

Ruthenium Catalyzed Reductive Coupling of Paraformaldehyde to Trifluoromethyl Allenes: CF₃-Bearing All-Carbon Quaternary Centers

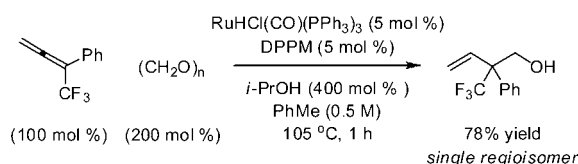
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ABSTRACT



Trifluoromethyl substituted allenes engage in ruthenium catalyzed reductive couplings with paraformaldehyde to form products of hydrohydroxymethylation as single regioisomers. This method enables generation of CF₃-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 allenes⁴), incomplete regioselectivities and “over-hydroformylation” to form dialdehyde products is often problematic. Alcohol mediated reductive couplings⁵

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 CF₃-substituted allenes to paraformaldehyde was undertaken.^{6a} Here, we report a ruthenium catalyzed reductive coupling of paraformaldehyde to CF₃-substituted allenes that displays complete levels of branched regioselectivity, thus delivering all-carbon quaternary stereocenters bearing CF₃ groups.^{7–9}

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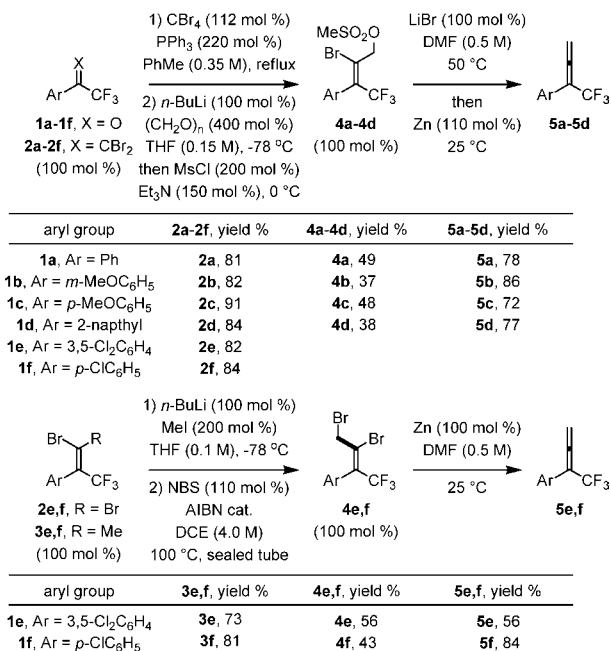
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Scheme 1. Synthesis of CF₃-Substituted Allenes 5a–5f^a



^aYields 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 CF₃ nucleophiles are reported,¹⁰ these methods do not permit formation of 1-aryl-1-trifluoromethylallenes. Syntheses involving introduction of the CF₃ 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

Table 1. Selected Optimization Experiments in the Ruthenium Catalyzed Reductive Coupling of CF₃-Substituted Allene 5a and Paraformaldehyde^a

entry	[Ru]	ligand	yield %	6a:7a
1	RuBr(CO) ₃ (B ³ -C ₃ H ₅)	<i>t</i> -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)(PPh₃)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

^aYields are of material isolated by silica gel chromatography. Ratios of 6:7 were determined by ¹⁹F 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*-BuPPh₂ (15 mol %).

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–1f¹³ delivers the corresponding methylene dibromides 2a–2f. Lithiation¹⁴ 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 dust¹⁵ to form allenes 5a–5d in good isolated yields. The vinyl-lithium 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

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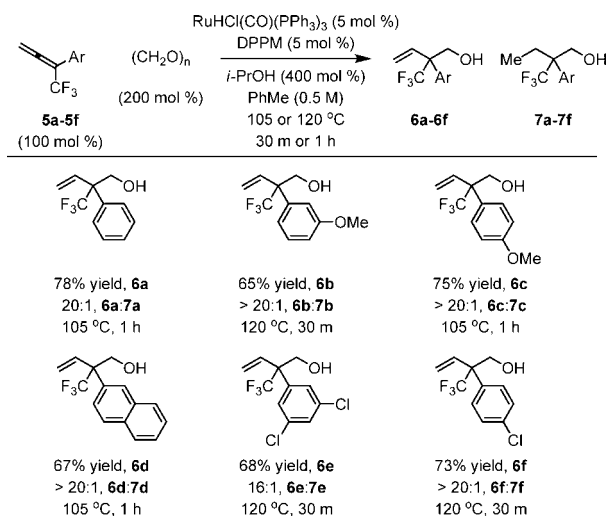


Figure 1. Ruthenium catalyzed reductive coupling of allenes **5a–5f** to paraformaldehyde to form CF₃-substituted neopentyl alcohols **6a–6f**. Yields are of material isolated by silica gel chromatography. Ratios of **6:7** were determined by ¹⁹F NMR analyses of crude reaction mixtures. See Supporting Information for further details.

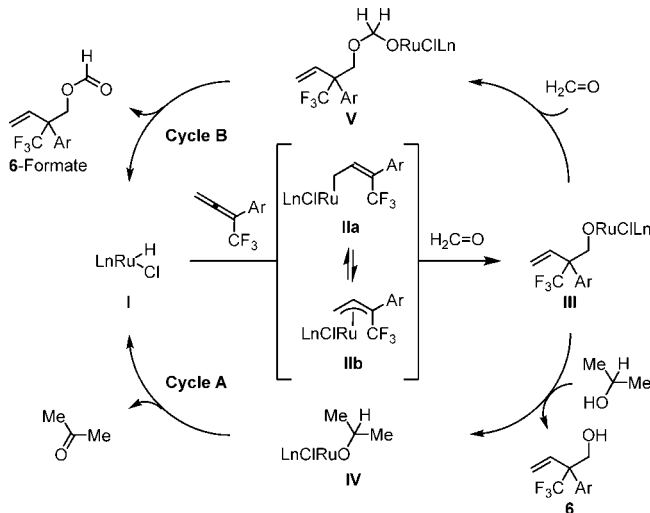
with scrambling of olefin geometry, followed by treatment with zinc dust provided allenes **5e,f**.

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)(PPh₃)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)(PPh₃)₃ and DPPM provided a 78% isolated yield of **6a** with nearly complete suppression of over-reduction (Table 1, entry 10).

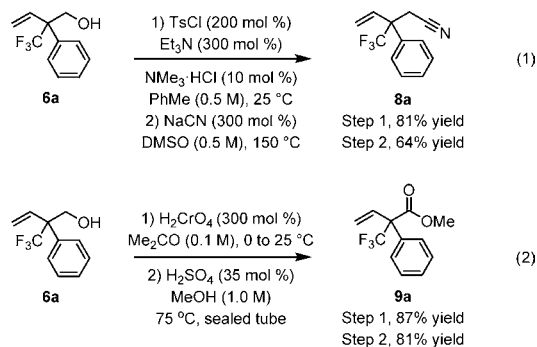
Under these conditions, 1-aryl-1-trifluoromethylallenes **5a–5f** were reductively coupled to paraformaldehyde to provide the CF₃-substituted primary neopentyl alcohols **6a–6f** in moderate to good isolated yields (Figure 1). In all cases, complete levels of branched regioselectivity were observed. 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)(PPh₃)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 CF₃-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 CF₃-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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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 CF₃-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 CF₃ 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 (¹H NMR, ¹³C NMR, ¹⁹F 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.