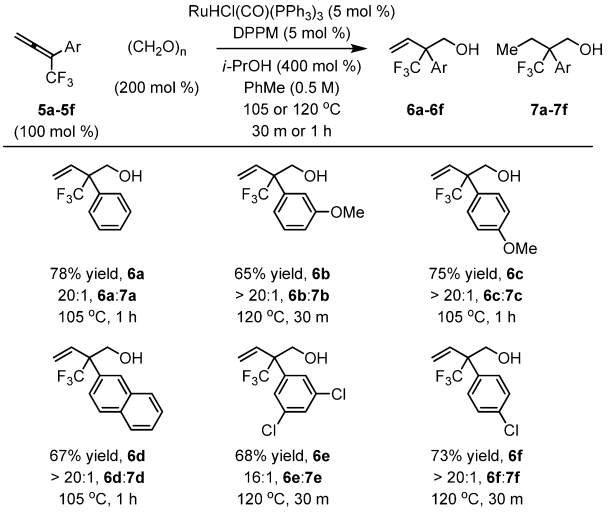


Figure 1. Ruthenium catalyzed reductive coupling of allenes **5a**–**5f** to paraformaldehyde to form CF_3-substituted neopentyl alcohols **6a**–**6f**. Yields are of material isolated by silica gel chromatography. Ratios of **6**:**7** were determined by ^{19}F NMR analyses of crude reaction mixtures. See Supporting Information for further details.

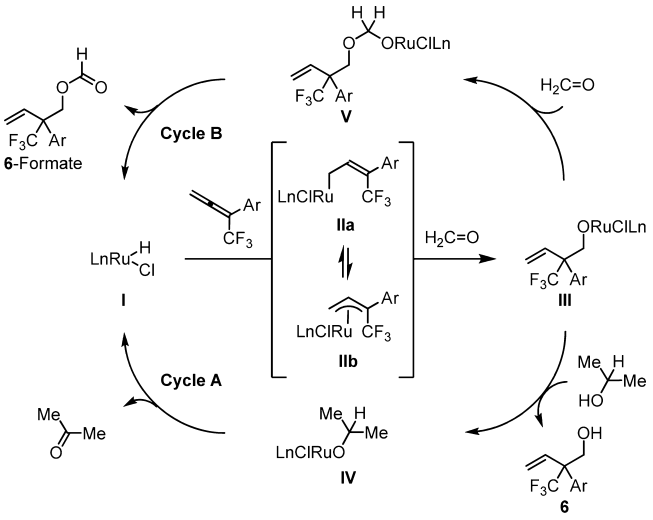
with scrambling of olefin geometry, followed by treatment with zinc dust provided allenes **5e**,**f**.

Having defined serviceable routes to allenes **5a**–**5f**, the reductive coupling of allene **5a** to paraformaldehyde was explored. Exposure to conditions previously developed for ruthenium catalyzed reductive coupling of 1,1-disubstituted allenes to paraformaldehyde provided the desired reductive coupling product **6a** in poor yield (Table 1, entry 1).[6a] Various ruthenium(II) complexes were evaluated (Table 1, entries 2–4). The commercially available complex $RuHCl(CO)(PPh_3)_3$ provided a promising 37% yield of **6a** (Table 1, entry 3).[16] Upon addition of DPPF, the isolated yield of **6a** increased to 68%; however, small quantities of over-reduction product **7a** were apparent (Table 1, entry 6). In fact, the extent of over-reduction and conversion exhibited a dramatic dependence on ligand (Table 1, entries 6–15). Eventually, it was found that the combination of $RuHCl(CO)(PPh_3)_3$ and DPPM provided a 78% isolated yield of **6a** with nearly complete suppression of over-reduction (Table 1, entry 10).

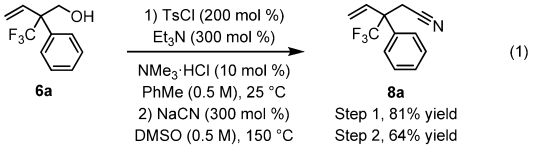
Under these conditions, 1-aryl-1-trifluoromethylallenes **5a**–**5f** were reductively coupled to paraformaldehyde to provide the CF_3-substituted primary neopentyl alcohols **6a**–**6f** in moderate to good isolated yields (Figure 1). In all cases, complete levels of branched regioselectivity were observed. Only in the coupling of allene **5e** was any significant quantity of over-reduction product **7e** observed. To illustrate the utility of the reaction products, neopentyl alcohol **6a** was converted to the corresponding

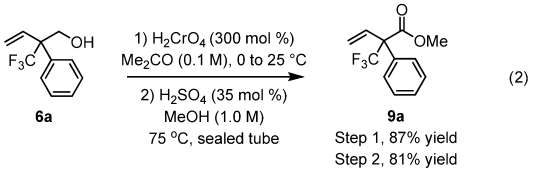
(16) The complex $RuHCl(CO)(PPh_3)_3$ served as an effective precatalyst in the redox neutral coupling of 1,1-disubstituted allenes and primary alcohols: Zbieg, J. R.; McInturff, E. L.; Leung, J. C.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 1141.

Scheme 2. Proposed Mechanism for Ruthenium Catalyzed Reductive Coupling of CF_3-Substituted Allenes **5a**–**5f** to Paraformaldehyde



p-toluenesulfonate and reacted with sodium cyanide in DMSO solvent. Despite the notoriously low rates typically observed in S_N2 reactions of neopentyl electrophiles, nitrile **8a** was formed in moderate yield (eq 1). Jones oxidation of neopentyl alcohol **6a** followed by Fischer esterification provides the methyl ester **9a** (eq 2).





A plausible catalytic mechanism for the ruthenium catalyzed reductive coupling of CF_3-substituted allenes **5a**–**5f** to paraformaldehyde has been proposed (Scheme 2). Ruthenium hydride **I** hydrometallates the allene to provide the allylruthenium haptomers **IIa** and **IIb**.[17,18] Addition to formaldehyde from the primary σ-allylruthenium haptomer **IIa** provides the ruthenium alkoxide **III**. At this stage, isopropanol can protonolytically cleave the ruthenium alkoxide

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(18) For studies involving π-allylruthenium complexes of the type $Ru(\eta^3\text{-allyl})(X)(CO)(PR_3)_2$, see: (a) Barnard, C. F. J.; Daniels, B. J. A.; Holland, P. R.; Mawby, R. J. *J. Chem. Soc., Dalton Trans.* **1980**, 2418. (b) Hiraki, K.; Matsunaga, T.; Kawano, H. *Organometallics* **1994**, *13*, 1878. (c) Sasabe, H.; Nakanishi, S.; Takata, T. *Inorg. Chem. Commun.* **2002**, *5*, 177. (d) Cadierno, V.; Crochet, P.; Diez, J.; Garcia-Garrido, S. E.; Gimeno, J. *Organometallics* **2003**, *22*, 5226.

III to liberate the product **6** and generate ruthenium isopropoxide **IV**, which upon β-hydride elimination regenerates ruthenium hydride **I**. Alternatively, ruthenium alkoxide **III** can undergo formaldehyde addition to form ruthenium alkoxide **V**, which upon β-hydride elimination provides the ester **6**-formate. In all prior ruthenium catalyzed reductive couplings of paraformaldehyde developed in our laboratory,[6] including reactions of allenes,[6a] formate esters are generated to a significant extent and are cleaved upon isolation of the product.

In summary, we report a ruthenium catalyzed reductive coupling of allenes **5a**−**5f** to paraformaldehyde to form CF_3-substituted neopentyl alcohols **6a**−**6f** under the conditions of isopropanol mediated transfer hydrogenation. This is one of very few methods available for the generation of all-carbon quaternary stereocenters bearing CF_3 groups.[8] Beyond access to these elusive functional group arrays, the present study also describes novel synthetic routes to 1-aryl-1-trifluoromethylallenes **5a**−**5f**, which may find use in other methodological endeavors. Future studies will focus on the development of related C−C bond forming transfer hydrogenations, including asymmetric variants of the transformations reported herein.

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Supporting Information Available. Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, ^{19}F NMR, IR, MS). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.