Published in final edited form as:

Org Lett. 2010 June 4; 12(11): 2514–2516. doi:10.1021/ol1007235.

Allenamide Hydro-Hydroxyalkylation: 1,2-Aminoalcohols via Ruthenium Catalyzed Carbonyl *anti*-Aminoallylation

Jason R. Zbieg, Emma L. McInturff, and Michael J. Krische*

University of Texas at Austin, Department of Chemistry and Biochemistry, Austin, TX 78712

Abstract

Exposure of alcohols to allenamides in the presence of RuHCl(CO)(PPh₃)₃ and dipfp [dipfp = bis (diisopropylphosphino)ferrocene] results in hydrogen transfer to generate aldehyde-allylruthenium pairs, which engage in C-C coupling to form products of carbonyl aminoallylation as single *anti*-diastereomers.

We have developed a broad family of catalytic C-C couplings wherein alcohol dehydrogenation drives reductive nucleophile generation from π -unsaturated reactants.^{1, 2} Using isopropanol as terminal reductant, aldehydes are reductively coupled to π -unsaturated reactants to furnish products of carbonyl addition. In most cases, alcohol reactants can serve dually as hydrogen donors and aldehyde precursors, enabling carbonyl addition directly from the alcohols oxidation level. Thus, identical carbonyl addition products are available from the aldehyde or alcohol oxidation levels. Such C-C bond forming transfer hydrogenations avoid the stoichiometric use of premetallated nucleophiles and the resulting metallic byproducts. Furthermore, reactions conducted from the alcohol oxidation are completely atom economic and circumvent manipulations otherwise required for discrete alcohol oxidation.

Using ruthenium-based catalysts, the transfer hydrogenative coupling of alcohols to dienes,³ enynes,⁴ alkynes⁵ and allenes⁶ has been achieved. Related alcohol-enal couplings catalyzed by ruthenium, where C-C bond formation is followed by redox isomerization, also have been

mkrische@mail.utexas.edu.

Supporting Information Available. 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>.

developed.⁷ Notably, unlike related iridium catalyzed processes,⁸ ruthenium catalyzed allene-carbonyl C-C couplings were only possible from the aldehyde oxidation level using $\text{RuBr}(\eta^3\text{-C}_3\text{H}_5)(\text{CO})_3$ as the ruthenium precatalyst in combination with monodentate phosphine ligands.⁶ Here, we report that the ruthenium catalyst obtained upon combination of $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ and dippf [dippf = bis(diisopropylphosphino)ferrocene] overcomes this limitation, enabling direct alcohol-allenamide C-C coupling to furnish *anti*-1,2-aminoalcohols as single diastereomers. These conditions also are applicable to the conventional 1,1-disubstituted allene **1b**.

Given the utility of allenes and allenamides in organic synthesis,⁹ the inability to promote allene-carbonyl C-C coupling from the alcohol oxidation level using previously established ruthenium catalysts prompted us to broaden our assay of phosphine modified ruthenium complexes. Carbonyl ligands are required substructures in all ruthenium catalyzed transfer hydrogenative couplings we have developed.^{1c-e,3-6} As suggested by Bäckvall,¹⁰ the carbonyl moiety likely provides a kinetic pathway alcohol exchange. In our case, increased Lewis acidity at the carbonyl bound ruthenium center also may assist carbonyl addition.

Allenamide **1a** and alcohol **2a** fail to provide adduct **3a** upon exposure to $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ in the absence of added phosphine ligand (Table 1, entry 1). Hence, $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ was used as a precatalyst for ligand screening. Notably, ligands effective in previously reported allene-aldehyde reductive couplings employing $\text{RuBr}(\eta^3\text{-C}_3\text{H}_5)(\text{CO})_3$ did not promote corresponding allene-alcohol C-C couplings (Table 1, entries 2 and 3).⁶ A promising result was obtained with dppf (Table 1, entry 7), which led to an assay of other ferrocene-based ligands. Eventually, it was found that the ruthenium complex obtained upon combination of $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ and dippf [dippf = bis(diisopropylphosphino)ferrocene]¹¹ promotes the coupling of allenamide **1a** and alcohol **2a** to provide adduct **3a** in 86% isolated yield (Table 1, entry 8). The phosphine-free precatalyst $\text{RuCl}_2(\text{CO})(\text{cymene})$ ¹² combines with dippf to furnish an even more effective catalyst (Table 1, entry 9). However, because the catalyst generated from $\text{RuCl}_2(\text{CO})(\text{cymene})$ and dippf showed greater air sensitivity, the $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ /dippf catalyst system was adopted as our standard conditions (Table 1).

Under these conditions, allenamide **1a** was coupled to structurally diverse alcohols **2a-2l**. Benzylic alcohols **2a-2f**, allylic alcohols **2g-2i** and simple aliphatic alcohols **2j-2l** are transformed to the corresponding products of carbonyl aminoallylation **3a-3f**, **2g-2i** and **2j-2l**, respectively. All adducts **3a-3l** appear as single *anti*-diastereomers (Scheme 1). The utility of these products was established in a prior study of the corresponding allenamide-aldehyde reductive coupling, where *N*-deprotection was established under mild conditions.^{6b}

To further probe the generality of these conditions, the coupling of alcohols **2d** and **2g** to 1,1-disubstituted allene **1b** was attempted. The anticipated products of C-C coupling **4d** and **4g** were obtained in good to excellent yield with complete branch-regioselectivity. However, these products appear as diastereomeric mixtures, likely due to incomplete partitioning of transient primary (*E*)- and (*Z*)- σ -allylruthenium intermediates (Scheme 2).

Our collective data on ruthenium catalyzed C-C couplings of allenes suggest that relatively electron deficient ruthenium centers, as in the $\text{RuBr}(\eta^3\text{-C}_3\text{H}_5)(\text{CO})_3$ /monophosphine catalyst system, are capable of dehydrogenating secondary alcohols, such as isopropanol. However, they are inefficient in dehydrogenations of primary alcohols, an energetically more demanding process.¹³ Furthermore, primary alcohols dehydrogenation to form aldehydes is often reversible. For the $\text{RuBr}(\eta^3\text{-C}_3\text{H}_5)(\text{CO})_3$ /monophosphine catalyst system the equilibrium may lie toward the alcohol. This is significant, as the electrophile-nucleophile pair obtained upon alcohol-allene hydrogen exchange would then be present in vanishingly small concentrations.

In summary, we report the first examples of ruthenium catalyzed alcohol-allene C-C coupling under transfer hydrogenation conditions. Whereas previously reported $\text{RuBr}(\eta^3\text{-C}_3\text{H}_5)(\text{CO})_3/\text{monophosphine}$ catalysts promote isopropanol-mediated allene-aldehyde reductive C-C bond formation,⁶ this catalyst was ineffective in corresponding allene-alcohol C-C couplings. Using the $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3/\text{dippf}$ catalyst system, this limitation is overcome. The alcohol-allenamide C-C coupling represents an alternative to the use of amino-substituted allylmetal reagents in carbonyl amino-allylation, such as amino-substituted allylboranes.¹⁴ Finally, these data provide further insight into the structural and interactional features of ruthenium-based catalysts for alcohol-unsaturated C-C coupling and related aldehyde-unsaturated reductive couplings driven by alcohol dehydrogenation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Acknowledgment is made to the Robert A. Welch Foundation and the NIH-NIGMS (RO1-GM069445) for partial support of this research.

References

1. For selected reviews on C-C bond forming hydrogenation and transfer hydrogenation, see: (a) Ngai MY, Kong JR, Krische MJ. *J Org Chem* 2007;72:1063. [PubMed: 17288361] (b) Skucas E, Ngai MY, Komanduri V, Krische MJ. *Acc Chem Res* 2007;40:1394. [PubMed: 17784728] (c) Shibahara F, Krische MJ. *Chem Lett* 2008;37:1102. (d) Patman RL, Bower JF, Kim IS, Krische MJ. *Aldrichim Acta* 2008;41:95. (e) Bower JF, Kim IS, Patman RL, Krische MJ. *Angew Chem Int Ed* 2009;48:34.
2. For related "hydrogen auto-transfer" reactions, alcohol dehydrogenation and nucleophile generation occur independently. Hence, conventional pre-activated nucleophiles are required. Such processes deliver products of formal alcohol substitution rather than carbonyl addition. For selected reviews, see: (a) Guillena G, Ramón DJ, Yus M. *Angew Chem Int Ed* 2007;46:2358. (b) Hamid MHSA, Slatford PA, Williams MJ. *Adv Synth Catal* 2007;349:1555. (c) Nixon TD, Whittlesey MK, Williams MJ. *Dalton Trans* 2009:753. [PubMed: 19156265] (d) Dobereiner GE, Crabtree RH. *Chem Rev* 2010;110:681. [PubMed: 19938813] (e) Guillena G, Ramón DJ, Yus M. *Chem Rev* 2010;110:1611. [PubMed: 19928825] Related dehydrogenative couplings of amines also require pre-activated nucleophiles, see: (f) Li CJ. *Acc Chem Res* 2009;42:335. [PubMed: 19220064]
3. For ruthenium catalyzed transfer hydrogenative coupling of alcohols to dienes, see: (a) Shibahara F, Bower JF, Krische MJ. *J Am Chem Soc* 2008;130:6338. [PubMed: 18444617] (b) Shibahara F, Bower JF, Krische MJ. *J Am Chem Soc* 2008;130:14120. [PubMed: 18841895] (c) Smejkal T, Han H, Breit B, Krische MJ. *J Am Chem Soc* 2009;131:10366. [PubMed: 19594163]
4. For ruthenium catalyzed transfer hydrogenative coupling of alcohols to enynes, see: Patman RL, Williams VM, Bower JF, Krische MJ. *Angew Chem Int Ed* 2008;47:5220.
5. For ruthenium catalyzed transfer hydrogenative coupling of alcohols to alkynes, see: (a) Patman RL, Chaulagain MR, Williams VM, Krische MJ. *J Am Chem Soc* 2009;131:2066. [PubMed: 19173651] (b) Williams VM, Leung JC, Patman RL, Krische MJ. *Tetrahedron* 2009;65:5024.
6. For ruthenium catalyzed transfer hydrogenative coupling of aldehydes to allenes, see: (a) Ngai MY, Skucas E, Krische MJ. *Org Lett* 2008;10:2705. [PubMed: 18533665] (b) Skucas E, Zbieg JR, Krische MJ. *J Am Chem Soc* 2009;131:5054. [PubMed: 19317402] (c) Grant CD, Krische MJ. *Org Lett* 2009;11:4485. [PubMed: 19764718]
7. Denichoux A, Fukuyama T, Doi T, Horiguchi J, Ryu I. *Org Lett* 2010;12:1. [PubMed: 19938848]
8. The coupling of alcohols to 1,1-dimethylallene has been achieved under the conditions of iridium catalyzed transfer hydrogenation: (a) Han SB, Kim IS, Han H, Krische MJ. *J Am Chem Soc* 2009;131:6916. [PubMed: 19453190] (b) Lu Y, Krische MJ. *Org Lett* 2009;11:3108. [PubMed: 19586066]

9. (a) Wei L-L, Xiong H, Hsung RP. *Acc Chem Res* 2003;36:773. [PubMed: 14567711] (b) Ma S. *Chem Rev* 2005;105:2829. [PubMed: 16011326]
10. (a) Aberg, Jenny B.; Nyhlen, Jonas; Martin-Matute, Belen; Privalov, Timofei; Baeckvall, Jan-E. *J Am Chem Soc* 2009;131:9500. [PubMed: 19534552] (b) Aberg, Jenny B.; Warner, Madeleine C.; Baeckvall, Jan-E. *J Am Chem Soc* 2009;131:13622. [PubMed: 19772359]
11. Butler IR, Cullen WR, Kim TJ. *Synth React Inorg Met-Org Chem* 1985;15:109.
12. Werner H, Werner R. *Chem Ber* 1982;115:3766.
13. For isopropanol dehydrogenation, $\Delta H = +65$ kJ/mol. For n-propanol dehydrogenation, $\Delta H = +73$ kJ/mol: (a) Buckley E, Herington EFG. *Trans Faraday Soc* 1965;61:1618. (b) Buckley E, Cox JD. *Trans Faraday Soc* 1967;63:895.
14. For carbonyl amino-allylation employing amino-substituted allylborane reagents, see: (a) Barrett AGM, Seefeld MA. *J Chem Soc, Chem Commun* 1993:339. (b) Barrett AGM, Seefeld MA. *Tetrahedron* 1993;49:7857. (c) Barrett AGM, Seefeld MA, Williams DJ. *J Chem Soc, Chem Commun* 1994:1053. (d) Barrett AGM, Seefeld MA, White AJP, Williams DJ. *J Org Chem* 1996;61:2677. [PubMed: 11667097]

Scheme 1.

anti-Diastereoselective coupling of allenamide **1a** to alcohols **2a-2l** to provide *anti*-aminoalcohols **3a-3l**.^a

^aAll reactions were performed in 13 x 100 mm pressure tubes. The cited yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ¹H NMR analysis of crude reaction mixtures. In each case, >20:1 *anti*-diastereoselectivity was observed. ^bThree equivalents of **1a** were used. See Supporting Information for experimental details.

Scheme 2. Catalytic C-C coupling of 1,1-disubstituted allene **1b** to alcohols **2d** and **2g**.^a^aAs described in Table 2. See Supporting Information for experimental details.

Table 1Defining an effective ruthenium catalyst for allene-alcohol C-C coupling.^a

entry	ligand (mol %)	precatalyst	yield 3a (dr)
1	---	RuHCl(CO)(PPh ₃) ₃	no reaction
2	PPh ₂ Bu ^t (15 mol %)	RuHCl(CO)(PPh ₃) ₃	no reaction
3	PCy ₃ (15 mol %)	RuHCl(CO)(PPh ₃) ₃	no reaction
4	<i>rac</i> -BINAP (5 mol %)	RuHCl(CO)(PPh ₃) ₃	no reaction
5	XANTPHOS (5 mol %)	RuHCl(CO)(PPh ₃) ₃	no reaction
6	BIPHEP (5 mol %)	RuHCl(CO)(PPh ₃) ₃	29% (≥ 20:1)
7	dppf (5 mol %)	RuHCl(CO)(PPh ₃) ₃	58% (≥ 20:1)
8	dippf (5 mol %)	RuHCl(CO)(PPh ₃) ₃	86% (≥ 20:1)
9	dippf (5 mol %)	RuCl ₂ (CO)(cymene)	90% (≥ 20:1)

^aReactions were performed in 13 × 100 mm pressure tubes. The cited yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ¹H NMR analysis of crude reaction mixtures. See Supporting Information for experimental details.