Allenamide Hydro–Hydroxyalkylation: 1,2-Amino Alcohols via Ruthenium-Catalyzed Carbonyl *anti*-Aminoallylation
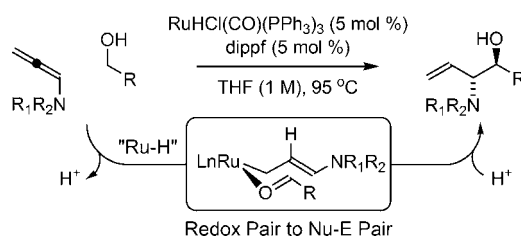
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ABSTRACT

Exposure of alcohols to allenamides in the presence of RuHCl(CO)(PPh₃)₃ and dippf [dippf = 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 2-propanol 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 alcohol oxidation level. Thus, identical carbonyl addition products are available from the aldehyde or alcohol oxidation levels. Such C–C bond-forming transfer hydrogenations avoid stoichiometric use of premetalated nucleophiles and resulting metallic byproducts. Furthermore, reactions conducted from the alcohol oxidation level 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] alkynes,[5] and allenes[6] has been achieved. Related alcohol–enal couplings

(1) For selected reviews on C–C bond-forming hydrogenation and transfer hydrogenation, see: (a) Ngai, M.-Y.; Kong, J. R.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 1063. (b) Skucas, E.; Ngai, M.-Y.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394. (c) Shibahara, F.; Krische, M. J. *Chem. Lett.* **2008**, *37*, 1102. (d) Patman, R. L.; Bower, J. F.; Kim, I. S.; Krische, M. J. *Aldrichim. Acta* **2008**, *41*, 95. (e) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *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, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358. (b) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555. (c) Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. J. *Dalton Trans.* **2009**, 753. (d) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681. (e) Guillena, G.; Ramón, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611. Related dehydrogenative couplings of amines also require preactivated nucleophiles; see: (f) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.

(3) For ruthenium-catalyzed transfer hydrogenative coupling of alcohols to dienes, see: (a) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6338. (b) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14120. (c) Smejkal, T.; Han, H.; Breit, B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 10366.

(4) For ruthenium-catalyzed transfer hydrogenative coupling of alcohols to enynes, see: Patman, R. L.; Williams, V. M.; Bower, J. F.; Krische, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 5220.

catalyzed by ruthenium, where C–C bond formation is followed by redox isomerization, also have been 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 RuBr(η^3-C$_3$H$_5$)(CO)$_3$ as the ruthenium precatalyst in combination with monodentate phosphine ligands.[6] Here, we report that the ruthenium catalyst obtained upon combination of RuHCl(CO)(PPh$_3$)$_3$ and dippf [dippf = bis(diisopropylphosphino)ferrocene] overcomes this limitation, enabling direct alcohol–allenamide C–C coupling to furnish *anti*-1,2-amino alcohols 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 for 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 RuHCl(CO)(PPh$_3$)$_3$ in the absence of added phosphine ligand (Table 1, entry 1). Hence, RuHCl(CO)(PPh$_3$)$_3$ was used as a precatalyst for ligand screening. Notably, ligands effective in previously reported allene–aldehyde reductive couplings employing RuBr(η^3-C$_3$H$_5$)(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 RuHCl(CO)(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 RuCl$_2$(CO)(cymene)[12] reacts with dippf to provide an even more effective catalyst (Table 1, entry 9). However, because the catalyst generated from RuCl$_2$(CO)(cymene) and dippf

showed greater air sensitivity, the RuHCl(CO)(PPh$_3$)$_3$/dippf catalyst system was adopted as our standard conditions (Table 1).

Table 1. Defining an Effective Ruthenium Catalyst for Allene–Alcohol C–C Coupling[a]

entry	ligand (mol %)	precatalyst	yield of **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	*rac*-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% ($\geq$20:1)
7	dppf (5 mol %)	RuHCl(CO)(PPh$_3$)$_3$	58% ($\geq$20:1)
8	dippf (5 mol %)	RuHCl(CO)(PPh$_3$)$_3$	86% ($\geq$20:1)
9	dippf (5 mol %)	RuCl$_2$(CO)(cymene)	90% ($\geq$20:1)

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

Scheme 1. *anti*-Diastereoselective Coupling of Allenamide **1a** to Alcohols **2a–l** To Provide *anti*-Amino Alcohols **3a–l**[a]
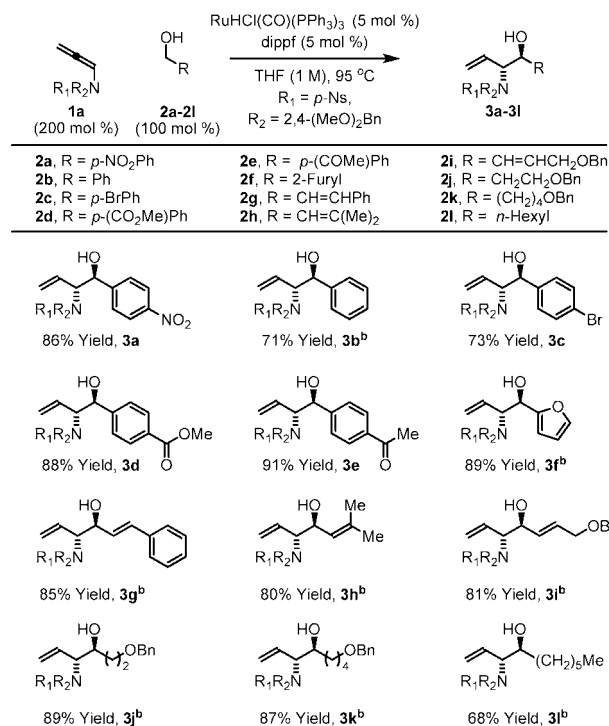
[a] All reactions were performed in 13 × 100 mm pressure tubes. The cited yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR analysis of crude reaction mixtures. In each case, >20:1 *anti*-diastereoselectivity was observed. [b] 3 equiv of **1a** was used. See the Supporting Information for experimental details.

(5) For ruthenium-catalyzed transfer hydrogenative coupling of alcohols to alkynes, see: (a) Patman, R. L.; Chaulagain, M. R.; Williams, V. M.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2066. (b) Williams, V. M.; Leung, J. C.; Patman, R. L.; Krische, M. J. *Tetrahedron* **2009**, *65*, 5024.

(6) For ruthenium-catalyzed transfer hydrogenative coupling of aldehydes to allenes, see: (a) Ngai, M.-Y.; Skucas, E.; Krische, M. J. *Org. Lett.* **2008**, *10*, 2705. (b) Skucas, E.; Zbieg, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 5054. (c) Grant, C. D.; Krische, M. J. *Org. Lett.* **2009**, *11*, 4485.

(7) Denichoux, A.; Fukuyama, T.; Doi, T.; Horiguchi, J.; Ryu, I. *Org. Lett.* **2010**, *12*, 1.

(8) The coupling of alcohols to 1,1-dimethylallene has been achieved under the conditions of iridium-catalyzed transfer hydrogenation: (a) Han, S. B.; Kim, I.-S.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 6916. (b) Lu, Y.; Krische, M. J. *Org. Lett.* **2009**, *11*, 3108.

(9) (a) Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773. (b) Ma, S. *Chem. Rev.* **2005**, *105*, 2829.

(10) (a) Aberg, J. B.; Nyhlen, J.; Martin-Matute, B.; Privalov, T.; Baeckvall, J.-E. *J. Am. Chem. Soc.* **2009**, *131*, 9500. (b) Aberg, J. B.; Warner, M. C.; Backvall, J.-E. *J. Am. Chem. Soc.* **2009**, *131*, 13622.

(11) Butler, I. R.; Cullen, W. R.; Kim, T.-J. *Synth. React. Inorg. Met.-Org. Chem.* **1985**, *15*, 109.

(12) Werner, H.; Werner, R. *Chem. Ber.* **1982**, *115*, 3766.

Under these conditions, allenamide **1a** was coupled to structurally diverse alcohols **2a–l**. Benzylic alcohols **2a–f**,

allylic alcohols **2g−i** and simple aliphatic alcohols **2j−l** are transformed to the corresponding products of carbonyl aminoallylation **3a−f**, **2g−i**, and **2j−l**, respectively. All adducts **3a−l** 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).

Scheme 2. Catalytic C−C Coupling of 1,1-Disubstituted Allene **1b** to Alcohols **2d** and **2g**[a]
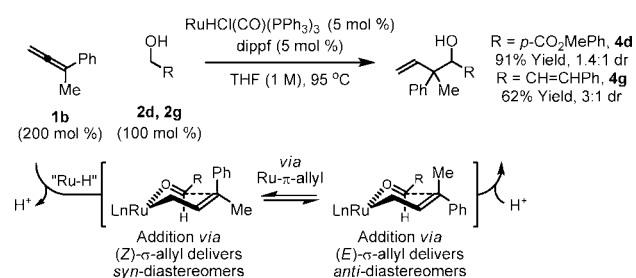
[a] As described in Table 2. See the Supporting Information for experimental details.

Our collective data on ruthenium-catalyzed C−C couplings of allenes suggest that relatively electron-deficient ruthenium centers, as in the RuBr(η^3-C$_3$H$_5$)(CO)$_3$/monophosphine catalyst system, are capable of dehydrogenating secondary alcohols, such as 2-propanol. However, they are inefficient in dehydrogenations of primary alcohols, which is an energetically more demanding process.[13] Furthermore, pri-

mary alcohol dehydrogenation to form aldehydes is likely reversible and, for the RuBr(η^3-C$_3$H$_5$)(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 RuBr(η^3-C$_3$H$_5$)(CO)$_3$/monophosphine catalysts promote 2-propanol-mediated allene−aldehyde reductive C−C bond formation,[6] this catalyst was ineffective in corresponding allene−alcohol C−C couplings. Using the RuHCl(CO)(PPh$_3$)$_3$/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−unsaturate reductive couplings driven by alcohol dehydrogenation.

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

(13) For 2-propanol dehydrogenation, DH = +65 kJ/mol. For *n*-propanol dehydrogenation, DH = +73 kJ/mol: (a) Buckley, E.; Herington, E. F. G. *Trans. Faraday Soc.* **1965**, *61*, 1618. (b) Buckley, E.; Cox, J. D. *Trans. Faraday Soc.* **1967**, *63*, 895.

(14) For carbonyl amino-allylation employing amino-substituted allylborane reagents, see: (a) Barrett, A. G. M.; Seefeld, M. A. *J. Chem. Soc., Chem. Commun.* **1993**, 339. (b) Barrett, A. G. M.; Seefeld, M. A. *Tetrahedron* **1993**, *49*, 7857. (c) Barrett, A. G. M.; Seefeld, M. A.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1053. (d) Barrett, A. G. M.; Seefeld, M. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1996**, *61*, 2677.