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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Ruthenium-BINAP Catalyzed Alcohol C–H *tert*-Prenylation via 1,3-Enyne Transfer Hydrogenation: Beyond Stoichiometric Carbanions in Enantioselective Carbonyl Propargylation

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Supporting Information

ABSTRACT: The chiral ruthenium complex formed *in situ* from $(TFA)_2Ru(CO)(PPh_3)_2$ and (*R*)-BINAP is found to catalyze the enantioselective C–C coupling of diverse primary alcohols with the 1,3-enyne, TMSC≡CC(Me)=CH_2, to form secondary homopropargyl alcohols bearing *gem*-dimethyl groups. All reagents for this byproduct-free coupling are inexpensive and commercially available, making this protocol a practical alternative to stoichiometric carbanions in enantioselective carbonyl reverse prenylation.

Merging the characteristics of carbonyl addition and transfer hydrogenation, we have developed a broad, new class of catalytic C–C couplings that directly convert lower alcohols to higher alcohols by way of transient carbonyl-organometal pairs.[1a] This suite of catalytic methods encompasses transformations relevant to polyketide construction,[1b] for example, enantioselective alcohol C–H allylation[2] and crotylation.[3−5] Neopentyl alcohols bearing *gem*-dimethyl groups are found in numerous polyketide natural products[6a] and are ubiquitous among terpenoid natural products (Figure 1).[6b,c] Preparation of these structural motifs in enantiomerically enriched form has been accomplished through the addition of prenylmetal reagents to carbonyl compounds.[7−10] The reductive coupling of carbonyl compounds with prenyl halides or 1,1-dimethyl allene—the very precursors from which the aforementioned prenylmetal reagents are derived—would further streamline the synthesis of such neopentyl alcohols.[11−13] While racemic variants exist,[11−13] catalytic asymmetric couplings of this type were unknown until our report on the enantioselective coupling of primary alcohols with 1,1-dimethyl allene via iridium catalyzed transfer hydrogenation.[14] Enantioselective carbonyl propargylations that generate *gem*-dimethyl bearing homopropargyl neopentyl alcohols have not been described.[15] Here, using an inexpensive chiral ruthenium complex formed *in situ* from $(TFA)_2Ru(CO)(PPh_3)_2$ and (*R*)-BINAP,[16] we report the first catalytic enantioselective carbonyl *tert*-prenylation via propargylation.[17,18]

In 2008, initial studies on ruthenium catalyzed propargylation mediated by 1,3-enynes were undertaken.[17] Despite years of investigation, highly enantioselective variants were elusive. For these reactions, which employ 1,3-enynes with unsubstituted vinyl moieties (RC≡CCH=CH_2), the stereochemical fidelity of two events ultimately determines enantioselectivity: (a) hydrometalation of the 1,3-enyne to form an axially chiral allenylruthenium intermediate, and (b) carbonyl addition to form the secondary homopropargyl alcohol. For the commercially available 1,3-enyne **1a**, TMSC≡CC(Me)=CH_2, hydrometalation is no longer enantiodetermining and carbonyl addition would occur by way of a more crowded transition structure. It was reasoned these features would simplify the optimization of enantioselectivity. In the event, 1,3-enyne **1a** was exposed to *p*-bromobenzyl alcohol **2b** in

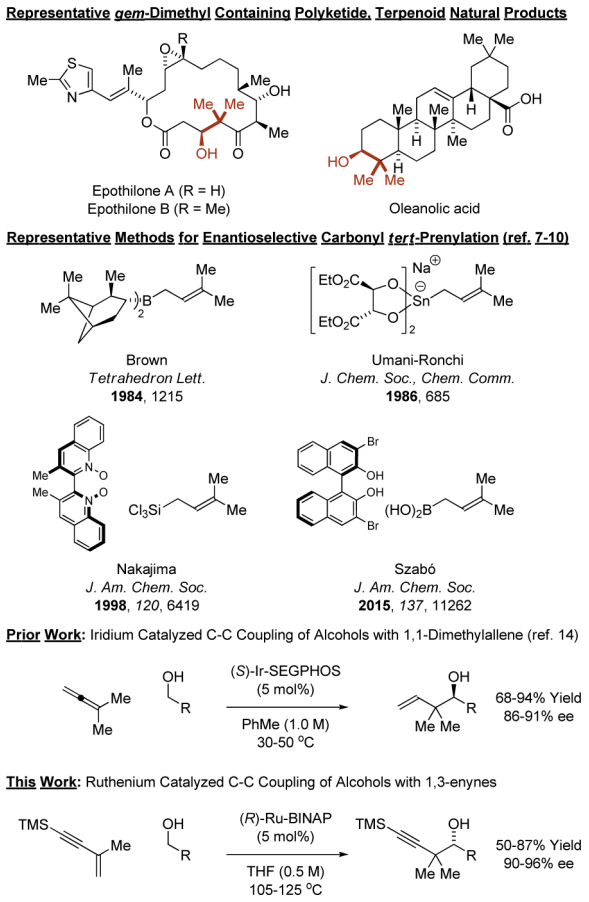


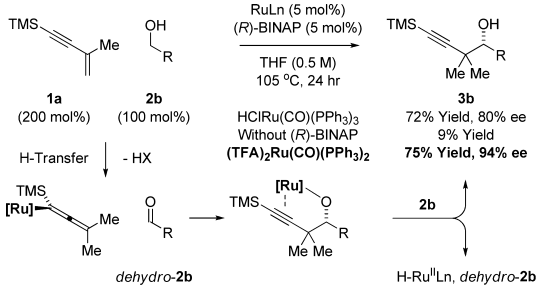
Figure 1. Carbonyl *tert*-prenylation for polyketide and terpenoid construction.

Received: March 1, 2016
Published: April 15, 2016

DOI: 10.1021/jacs.6b02279
J. Am. Chem. Soc. 2016, 138, 5238−5241

the presence of the ruthenium catalyst generated *in situ* from $HClRu(CO)(PPh_3)_3$ and (*R*)-BINAP in THF (0.5 M) at 105 °C. The desired *gem*-dimethyl bearing homopropargyl neopentyl alcohol **3b** was formed in 72% isolated yield and 80% ee (Scheme 1).

Scheme 1. Key Optimization Experiments for the Enantioselective Ruthenium C−C Catalyzed Coupling of 1,3-Enyne 1a with Benzylic Alcohol 2b[a]

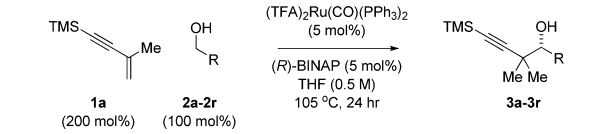


[a]Yields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. See Supporting Information for further details.

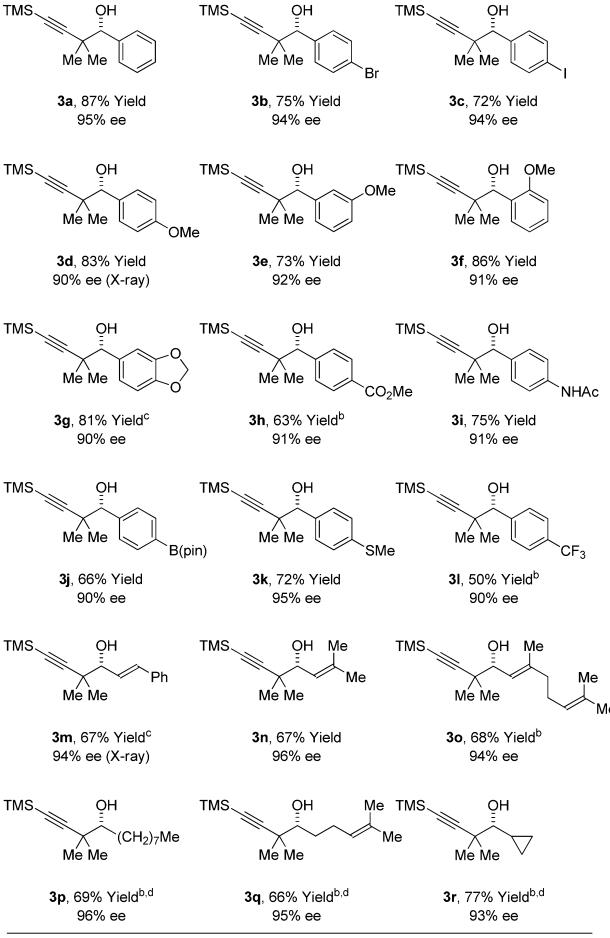
In the absence of (*R*)-BINAP under otherwise identical conditions, a racemic background reaction was identified, which might compromise the level of asymmetric induction. Using commercially available $(TFA)_2Ru(CO)(PPh_3)_2$ (TFA = F_3CCO_2) as precatalyst, a background reaction was not evident and the adduct **3b** could be obtained in 75% yield and 94% enantiomeric excess. These key optimization experiments represent only a small fraction of those performed. Further variation of the reaction parameters, including ligand, ruthenium precatalyst, temperature, solvent, and reactant stoichiometry, did not enhance conversion or selectivity. Attempted couplings using 1,3-enynes substituted by alternate trialkylsilyl groups ($Ph_2{}^tBuSi$, Me_2PhSi, $^iPr_3Si$) resulted in low conversion (Scheme 1).

To assess the scope of this process, our optimal conditions were applied to the coupling of 1,3-enyne **1a** with primary alcohols **2a−2r** (Table 1). Benzylic alcohols **2a−2l** were converted to adducts **3a−3l**, respectively, in moderate to excellent isolated yields and uniformly high levels of enantioselectivity. A range of functional groups and substitution patterns are tolerated. However, electron-deficient benzylic alcohols, for example, *p*-CF_3-substituted benzyl alcohol **2l**, were less efficient partners for coupling, which may be due to a higher energetic barrier for dehydrogenation. Allylic alcohols **2m−2o** were converted to 1,5-enynes **3m−3o**, respectively, in good yield with high enantioselectivities. Aliphatic alcohols **2p−2r** were converted to the homopropargyl neopentyl alcohols **3p−3r**, respectively, in good yield with consistently high enantioselectivity. Absolute stereochemistry was determined by single crystal X-ray diffraction analysis of compounds **3d** and **3m**. The stereochemistry of all other adducts was assigned in analogy. The chiral *β*-stereogenic alcohol citronellol **2s** undergoes coupling with complete levels of catalyst directed diastereoselectivity using the ruthenium catalyst modified by either (*R*)- or (*S*)-BINAP (eqs 1 and 2, respectively). Finally, beyond redox-neutral couplings of alcohols, 2-propanol mediated reductive coupling from the aldehyde oxidation level is possible, as illustrated in the conversion of *dehydro*-**2a** and *dehydro*-**2r** to homopropargyl alcohols **3a** and **3r**, respectively (eq 3).

Table 1. Enantioselective Ruthenium Catalyzed C−C Coupling of 1,3-Enyne 1a with Alcohols 2a−2r to Form Homopropargyl Neopentyl Alcohols 3a−3r[a]



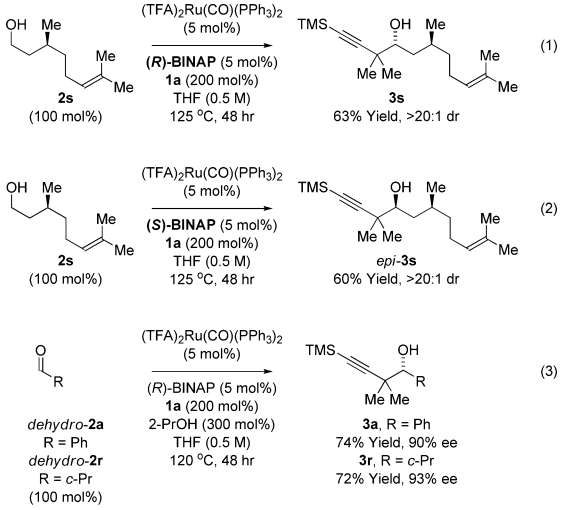
2a, R = Ph; **2b**, R = 4-Br-Ph; **2c**, R = 4-I-Ph
2d, R = 4-MeO-Ph; **2e**, R = 3-MeO-Ph; **2f**, R = 2-MeO-Ph
2g, R = 5-benzodioxole; **2h**, R = CO_2Me; **2i**, R = 4-NHAc-Ph
2j, R = 4-(pin)B-Ph; **2k**, R = 4-MeS-Ph; **2l**, R = 4-CF_3-Ph
2m, R = HC=CHPh; **2n**, R = HC=CMe_2; **2o**, geraniol
2p, R = $(CH_2)_7Me$; **2q**, R = $(CH_2)_2HC=CMe_2$; **2r**, R = *c*-Pr



[a]Yields of material isolated by silica gel chromatography. See Supporting Information for further experimental details. [b]120 °C. [c]95 °C. [d]48 h.

A catalytic mechanism has been proposed, as illustrated in the coupling of enyne **1a** with benzyl alcohol **2a** (Scheme 2). Substitution of trifluoroacetate with benzyl alcohol **2a** provides the ruthenium alkoxide **I**, which undergoes *β*-hydride elimination to furnish the aldehyde *dehydro*-**2a** and the ruthenium hydride **II**.[19] Enyne hydrometalation delivers the tertiary *σ*-propargyl complex **III**, which isomerizes to the thermodynamically favored *σ*-allenyl complex **IV**. The stoichiometric reaction of $HClRu(CO)(PPh_3)_3$ with conjugated enynes to form *σ*-allenyl complexes characterized by single crystal X-ray diffraction has been reported.[20] Coordination of the aldehyde as in complex **V** precedes carbonyl addition to form the homopropargylic ruthenium alkoxide **VI**. At this stage, release of the homopropargyl alcohol **3a** may occur with the assistance of

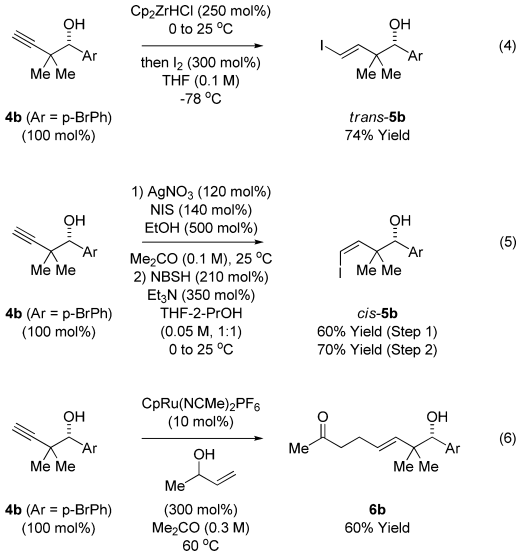
DOI: 10.1021/jacs.6b02279
J. Am. Chem. Soc. 2016, 138, 5238−5241



trifluoroacetic acid or through direct exchange with benzyl alcohol **2a**.

The veracity of our interpretation of the catalytic mechanism was challenged through two deuterium labeling experiments (Scheme 2). In both experiments, adventitious water may contribute to the loss of deuterium.[21] Ruthenium catalyzed C−C coupling of 1,3-enyne **1a** with *deuterio*-**2b** under standard conditions delivered *deuterio*-**3b** in 67% yield. Deuterium is largely retained at the carbinol position (H_c = 87% ^{2}H), suggesting there is little reversibility in the hydrogen transfer between enyne **1a** and primary alcohol *deuterio*-**2b** and that the homopropargylic alcohol product is resistant to dehydrogenation, which would erode enantioselectivity. Deuterium is incorporated at the diastereotopic methyl groups ($H_{a,b}$ = 70% ^{2}H) in a 3:1 ratio,[22] suggesting interconversion between the σ-propargyl- and σ-allenylruthenium intermediates is slightly slower than carbonyl addition. The pattern of deuterium incorporation in the reductive coupling of 1,3-enyne **1a** with *dehydro*-**2b** mediated by d_8-2-propanol is consistent with reversible hydrogen transfer between d_8-2-propanol, 1,3-enyne **1a** and *dehydro*-**2b** in advance of carbonyl addition. In the reductive coupling, which is performed at higher temperature (120 °C), a 1.7:1 ratio of deuterium is observed at the diastereotopic methyl groups ($H_{a,b}$ = 130% ^{2}H).[22]

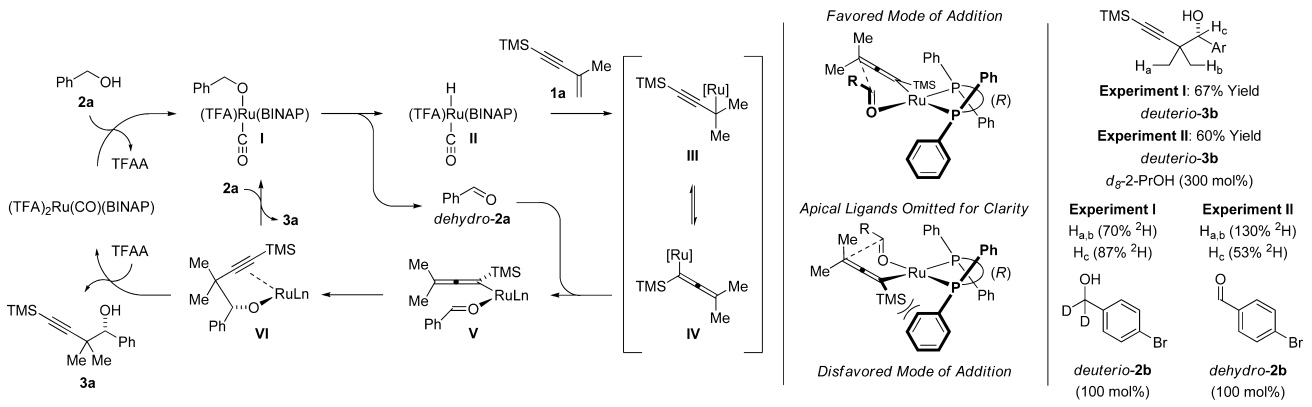
To illustrate the utility of this methodology, adduct **3b** was desilylated (not shown) and the resulting terminal alkyne **4b** was subjected to a series of transformations in the absence of hydroxyl protection (eqs 4−6). Hydrozirconation of **4b** followed by treatment with elemental iodine delivers the vinyl



iodide *trans*-**5b** in good yield (eq 4).[23] Conversion of **4b** to the corresponding acetylenic iodide[24] followed by diimide reduction of the alkyne using 2-nitrobenzenesulfonylhydrazide (NBSH)[25] delivers the isomeric vinyl iodide *cis*-**5b** (eq 5). Finally, exposure of **4b** to 3-buten-2-ol in the presence of the indicated cationic Cp-ruthenium(II) catalyst results in formation of γ,δ-unsaturated ketone **6b** (eq 6).[26]

In summary, under the conditions of transfer hydrogenation using a simple ruthenium-BINAP catalyst, diverse primary alcohols **2a**−**2s** couple with conjugated enyne **1a** to form secondary homopropargyl alcohols **3a**−**3s** bearing *gem*-dimethyl groups with uniformly high levels of enantioselectivity. Further, the same catalytic conditions promote the 2-propanol-mediated reductive coupling of aldehydes with enyne **1a** to furnish identical products in an equally efficient and selective manner. More broadly, this work and earlier studies from our laboratory[1] demonstrate that the merger of transfer hydrogenation and carbonyl addition enable a departure from stoichiometric carbanion chemistry in an ever-increasing variety of C−C bond forming processes.

Scheme 2. General Catalytic Mechanism, Stereochemical Model, and Deuterium Labeling Studies



DOI: 10.1021/jacs.6b02279
J. Am. Chem. Soc. 2016, 138, 5238−5241

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b02279.

Experimental procedures and spectral data. HPLC traces corresponding to racemic and enantiomerically enriched samples (PDF)

Single crystal X-ray diffraction data for compound **3d** (CIF)

Single crystal X-ray diffraction data for compound **3m** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The Robert A. Welch Foundation (F-0038), the NIH-NIGMS (RO1-GM069445), and the Feodor Lynen postdoctoral fellowship program administered by the Alexander von Humboldt Foundation are acknowledged for partial support of this research. We thank Mr. Daniel Eppel for skillful technical assistance.

■ REFERENCES

(1) Reviews: (a) Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 9142. (b) Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Gao, X.; Itoh, T.; Krische, M. J. *Nat. Prod. Rep.* **2014**, *31*, 504.

(2) Enantioselective alcohol C−H allylation: Shin, I.; Wang, G.; Krische, M. J. *Chem. - Eur. J.* **2014**, *20*, 13382 and references cited therein.

(3) Enantioselective alcohol C−H crotylation (iridium): Gao, X.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 12795 and references cited therein..

(4) Enantioselective alcohol C−H crotylation (ruthenium): (a) Zbieg, J. R.; Yamaguchi, E.; McInturff, E. L.; Krische, M. J. *Science* **2012**, *336*, 324. (b) McInturff, E. L.; Yamaguchi, E.; Krische, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 20628 and references cited therein.

(5) For selected reviews on enantioselective carbonyl allylation and crotylation, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23. (c) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732. (d) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (e) Yu, C.-M.; Youn, J.; Jung, H.-K. *Bull. Korean Chem. Soc.* **2006**, *27*, 463. (f) Marek, I.; Sklute, G. *Chem. Commun.* **2007**, 1683. (g) Hall, D. G. *Synlett* **2007**, *2007*, 1644. (h) Li, J.; Menche, D. *Synthesis* **2009**, *2009*, 2293. (i) Leighton, J. L. *Aldrichimica Acta* **2010**, *43*, 3. (j) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774. (k) Pasco, M.; Gilboa, N.; Mejuch, T.; Marek, I. *Organometallics* **2013**, *32*, 942.

(6) (a) Barton, D.; Nakanishi, K.; Meth-Cohn, O. Polyketides and Other Secondary Metabolites Including Fatty Acids and Their Derivatives. In *Comprehensive Natural Products Chemistry*, 1st ed.; Sankawa, U., Ed.; Elsevier: Oxford, UK, 1999; Vol. *1*. (b) *Encyclopedia of the Terpenoids*; Glasby, J. S., Ed.; Wiley: New York, 1982. (c) *Terpenes Flavors, Fragrances, Pharmaca, Pheromones*; Breitmaier, E., Ed.; Wiley-VCH: Weinheim, 2006.

(7) For enantioselective carbonyl *tert*-prenylation employing allylboron reagents, see: (a) Brown, H. C.; Jadhav, P. K. *Tetrahedron Lett.* **1984**, *25*, 1215. (b) Jadhav, P. K.; Bhat, K. S.; Perumal, T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432. (c) Roush, W. R.; Marron, T. G. *Tetrahedron Lett.* **1993**, *34*, 5421. (d) Alam, R.; Vollgraff, T.; Eriksson, L.; Szabó, K. J. *J. Am. Chem. Soc.* **2015**, *137*, 11262.

(8) For enantioselective carbonyl *tert*-prenylation employing allylindium reagents, see: (a) Loh, T.-P.; Zhou, J. R.; Li, X.-R. *Tetrahedron Lett.* **1999**, *40*, 9333. (b) Loh, T.-P.; Zhou, J. R.; Yin, Z. *Org. Lett.* **1999**, *1*, 1855.

(9) For enantioselective carbonyl *tert*-prenylation employing allylsilicon reagents, see: (a) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S.-I. *J. Am. Chem. Soc.* **1998**, *120*, 6419. (b) Nakajima, M.; Kotani, S.; Ishizuka, T.; Hashimoto, S. *Tetrahedron Lett.* **2005**, *46*, 157. (c) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488. (d) Denmark, S. E.; Fu, J.; Lawler, M. J. *J. Org. Chem.* **2006**, *71*, 1523.

(10) For enantioselective carbonyl *tert*-prenylation employing allyltin reagents, see: (a) Boldrini, G. P.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Chem. Soc., Chem. Commun.* **1986**, 685. (b) Boldrini, G. P.; Lodi, L.; Tagliavini, E.; Tarasco, C.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1987**, *52*, 5447.

(11) For Lewis acid catalyzed reductive coupling of prenyl bromide with carbonyl compounds mediated by zinc to form racemic products of *tert*-prenylation, see: (a) Maeda, H.; Shono, K.; Ohmori, H. *Chem. Pharm. Bull.* **1994**, *42*, 1808. (b) Fleury, L. M.; Kosal, A. D.; Masters, J. T.; Ashfeld, B. L. *J. Org. Chem.* **2013**, *78*, 253.

(12) For palladium catalyzed reductive coupling of 1,1-dimethylallene to carbonyl compounds mediated by $SnCl_2$ to form racemic products of *tert*-prenylation, see: Chang, H.-M.; Cheng, C.-H. *Org. Lett.* **2000**, *2*, 3439.

(13) For nickel catalyzed reductive coupling of prenyl acetate with carbonyl compounds mediated by $B_2(pin)_2$ to form racemic products of *tert*-prenylation, see: Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett.* **2012**, *14*, 1416.

(14) Han, S. B.; Kim, I. S.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 6916; Addition/Correction: *J. Am. Chem. Soc.* **2010**, *132*, 12517.

(15) For carbonyl *tert*-propargylation to form racemic *gem*-dimethyl bearing homopropargylic neopentyl alcohols, see: (a) Satoh, M.; Nomoto, Y.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1989**, *30*, 3789. (b) Nakagawa, T.; Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3207. (c) Yang, F.; Zhao, G.; Ding, Y. *Tetrahedron Lett.* **2001**, *42*, 2839. (d) Ito, H.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 15774.

(16) For the first examples of highly enantioselective ruthenium catalyzed transfer hydrogenation, see: Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562.

(17) For ruthenium catalyzed 1,3-enyne-mediated propargylations to form racemic products, see: (a) Patman, R. L.; Williams, V. M.; Bower, J. F.; Krische, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 5220. (b) Geary, L. M.; Leung, J. C.; Krische, M. J. *Chem. - Eur. J.* **2012**, *18*, 16823.

(18) For iridium catalyzed propargylations to form enantiomerically enriched products mediated by 1,3-enyne or propargyl chlorides, see: (a) Geary, L. M.; Woo, S. K.; Leung, J. C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 2972. (b) Woo, S. K.; Geary, L. M.; Krische, M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 7830.

(19) Dobson, A.; Robinson, S. D. *Inorg. Chem.* **1977**, *16*, 137.

(20) Wakatsuki, Y.; Yamazaki, H.; Maruyama, Y.; Shimizu, I. *J. Chem. Soc., Chem. Commun.* **1991**, 261.

(21) Tse, S. K. S.; Xue, P.; Lin, Z.; Jia, G. *Adv. Synth. Catal.* **2010**, *352*, 1512.

(22) The diastereotopic methyl groups of *deuterio*-**3b** could not be assigned.

(23) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679.

(24) Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 727.

(25) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.

(26) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067.

DOI: 10.1021/jacs.6b02279
J. Am. Chem. Soc. 2016, 138, 5238−5241