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Direct, Redox Neutral Prenylation and Geranylation of Secondary Carbinol C-H Bonds: C4 Regioselectivity in Ruthenium Catalyzed C-C Couplings of Dienes to α-Hydroxy Esters

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Abstract

The ruthenium catalyst generated *in situ* from $Ru_3(CO)_{12}$ and tricyclohexylphosphine, PCy_3 , promotes the redox-neutral C-C coupling of aryl substituted α -hydroxy esters to isoprene and myrcene at the diene C4-position, resulting in direct carbinol C-H prenylation and geranylation, respectively. This process enables direct conversion of secondary to tertiary alcohols in the absence of stoichiometric byproducts or premetallated reagents, and is the first example of C4-regioselectivity in catalytic C-C couplings of 2-substituted dienes to carbonyl partners. Mechanistic studies corroborate a catalytic cycle involving diene-carbonyl oxidative coupling.

The ability to transform abundant feedstocks to value-added products in the absence of stoichiometric byproducts is a principal characteristic of a "process-relevant" method. This attribute is exemplified by catalytic hydrogenation, which is applied across all segments of the chemical industry including the manufacture of chiral pharmaceutical ingredients on scale, and alkene hydroformylation, which may be viewed as the prototypical C-C bond forming hydrogenation. As part of an effort aimed at the development of C-C bond forming hydrogenations beyond hydroformylation, we have found that hydrogen transfer between primary alcohols and π -unsaturated reactants generates organometal-aldehyde pairs that combine to form products of carbonyl addition, representing a departure from stoichiometric organometallic reagents in a range of C=X (X = O, NR) addition processes. 4

Although primary alcohols participate in transfer hydrogenative C-C couplings to dienes 5,6 and other π -unsaturated reactants (allenes, enynes, alkynes and allylic acetates), 4 to date, secondary alcohols have proven uniformly unreactive, presumably due to the relatively low electrophilicity of the transient ketones that arise upon dehydrogenation. It was reasoned that the transfer hydrogenative coupling of related α -hydroxy esters and π -unsaturated reactants might be feasible, as the transient α -ketoester esters are highly susceptible to nucleophilic addition. However, dehydrogenation of α -hydroxy esters is challenging from both a thermodynamic and a kinetic standpoint. Here, we report that the ruthenium catalyst generated from Ru₃(CO)₁₂ and tricyclohexylphosphine promotes efficient redox-neutral C-C coupling of aryl substituted α -hydroxy esters 1a-1f to isoprene 2a and myrcene 2b with unique regioselectivity for coupling at the diene C4-position, enabling direct carbinol C-H prenylation and geranylation, respectively (Figure 1). $^{5-21}$

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In preliminary experiments, a range of ruthenium and iridium catalysts were assayed for their ability to promote the C-C coupling of racemic ethyl mandelate 1a to isoprene 2a. These attempts were either completely unsuccessful or provided only trace quantities C-C coupling product or the α-ketoester, oxo-1a. Recently, however, Beller demonstrated that the catalyst generated from Ru₃(CO)₁₂ and Cy₂P(CH₂)₂PCy₂ in t-amyl alcohol at 150 °C promote the direct conversion of α-hydroxy amides to α-amino amides through dehydrogenation of the former.²² While these conditions did not translate directly to the coupling of ethyl mandelate 1a and isoprene 2a (Table 1, entry 1), simply changing the solvent to THF and increasing the loading of ligand led to a 45% isolated yield of the nprenylated hydroxy ester 3a (Table 1, entry 2). Other bidentate phosphine ligands such as ferrocene-derived ligands DPPF, DiPPF and BINAP-PCy2 were assayed under these conditions, however, conversion to 3a was not observed (Table 1, entries 3-5). In contrast, use of the simple monodentate phosphine ligand PCy₃ (12 mol%) under these conditions led to a 59% isolated yield of 3a (Table 1, entry 6). A comparable isolated yield of 3a could be obtained at 130 °C by extending the reaction time (Table 1, entry 7). At this stage, different solvents were evaluated (Table 1, entries 8-10). By conducting the reaction in toluene, the *n*prenylated product 3a was obtained in 68% isolated yield (Table 1, entry 10). Variation of ligand loading did not improve the isolated yield of 3a (Table 1, entry 11), nor did changes in concentration (Table 1, entries 12, 13). However, by decreasing reaction time and increasing the loading of isoprene (500 mol%), a 75% isolated yield of the n-prenylated product 3a was obtained (Table 1, entry 15).

Under these optimal conditions, the redox neutral C-C coupling of aryl substituted α -hydroxy esters **1a-1f** and isoprene **2a** was explored (Table 2). In each case, the corresponding *n*-prenylated products **3a-3f** were isolated in good yield as single regioisomers. Alkyl substituted α -hydroxy esters such as ethyl lactate provide low isolated yields of C-C coupling product using this first generation catalyst. However, analogous coupling reactions of aryl substituted α -hydroxy esters **1a-1f** with myrcene **2b** were successful, delivering products of geranylation **4a-4f** with complete control of olefin geometry (Table 3). Thus, direct secondary carbinol C-H prenylation and geranylation is achieved under redox neutral conditions in the absence of stoichiometric byproducts or premetallated reagents. Reaction using 2,3-dimethylbutadiene, 1,3-pentadiene and 3-methyl-1,3-pentadiene were attempted under standard conditions, but only trace quantities of product were observed.

To probe the catalytic mechanism and gain insight into the origins of regioselectivity, deuterated rac-ethyl mandelate, deuterio- $\mathbf{1a}$, was exposed to isoprene $\mathbf{2a}$ under standard conditions for redox-neutral C-C coupling (eqn. 1). Notably, the n-prenylated adduct deuterio- $\mathbf{1a}$ incorporates deuterium exclusively at the cis-methyl group of the n-prenyl moiety (2 H 50%). Incomplete deuterium incorporation may be attributed to the reversible transfer of hydrogen between deuterio- $\mathbf{1a}$ and isoprene, as corroborated by deuterium loss in recovered deuterio- $\mathbf{1a}$ (2 H 54%). The regioselectivity and extent of 2 H incorporation were evaluated using 1 H and 2 H NMR spectroscopy. Also, recovered from this reaction in 9% yield is the α -ketoester, oxo-oxe-

(eqn. 1)

The regioselectivity of C-C coupling and deuterium incorporation are each consistent with the indicated catalytic cycle, which involves diene-carbonyl oxidative coupling (Scheme 1). To further challenge this mechanistic hypothesis, the redox neutral coupling of *rac*-ethyl mandelate **1a** and butadiene **2c** was performed under standard conditions. The product of C-C coupling **5a** is formed as (Z)-stereoisomer, which is consistent with the proposed oxidative coupling mechanism (eqn. 2).

(eqn. 2)

In other hydrohydroxyalkylations we have developed, which employing ruthenium(II) catalysts, mechanisms involving diene hydrometallation to form $\pi\text{-allylruthenium}$ intermediates appear operative. The present ruthenium(0) catalyst system is unique in its ability to promote both alcohol dehydrogenation and diene-carbonyl oxidative C-C coupling, as illustrated in the formation of oxametallacycle I (Scheme 1) and as found in related Pauson-Khand type reactions of 1,2-diones. As suggested by Beller's work and our collective studies, the $Ru_3(CO)_{12}$ /phosphine catalyst system also appears better at promoting alcohol dehydrogenations that require β -hydride elimination of electron deficient carbinol C-H bonds, in comparison to ruthenium(II) catalysts.

In summary, the redox neutral prenylations and geranylations reported herein represent the first examples of the transfer hydrogenative C-C coupling of secondary alcohols. Further, the C4-regioselectivity displayed by these processes is unique among catalytic dienecarbonyl C-C couplings. As corroborated by mechanistic studies (eqns. 1 and 2), this unique regioselectivity is a consequence of a novel catalytic mechanism that links alcohol dehydrogenation and dienecarbonyl oxidative coupling. Direct prenylations and geranylations of secondary carbinol C-H bonds employing isoprene and myrcene, respectively, should facilitate access to diverse terpenoid natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. For selected reviews, see: Butters M, Catterick D, Craig A, Curzons A, Dale D, Gillmore A, Green SP, Marziano I, Sherlock J-P, White W. Chem. Rev. 2006; 106:3002. [PubMed: 16836307] Sheldon RA. Green Chem. 2007; 9:1273.Beller M. Eur. J. Lipid Sci. Technol. 2008; 110:789.

- For selected reviews, see: Hawkins JM, Watson TJN. Angew. Chem. Int. Ed. 2004;
 43:3224. Thommen M. Spec. Chem. Mag. 2005; 25:26. Thayer AM. Chem. Eng. News. 2005;
 83:40. Jäkel C, Paciello R. Chem. Rev. 2006; 106:2912. [PubMed: 16836304] Farina V, Reeves JT, Senanayake CH, Song JJ. Chem. Rev. 2006; 106:2734. [PubMed: 16836298] Carey JS, Laffan D, Thomson C, Williams MT. Org. Biomol. Chem. 2006; 4:2337. [PubMed: 16763676] Constable DJC, Dunn PJ, Hayler JD, Humphrey GR, Leazer JL Jr. Linderman RJ, Lorenz K, Manley J, Pearlman BA, Wells A, Zaks A, Zhang TY. Green Chem. 2007; 9:411. Blaser H-U, Pugin B, Spindler F, Thommen M. Acc. Chem. Res. 2007; 40:1240. [PubMed: 17715990] Busacca CA, Fandrick DR, Song JJ, Senanayake CH. Adv. Synth. Catal. 2011; 353:1825.
- 3. For selected reviews on alkene hydroformylation, see: Beller M, Cornils B, Frohning CD, Kohlpaintner CW. J. Mol. Catal. A. 1995; 104:17.Frohning CD, Kohlpaintner CW, Bohnen H–W. Cornils B, Herrmann WA. Carbon Monoxide and Synthesis Gas Chemistry. Applied Homogeneous Catalysis with Organometallic Compounds. 1996; 1:29–104.Wiley-VCHWeinheimvan Leeuwen PWNM, Claver C. Rhodium Catalyzed Hydroformylation. 2000Kluwer Academic PublishersNorwell, MABreit B, Seiche W. Synthesis. 2001:1–36.Weissermel K, Arpe H-J. Synthesis involving Carbon Monoxide. Industrial Organic Chemistry (4th Ed). 2003:127–144.Wiley-VCHWeinheimvan Leeuwen PWNM. Homogeneous Catalysis: Understanding the Art. 2004KluwerDordrecht
- For selected reviews on C-C bond forming hydrogenation and transfer hydrogenation, see: Bower
 JF, Krische MJ. Top. Organomet. Chem. 2011; 43:107. [PubMed: 21822399] Hassan A, Krische
 MJ. Org. Proc. Res. Devel. 2011; 15:1236.Moran J, Krische MJ. Pure Appl. Chem. 2012; 84:1729.
- 5. For ruthenium catalyzed transfer hydrogenative coupling of primary alcohols to dienes to form secondary alcohols, see: Shibahara F, Bower JF, Krische MJ. J. Am. Chem. Soc. 2008; 130:6338. [PubMed: 18444617] Han H, Krische MJ. Org. Lett. 2010; 12:2844. [PubMed: 20491487] Zbieg JR, Moran J, Krische MJ. J. Am. Chem. Soc. 2011; 133:10582. [PubMed: 21627316] Zbieg JR, Yamaguchi E, McInturff EL, Krische MJ. Science. 2012; 336:324. [PubMed: 22442385] Also, see reference 10.
- For iridium catalyzed transfer hydrogenative coupling of primary alcohols to dienes to form secondary alcohols, see: Bower JF, Patman RL, Krische MJ. Org. Lett. 2008; 10:1033. [PubMed: 18254642] Zbieg JR, Fukuzumi T, Krische MJ. Adv. Synth. Catal. 2010; 352:2416. [PubMed: 21165157]
- For nickel catalyzed intermolecular diene-aldehyde reductive coupling, see: Kimura M, Ezoe A, Shibata K, Tamaru Y. J. Am. Chem. Soc. 1998; 120:4033. Takimoto M, Hiraga Y, Sato Y, Mori M. Tetrahedron Lett. 1998; 39:4543. Kimura M, Fujimatsu H, Ezoe A, Shibata K, Shimizu M, Matsumoto S, Tamaru Y. Angew. Chem. Int. Ed. 1999; 38:397. Kimura M, Shibata K, Koudahashi Y, Tamaru Y. Tetrahedron Lett. 2000; 41:6789. Kimura M, Ezoe A, Tanaka S, Tamaru Y. Angew. Chem. Int. Ed. 2001; 40:3600. Loh T-P, Song H-Y, Zhou Y. Org. Lett. 2002; 4:2715. [PubMed: 12153217] Sato Y, Sawaki R, Saito N, Mori M. J. Org. Chem. 2002; 67:656. [PubMed: 11856003] Kimura M, Ezoe A, Mori M, Iwata K, Tamaru Y. J. Am. Chem. Soc. 2006; 128:8559. [PubMed: 16802822] Yang Y, Zhu S-F, Duan H-F, Zhou C-Y, Wang L-X, Zhou Q-L. J. Am. Chem. Soc. 2007; 129:2248. [PubMed: 17269780] Sato Y, Hinata Y, Seki R, Oonishi Y, Saito N. Org. Lett. 2007; 9:5597. [PubMed: 18020355]
- 8. For rhodium catalyzed intermolecular diene-aldehyde reductive coupling, see: Jang H-Y, Huddleston RR, Krische MJ. Angew. Chem. Int. Ed. 2003; 42:4074.Kimura M, Nojiri D, Fukushima M, Oi S, Sonoda Y, Inoue Y. Org. Lett. 2009; 11:3794. [PubMed: 19663391]
- 9. For titanium catalyzed intermolecular diene-aldehyde reductive coupling, see: Bareille L, Le Gendre P, Moïse C. Chem. Commun. 2005:775.
- Smejkal T, Han H, Breit B, Krische MJ. J. Am. Chem. Soc. 2009; 131:10366. [PubMed: 19594163]
- 11. For nickel catalyzed intramolecular diene-aldehyde reductive coupling, see: Sato Y, Takimoto M, Hayashi K, Katsuhara T, Takagi K, Mori M. J. Am. Chem. Soc. 1994; 116:9771.Sato Y, Takimoto

M, Mori M. Tetrahedron Lett. 1996; 37:887.Sato Y, Saito N, Mori M. Tetrahedron Lett. 1997; 38:3931.Sato Y, Takanashi T, Hoshiba M, Mori M. Tetrahedron Lett. 1998; 39:5579.Sato Y, Takimoto M, Mori M. J. Am. Chem. Soc. 2000; 122:1624.Sato Y, Saito N, Mori M. J. Am. Chem. Soc. 2000; 122:2371.Shibata K, Kimura M, Shimizu M, Tamaru Y. Org. Lett. 2001; 3:2181. [PubMed: 11440574] Sato Y, Saito N, Mori M. J. Org. Chem. 2002; 67:9310. [PubMed: 12492333] Sato Y, Takanashi T, Hoshiba M, Mori M. J. Organomet. Chem. 2003; 688:36.Yu C-M, Youn J, Yoon S-K, Hong Y-T. Org. Lett. 2005; 7:4507. [PubMed: 16178570]

- For selected examples of diene hydroboration-carbonyl allylation, see: Brown HC, Liotta R, Kramer GW. J. Org. Chem. 1978; 43:1058.Satoh M, Nomoto Y, Miyaura N, Suzuki A. Tetrahedron Lett. 1989; 30:3789.
- For selected examples of diene diboration-carbonyl allylation, see: Morgan JB, Morken JP. Org. Lett. 2003; 5:2573. [PubMed: 12841784] Ballard CE, Morken JP. Synlett. 2004; 1321Cho HY, Morken JP. J. Am. Chem. Soc. 2008; 130:16140. [PubMed: 18998642] Burks HE, Kliman LT, Morken JP. J. Am. Chem. Soc. 2009; 131:9134. [PubMed: 19505078] Ely RJ, Morken JP. J. Am. Chem. Soc. 2010; 132:2534. [PubMed: 20136142] Cho HY, Morken JP. J. Am. Chem. Soc. 2010; 132:7576. [PubMed: 20481451] Hong K, Morken JP. J. Org. Chem. 2011; 76:9102. [PubMed: 21932816] Cho HY, Yu Z, Morken JP. Org. Lett. 2011; 13:5269.Kliman LT, Mlynarski SN, Ferris GE, Morken JP. Angew. Chem. Int. Ed. 2012; 51:521.
- For selected examples of diene hydroalumination-carbonyl allylation, see: (a) Takaya J, Sasano K, Iwasawa N. Org. Lett. 2011; 13:1698. [PubMed: 21370864]
- For selected examples of diene hydrosilylation-carbonyl allylation, see: Kira M, Hino T, Sakurai H. Tetrahedron Lett. 1989; 30:1099.Kobayashi S, Nishio K. Synthesis. 1994:457.Kobayashi S, Nishio K. J. Org. Chem. 1994; 59:6620.
- For selected examples of diene hydrostannation-carbonyl allylation, see: Masuyama Y, Tsunoda M, Kurusu Y. J. Chem. Soc., Chem. Commun. 1994:1451.
- 17. For selected examples of diene hydrotitanation-carbonyl allylation, see: Kobayashi Y, Umeyama K, Sato F. J. Chem. Soc., Chem. Commun. 1984:621.Collins S, Dean WP, Ward DG. Organometallics. 1988; 7:2289.Szymoniak J, Thery N, Moïse C. Synlett. 1997:1239.Quan LG, Cha JK. Org. Lett. 2001; 3:2745. [PubMed: 11506624]
- 18. For selected examples of diene hydrozincation-carbonyl allylation, see: Gao Y, Urabe H, Sato F. J. Org. Chem. 1994; 59:5521. and references cited therein.
- 19. For selected examples of diene hydromagnesiation-carbonyl allylation, see: Sato F, Ishikawa H, Sato M. Tetrahedron Lett. 1980; 21:365.Sato F, Kusakabe M, Kobayashi Y. J. Chem. Soc., Chem. Comm. 1984:1130. Also, see: Sell MS, Klein WR, Rieke RD. J. Org. Chem. 1995; 60:1077.
- 20. For an example of diene hydrochromination-carbonyl allylation, see: Takai K, Toratsu C. J. Org. Chem. 1998; 63:6450.
- 21. For selected examples of diene hydroindation-carbonyl allylation, see: Hayashi N, Honda H, Yasuda M, Shibata I, Baba A. Org. Lett. 2006; 8:4553. [PubMed: 16986948] Hayashi N, Honda H, Shibata I, Yasuda M, Baba A. Synlett. 2008:1407.
- 22. Zhang M, Imm S, Bahn S, Neumann H, Beller M. Angew. Chem. Int. Ed. 2011; 50:11197.
- 23. a Chatani N, Tobisu M, Asaumi T, Fukumoto Y, Murai S. J. Am. Chem. Soc. 1999; 121:7160.b Tobisu M, Chatani N, Asaumi T, Amako K, Ie Y, Fukumoto Y, Murai S. J. Am. Chem. Soc. 2000; 122:12663.

Figure 1. Regioselectivity in intermolecular metal catalyzed C-C couplings of 2-substituted dienes to carbonyl partners.^a

^aFor catalytic intramolecular diene-aldehyde reductive couplings, see reference 10. For catalyzed and non-catalyzed stoichiometric generation of allylmetal species from dienes followed by carbonyl allylboration, see references 11-21.

Scheme 1.

Plausible catalytic mechanism for the redox neutral C-C coupling of *deuterio-1a* to isoprene 2a.

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Table 1

Selected optimization experiments in the C-C coupling of α -hydroxy ester 1 to isoprene $2a.^a$

		1														
	Yield%	<10p	45	NR	NR	NR	59	99	09	NR	89	.89°	59	50	42	75
O Ph OH 3a	Time (hr)	48	48	48	48	48	48	72	72	72	72	72	72	72	48	48
Me Me	$T(^{\circ}C)$	150	150	150	150	150	150	130	130	130	130	130	130	130	130	130
Ru ₃ (CO) ₁₂ (2 mol%) Ligand (12 mol%) Solvent (2.0 M) T °C, Time (hr)	Solvent (M)	<i>t</i> -AmOH (2.0)	THF (2.0)	THF (2.0)	THF (2.0)	THF (2.0)	THF (2.0)	THF (2.0)	Dioxane (2.0)	DCE (2.0)	PhMe (2.0)	PhMe (2.0)	PhMe (1.0)	PhMe (0.5)	PhMe (2.0)	PhMe (2.0)
Me Za	Ligand	Cy ₂ P(CH ₂) ₂ PCy ₂	Cy ₂ P(CH ₂) ₂ PCy ₂	DPPF	DiPPF	BINAP-PC y_2	PCy_3	PCy_3	PCy_3	PCy_3	PCy_3	PCy_3	PCy_3	PCy_3	PCy_3	PCy_3
Ph OEt OH 18	2 (mol%)	400	400	400	400	400	400	400	400	400	400	400	400	400	400	200
	Entry		2	3	4	5	9	7	∞	6	10	Ξ	12	13	14	() 13

 4 Yields are of material isolated by silica gel chromatography. See Supporting Information for further details.

 b Cy2P(CH2)2PCy2 (6 mol%).

 $^{\mathcal{C}}$ Cy3P (18 mol%).

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 $\label{eq:Table 2} \textbf{Table 2}$ Prenylation of \$\alpha\$-hydroxy esters 1a-1f \$via\$ ruthenium catalyzed hydrohydroxyalkylation of isoprene 2a.\$a\$

OH 1a-1f 2a (100 mol%) (500 mol%)	Ru ₃ (CO) ₁₂ (2 mol%) PCy ₃ (12 mol%) PhMe (2.0 M) 130 °C	Me O OEt Ar OH 3a-3f
1a , Ar = Ph	1b , Ar = <i>p</i> -Tol	1c , Ar = <i>p</i> -BrPh
1d , Ar = <i>p</i> -CF ₃ Ph	1e , Ar = <i>p</i> -MeOPh	1f , Ar = piperonyl
Me OOEt Me	Me O OEt OH	Me O OEt OH
75% Yield, 3a	59% Yield, 3b	67% Yield, 3c
48 hr	72 hr ^b	72 hr
Me OOH OEt Me	Me O OEt OH	Me O OEt
72% Yield, 3d	66% Yield, 3e	72% Yield, 3f
48 hr	72 hr ^b	96 hr ^b

^aYields are of material isolated by silica gel chromatography. See Supporting Information for further details. ^bisoprene **2a** (600 mol%).

 $\label{eq:Table 3}$ Geranylation of α -hydroxy esters 1a-1f \emph{via} ruthenium catalyzed hydrohydroxyalkylation of myrcene 2b. a

^aAs described for Table 2. See Supporting Information for further details. ^bmyrcene **2b** (400 mol%).