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Ruthenium Catalyzed C-C Bond Formation *via* Transfer Hydrogenation: Branch-Selective Reductive Coupling of Allenes to Paraformaldehyde and Higher Aldehydes

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Abstract

Upon exposure to the conditions of ruthenium catalyzed transfer hydrogenation employing isopropanol as the terminal reductant, 1,1-disubstituted allenes **1a-1h** engage in reductive coupling to paraformaldehyde to furnish homoallylic alcohols **2a-2h**. Under identical transfer hydrogenation conditions, 1,2-disubstituted allenes engage in reductive coupling to aldehydes **3a-3f** to furnish homoallylic alcohols **4a-4n**. In all cases, reductive coupling occurs with branched regioselectivity to deliver homoallylic alcohols bearing all-carbon quaternary centers.

Although ruthenium catalyzed transfer hydrogenation ranks among the foremost methods for enantioselective ketone reduction,¹ reductive C-C bond formation catalyzed by ruthenium is highly uncommon.^{2,3,4} We have developed a family of reductive C-C bond formations employing elemental hydrogen as the terminal reductant.^{5,6} More recently, we discovered that reductive C-C bond formation could be achieved under the conditions of iridium catalyzed transfer hydrogenation, wherein allenes or cyclohexadiene are coupled to aldehydes and, remarkably, alcohols.⁷ In an effort to expand the scope of such “*transfer hydrogenative C-C bond formations*,” ruthenium catalysts were found to promote the coupling of acyclic 1,3-dienes or 1,3-enynes to both aldehydes and alcohols to furnish products of carbonyl allylation and propargylation, respectively.⁸ For these transfer hydrogenative processes, rather than using elemental hydrogen as reductant, hydrogen embedded in isopropanol or an alcoholic substrate is redistributed among reactants to generate nucleophile-electrophile pairs, enabling carbonyl addition from the aldehyde or alcohol oxidation level (Scheme 1).

As part of a continuing effort to broaden this emergent class of C-C couplings, we investigated the coupling of 1,1-disubstituted allenes to paraformaldehyde and higher aldehydes under the conditions of ruthenium catalysis. Here we disclose that allenes **1a-8a** engage in branch-selective reductive coupling to paraformaldehyde and higher aldehydes under the conditions of ruthenium catalyzed transfer hydrogenation employing isopropanol as the terminal reductant

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Supporting Information Available. Experimental procedures and spectral data for all new compounds (¹H NMR, ¹³C NMR, IR, HRMS). This material is available free of charge *via* the internet at <http://pubs.acs.org>.

to furnish homoallylic alcohols **2a-2h** and **4a-4n**, respectively, bearing all-carbon quaternary centers. Additionally, we report isotopic labeling studies that provide further insight into key mechanistic features of these processes.

In an initial set of experiments, structurally diverse ruthenium complexes were assayed for their ability to catalyze the reductive coupling of allene **1a** to paraformaldehyde using isopropanol as the terminal reductant (Table 1, entries 1–7). It was found that the complex prepared *in situ* from [RuBr(CO)₃(η³-C₃H₅)] (5 mol%) and PPh₃ (15 mol%) in toluene (0.5 M) at 75°C catalyzes the reductive C-C coupling of **1a** to paraformaldehyde to provide the desired adduct **2a** in 55% isolated yield along with small quantities of the corresponding formate ester, which is hydrolytically cleaved upon isolation (Table 1, entry 7).⁹ Notably, only trace quantities of adduct are formed in the absence of PPh₃ (Table 1, entry 8), suggesting that appropriate selection of ligand is crucial. Indeed, screening the precatalyst [RuBr(CO)₃(η³-C₃H₅)] against a series of phosphine ligands (Table 1, entries 9–13) reveals that monodentate ligands promote greater conversion than bidentate or tridentate ligands (Table 1, entries 9 and 10). Under optimal conditions employing [RuBr(CO)₃(η³-C₃H₅)] (5 mol%) as precatalyst in combination with *t*-BuPPh₂ (15 mol%) as ligand in toluene (0.5 M) at 75°C, the coupling product **2a** is obtained in 81% isolated yield (Table 1, entry 12). By increasing the concentration of the reaction mixture (1.0 M in toluene), the isolated yield was increased to 86% (Table 1, entry 13). These optimized reaction conditions proved to be quite general, as demonstrated by the coupling of paraformaldehyde to 1,1-disubstituted allenes **1a-1h** to furnish the homoallylic alcohols **2a-2h** (Figure 1).

Under identical conditions, the coupling of allenes to higher aldehydes was explored. It was found that aromatic aldehydes (Table 2, entries 1 and 2), heteroaromatic aldehydes (Table 2, entry 3), α, β-unsaturated aldehydes (Table 2, entry 4), and aliphatic aldehydes (Table 2, entries 5 and 6) couple to a range of 1,1-disubstituted allenes in good yields but with low diastereoselectivity. Under standard conditions, electron rich aldehydes couple less efficiently, as demonstrated by the coupling of allene **1a** to hexanal, which occurs in 38% yield to provide a 4:1 diastereomeric ratio of adducts.

To gain insight into the catalytic mechanism, the coupling of paraformaldehyde and allene **1a** was conducted employing d₈-isopropanol as the terminal reductant. As revealed by ¹H NMR analysis, deuterium is incorporated solely at the vinylic position (30% ²H). Similarly, coupling of allene **1a** to *p*-nitrobenzaldehyde **3a** employing d₈-isopropanol as the terminal reductant also results in deuterium incorporation exclusively at the vinylic position, but to a far greater extent (80% ²H). Notably, the isolated yield of coupling products in reactions employing d₈-isopropanol as the terminal reductant are substantially lower than the isolated yields obtained in the parent reactions (Scheme 2).¹⁰ A plausible catalytic cycle accounting for the relatively low levels of deuterium incorporation in the reaction of paraformaldehyde and allene **1a** is indicated (Scheme 3). Reaction of the precatalyst [RuBr(CO)₃(η³-C₃H₅)] with formaldehyde in the presence of isopropanol generates the homoallylic alcohol **I** and active catalyst **II**,¹¹ which hydrometallates allene **1a** to furnish the allyl ruthenium complexes **IIIa** and **IIIb**.¹² Allyl transfer to the aldehyde delivers the ruthenium alkoxide **IV**. The intermediate **IV** may react with isopropanol to provide the coupling product **V** and ruthenium isopropoxide **VI**, which upon β-hydride elimination regenerates the active catalyst **II** (Cycle A). Alternatively, the intermediate **IV** may react with another molecule of aldehyde to form ruthenium complex **VII**,¹³ which delivers ester **VIII** upon β-hydride elimination and regenerates the active catalyst **II** (Cycle B). The latter catalytic cycle suggests that the aldehyde may serve as a hydride donor. Indeed, when the coupling of paraformaldehyde and **1a** is carried out in the absence of isopropanol, substantial quantities of the formate ester **VIII** (R = H) are detected. Mechanisms involving ruthenium catalyzed allene hydroacylation with subsequent isopropanol-mediated reduction of the resulting aldehyde are inconsistent with the results of deuterium incorporation.

Upon resubjecting diastereomerically enriched adduct **4a** to standard coupling conditions, a 2:1 ratio of diastereomeric ratio is reestablished, suggesting redox equilibration of the homoallylic alcohol under coupling conditions. That is, the diastereomeric ratio of adducts appears to be thermodynamically controlled.

In summary, ruthenium catalyzed transfer hydrogenation ranks among the most powerful methods available for the reduction of polar functional groups, yet reductive C-C couplings under the conditions of ruthenium catalysis are highly uncommon. Recent studies from our laboratory are aimed at addressing this deficiency, with the ultimate goal of developing a broad new family of “*transfer hydrogenative C-C bond formations*.” In prior work, ruthenium catalyzed transfer hydrogenation was applied to the coupling of acyclic 1,3-dienes (butadiene, isoprene and 2,3-dimethylbutadiene) and 1,3-enynes to aldehydes or alcohols. Here, we demonstrate the ruthenium catalyzed reductive coupling of 1,2-disubstituted allenes **1a-1h** to paraformaldehyde and higher aldehydes **3a-3f** to furnish homoallylic alcohols **2a-2h** and **4a-4n**, respectively. Stereoselective variants of these transformations and the development of new transfer hydrogenative couplings, including imine additions from the amine oxidation level, are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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9. See supporting information for detailed experimental procedures.
10. Couplings employing d₈-isopropanol as terminal reductant were conducted twice. The isolated yields and levels of deuterium incorporation .for *deuterio-2a* and *deuterio-4a* were reproducible within experimental error.
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Figure 1. Ruthenium catalyzed reductive coupling of paraformaldehyde to 1,1-disubstituted allenes 1a-1h via transfer hydrogenation.^a

^aCited yields are of isolated material. Standard conditions employ 1 equivalent of allene and 4 equivalents of paraformaldehyde. See Supporting Information for detailed experimental procedures.

Scheme 1.

Carbonyl allylation from the aldehyde or alcohol oxidation level *via* transfer hydrogenative C-C coupling of allenes.

Scheme 2. Ruthenium catalyzed coupling of allene **1a to paraformaldehyde and *p*-nitrobenzaldehyde employing d₈-isopropanol as the terminal reductant.^a**

^aCited yields are of isolated material. See Supporting Information for detailed experimental procedures.

Scheme 3.
Plausible catalytic mechanisms as supported by deuterium labeling studies.

Table 1

Optimization of ruthenium catalyzed coupling of paraformaldehyde to 1-methyl-1-phenylallene (**1a**) *via* transfer hydrogenation.^a

<p> $(\text{CH}_2\text{O})_n$ (400 mol %) + 1a (100 mol %) $\xrightarrow[\text{PhMe, 75 } ^\circ\text{C}]{\text{Catalyst, Ligand, } i\text{-PrOH (400 mol \%)}}$ 2a </p>				
entry	catalyst ^b	ligand (mol%)	concn (M)	yield%
1	[Cp(<i>p</i> -cymene)Ru]PF ₆	PPh ₃ (15)	0.5	---
2	CpRuCl(PPh ₃) ₃	---	0.5	---
3	Ru ₃ (CO) ₁₂	PPh ₃ (15)	0.5	---
4	RuHCl(PPh ₃) ₃ .Toluene	---	0.5	Trace
5	[Ru(cod)Cl ₂] _n	PPh ₃ (15)	0.5	18
6	RuHCl(CO)(PPh ₃) ₃	---	0.5	20
7	[RuBr(CO) ₃ (η ³ -C ₃ H ₅)]	PPh ₃ (15)	0.5	55
8	[RuBr(CO) ₃ (η ³ -C ₃ H ₅)]	---	0.5	Trace
9	[RuBr(CO) ₃ (η ³ -C ₃ H ₅)]	BINAP (7.5)	0.5	49
10	[RuBr(CO) ₃ (η ³ -C ₃ H ₅)]	MeC[CH ₂ PPh ₂] ₃ (5)	0.5	Trace
11	[RuBr(CO) ₃ (η ³ -C ₃ H ₅)]	CataCXium A (15)	0.5	72
12	[RuBr(CO) ₃ (η ³ -C ₃ H ₅)]	<i>t</i> -BuPPh ₂ (5)	0.5	81
13	[RuBr(CO) ₃ (η ³ -C ₃ H ₅)]	<i>t</i> -BuPPh ₂ (5)	1.0	86

^a Cited yields are of isolated material.

^b 5 mol % with respect to ruthenium content. See Supporting Information for detailed experimental procedures.

Table 2

Ru-catalyzed reductive coupling of aldehydes **3a-3f** to 1,1-disubstituted allenes *via* transfer hydrogenation.^a

3a, R = <i>p</i>-NO₂Ph		3c, R = 2-(4-NO₂-Furyl)	
3b, R = <i>p</i>-(CO₂Me)Ph		3d, R = <i>o</i>-NO₂-Cinnamyl	
entry	RCHO, allene	product	
1
	3a, 1a	4a, R₁ = Me, R₂ = Ph	
	3a, 1b	4b, R₁ = Me, R₂ = <i>p</i>-FPh	
	3a, 1d	4c, R₁ = CH₂OMe R₂ = <i>p</i>-MeOPh	
	3a, 1f	4d, R₁ = Me, R₂ = CH₂Ph	
	3a, 1g	4e, R₁ = Et, R₂ = <i>n</i>-Bu	
2
	3b, 1a	4f	
3
	3c, 1a	4g

3a, R = *p*-NO₂Ph

3c, R = 2-(4-NO₂-Furyl)

3b, R = *p*-(CO₂Me)Ph

3d, R = *o*-NO₂-Cinnamyl

entry	RCHO, allene	product
4		<p>4h</p>
5	3d, 1a	
	3e, 1a	4i, R ₁ = Me, R ₂ = Ph
	3e, 1d	4j, R ₁ = CH ₂ OMe R ₂ = <i>p</i> -MeOPh
	3e, 1g	4k, R ₁ = Et, R ₂ = <i>n</i> -Bu
6		
	3f, 1a	4l, R ₁ = Me, R ₂ = Ph
	3f, 1b	4m, R ₁ = Me, R ₂ = <i>p</i> -FPh
	3f, 1g	4n, R ₁ = Et, R ₂ = <i>n</i> -Bu

^a Cited yields are of pure isolated material. See Supporting Information for detailed experimental procedures.