

Redox-Triggered C–C Coupling of Alcohols and Vinyl Epoxides: Diastereo- and Enantioselective Formation of All-Carbon Quaternary Centers *via tert*-(Hydroxy)-Prenylation

Jiajie Feng, Victoria J. Garza, and Michael J. Krische*

Department of Chemistry, University of Texas at Austin, Austin, Texas 78712, United States

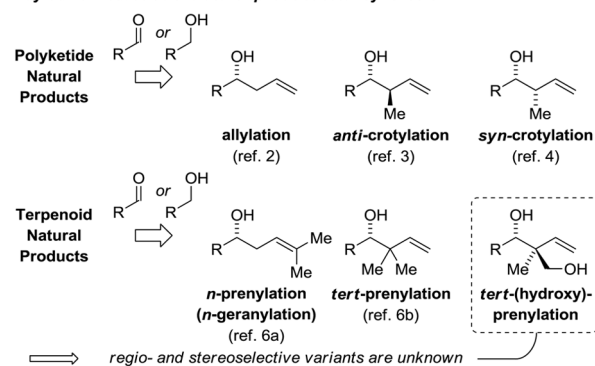
S Supporting Information

ABSTRACT: Iridium catalyzed primary alcohol oxidation triggers reductive C–O bond cleavage of isoprene oxide to form aldehyde-allyliridium pairs that combine to form products of *tert*-(hydroxy)-prenylation, a motif found in >2000 terpenoid natural products. Curtin–Hammett effects are exploited to enforce high levels of *anti*-diastereo- and enantioselectivity in the formation of an all-carbon quaternary center. The present redox-triggered carbonyl additions occur in the absence of stoichiometric by-products, premetallated reagents, and discrete alcohol-to-aldehyde redox manipulations.

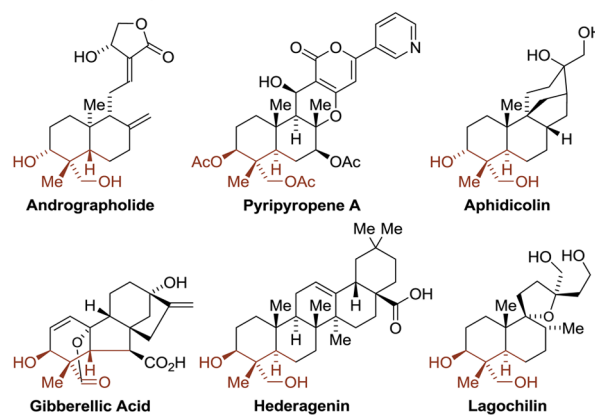
Based on a pattern of reactivity wherein alcohol oxidation triggers reductive C–C coupling,¹ a suite of catalytic enantioselective transformations for polyketide construction were developed in our laboratory (alcohol C–H allylation,² crotylation,^{3,4} and propargylation⁵). As illustrated in several total syntheses, these merged “redox-construction” protocols streamline polyketide construction, enabling the most concise routes reported, to date, to members of several natural product families.¹ To access substructures evident in terpenoid natural products, related protocols for alcohol C–H *n*-prenylation^{6a} and *tert*-prenylation^{6b} were developed. Despite the ubiquity of the *tert*-(hydroxy)-prenyl motif, which is found in over 2000 terpenoid natural products, enantioselective carbonyl *tert*-(hydroxy)-prenylation remains an unmet challenge (Figure 1).^{7,8} Here, we disclose a catalytic protocol for direct regio-, diastereo-, and enantioselective C–C coupling of primary alcohols and isoprene oxide to form products of *tert*-(hydroxy)-prenylation, and related aldehyde-isoprene oxide reductive couplings mediated by isopropanol. These alcohol C–C couplings occur in the absence of stoichiometric byproducts and represent the first enantioselective unpoled carbonyl allylations through the use of vinyl epoxides.^{7–9}

The prospect of utilizing vinyl epoxides in metal catalyzed C–C couplings of primary alcohols is rendered uncertain by competing epoxide ring opening to furnish products of *O*-allylation,^{9–12} as well as the propensity of vinyl epoxides to engage in metal catalyzed ring expansion.¹³ Remarkably, exposure of *p*-bromobenzyl alcohol **1a** to isoprene oxide **3a** in the presence of the chromatographically purified iridium–SEGPHOS complex (*R*)-Ir-**1b** in THF (0.5 M) at 60 °C led to a promising 37% yield of the desired product of *tert*-(hydroxy)-prenylation **4a** as a single regioisomer with 2:1 *anti*-diastereoselectivity and 93% enantiomeric excess (Table 1, entry 1). Use of

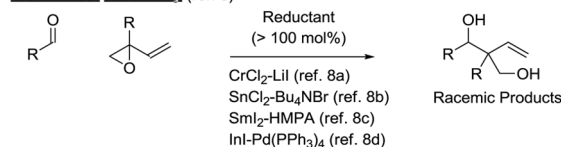
Allylative methods for natural product total synthesis



The *tert*-(hydroxy)-prenyl motif: >2000 terpenoid natural products



Established Chemistry (ref. 8)



This Work: diastereo- and enantioselective, no stoichiometric metals

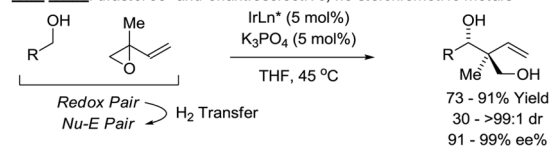
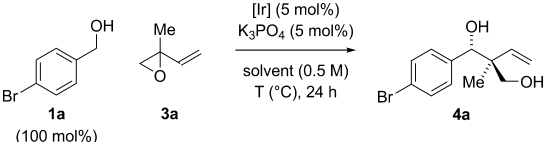


Figure 1. The *tert*-(hydroxy)-prenyl motif is found in over 2000 terpenoid natural products, yet direct methods for its regio- and stereoselective construction were hitherto unknown.

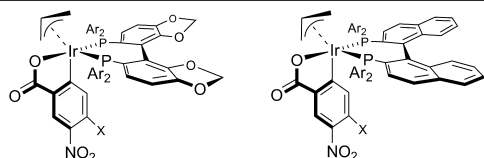
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Table 1. Selected Optimization Experiments in the Iridium Catalyzed *tert*-(Hydroxy)-Prenylation of *p*-Bromobenzyl Alcohol 1a with Isoprene Oxide 3a^a



Entry	3a (mol%)	T (°C)	[Ir]	solvent	4a yield (dr, ee%)
1 ^b	200	60	(<i>R</i>)-Ir-1b	THF	37% (2:1, 93)
2	200	60	(<i>R</i>)-Ir-1b	THF	90% (4:1, 93)
3 ^c	200	25	(<i>R</i>)-Ir-1b	THF	trace
4	200	45	(<i>R</i>)-Ir-1b	THF	95% (2.5:1, 93)
5	200	90	(<i>R</i>)-Ir-1b	THF	60% (4:1, 75)
6	200	45	(<i>R</i>)-Ir-IVb	THF	71% (30:1, 93)
⇒ 7	300	45	(<i>R</i>)-Ir-IVb	THF	91% (40:1, 94)
8	300	45	(<i>R</i>)-Ir-1a	THF	72% (17:1, 94)
9	300	45	(<i>R</i>)-Ir-1b	THF	98% (4:1, 89)
10	300	45	(<i>R</i>)-Ir-1Ia	THF	17% (17:1, 94)
11	300	45	(<i>R</i>)-Ir-1Ib	THF	71% (8:1, 94)
12	300	45	(<i>R</i>)-Ir-1IIa	THF	81% (30:1, 91)
13	300	45	(<i>R</i>)-Ir-1IIb	THF	84% (30:1, 91)
14	300	45	(<i>R</i>)-Ir-IVa	THF	66% (30:1, 92)
15	300	45	(<i>R</i>)-Ir-IVb	PhMe	45% (12:1, 95)
16	300	45	(<i>R</i>)-Ir-IVb	dioxane	91% (20:1, 93)
17	300	45	(<i>R</i>)-Ir-IVb	EtOAc	81% (30:1, 95)



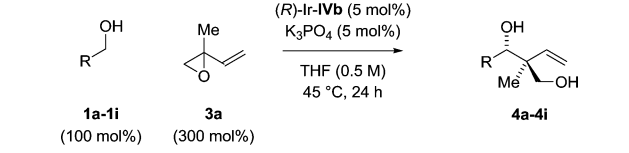
(*R*)-Ir-1a, Ar = Ph, X = H
 (*R*)-Ir-1b, Ar = Ph, X = CN
 (*R*)-Ir-1IIa, Ar = 3,5-Me₂Ph, X = H
 (*R*)-Ir-1IIb, Ar = 3,5-Me₂Ph, X = CN
 (*R*)-Ir-1IIIa, Ar = Ph, X = H
 (*R*)-Ir-1IIIb, Ar = Ph, X = CN
 (*R*)-Ir-1IVa, Ar = 4-MePh, X = H
 (*R*)-Ir-1IVb, Ar = 4-MePh, X = CN

^aYields are of material isolated by silica gel chromatography. Ir-1a (ref 6b) and Ir-1IIa (ref 2a) are characterized by X-ray diffraction. See Supporting Information for further details. ^bK₃PO₄ was omitted. ^c48 h.

K₃PO₄ (5 mol %) under these conditions improved conversion, providing 4a in 90% yield with 4:1 *anti*-diastereoselectivity and 93% enantiomeric excess (Table 1, entry 2). Although the reaction does not proceed at ambient temperature, excellent conversion is observed at 45 °C (Table 1, entries 3 and 4, respectively). Higher temperatures erode conversion and enantiomeric enrichment (Table 1, entry 5). At this stage, to identify optimal structural features of the catalyst, a series of eight chromatographically purified iridium complexes were evaluated (Table 1, entries 7–14). It became evident that, to achieve optimal energetic partitioning of the transient (*E*)- and (*Z*)- σ -allyliridium intermediates in the transition state for aldehyde addition, use of a more electron-deficient C,O-benzoate complex that embodies greater steric demand is required. This ultimately led to the identification of Ir-IVb, the (*R*)-Tol-BINAP modified C,O-benzoate complex derived from 4-CN-3-NO₂-benzoic acid, as the catalyst of choice (Table 1, entry 7). Using Ir-IVb, adduct 4a was obtained in 91% yield, 40:1 *anti*-diastereoselectivity, and 94% enantiomeric excess.

Under optimized conditions that utilize Ir-IVb as the catalyst, primary benzylic alcohols 1a–1c, allylic alcohols 1d–1f, and aliphatic alcohols 1g–1i are converted to the corresponding products of *tert*-(hydroxy)-prenylation 4a–4i (Table 2). Good to excellent isolated yields were accompanied by uniformly high levels of *anti*-diastereo- and enantioselectivity. Corresponding reactions conducted from the aldehyde oxidation level were achieved with isopropanol as a terminal reductant (Table 3). Here, as shown in the *tert*-(hydroxy)-prenylation of aldehyde

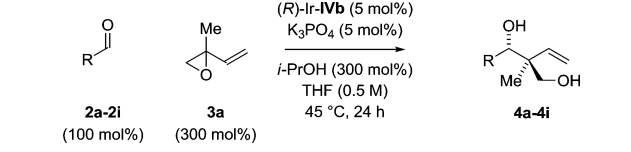
Table 2. Regio-, Diastereo-, and Enantioselective Iridium Catalyzed *tert*-(Hydroxy)-Prenylation of Alcohols 1a–1i with Isoprene Oxide 3a^a



1a, R = 4-Br-Ph 1d, geraniol 1g, R = <i>n</i> -hexyl	1b, R = piperonyl 1e, prenol alcohol 1h, R = 2-phenethyl	1c, R = 2-furyl 1f, cinnamyl alcohol 1i, R = <i>c</i> -hexylmethyl
4a, 91% Yield 40:1 dr, 94% ee (X-ray)	4b, 89% Yield 60:1 dr, 91% ee ^b	4c, 91% Yield 30:1 dr, 98% ee
4d, 73% Yield 30:1 dr, 91% ee ^{c,d}	4e, 85% Yield >99:1 dr, 93% ee ^{b,c}	4f, 85% Yield 40:1 dr, 93% ee ^d
4g, 74% Yield 40:1 dr, 93% ee ^{c,e}	4h, 76% Yield 30:1 dr, 93% ee ^e	4i, 76% Yield 30:1 dr, 99% ee ^{c,e}

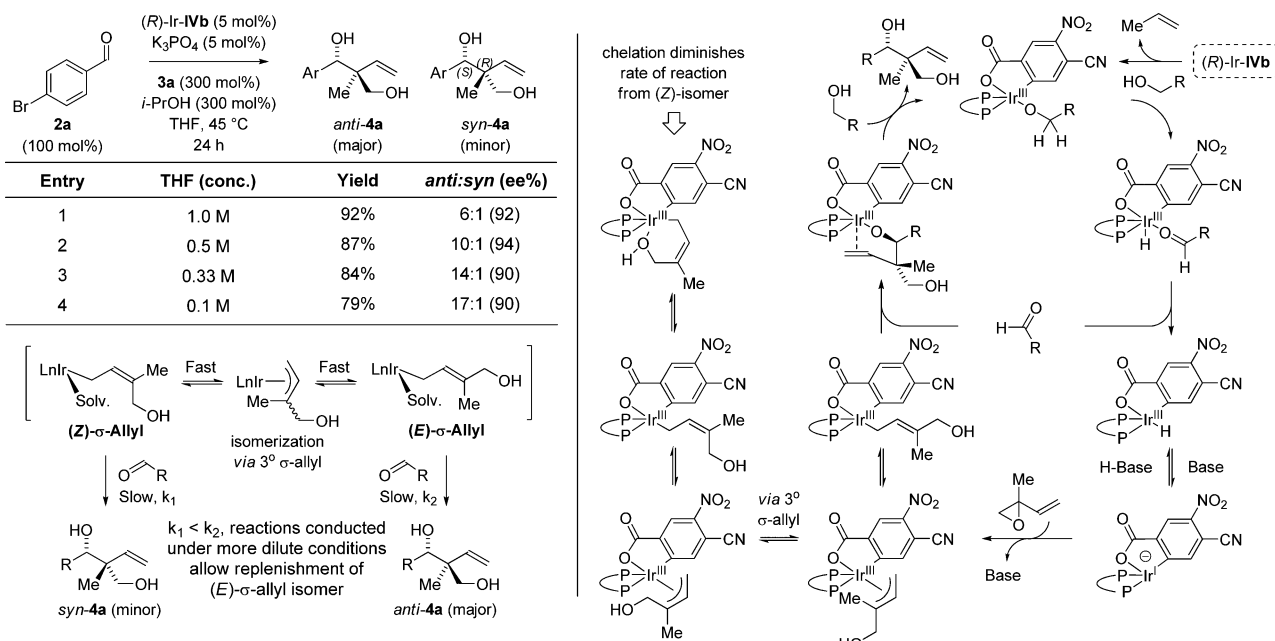
^aYields are of material isolated by silica gel chromatography. ^bTHF (1.0 M). ^c3a (400 mol %). ^dTHF (0.33 M). ^e60 °C. See Supporting Information for further details.

Table 3. Regio-, Diastereo-, and Enantioselective Iridium Catalyzed *tert*-(Hydroxy)-Prenylation of Aldehydes 2a–2i with Isoprene Oxide 3a^a



2a, R = 4-Br-Ph 2d, geraniol 2g, R = <i>n</i> -hexyl	2b, R = piperonyl 2e, R = CH=CMe ₂ 2h, R = 2-phenethyl	2c, R = 2-furyl 2f, cinnamaldehyde 2i, R = <i>c</i> -hexylmethyl
4a, 87% Yield 10:1 dr, 94% ee (X-ray)	4b, 90% Yield 50:1 dr, 90% ee ^b	4c, 91% Yield 5:1 dr, 94% ee ^{c,d}
4d, 77% Yield 20:1 dr, 94% ee	4e, 81% Yield 20:1 dr, 86% ee	4f, 76% Yield 10:1 dr, 91% ee ^e
4g, 73% Yield 12:1 dr, 93% ee ^f	4h, 91% Yield 5:1 dr, 85% ee ^f	4i, 65% Yield 20:1 dr, 95% ee ^g

^aYields are of material isolated by silica gel chromatography. ^bTHF (1.0 M). ^cTHF (0.33 M). ^d35 °C. ^eTHF (0.1 M). ^f60 °C. ^g70 °C. See Supporting Information for further details.

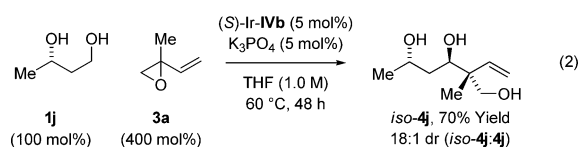
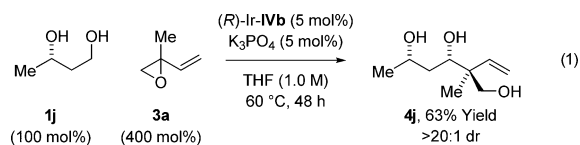
Scheme 1. Concentration Dependent *anti*-Diastereoselectivity As Illustrated in the Iridium Catalyzed *tert*-(Hydroxy)-Prenylation of Aldehyde **2a** with Isoprene Oxide **3a** and General Catalytic Mechanism^a

^aYields are of material isolated by silica gel chromatography.

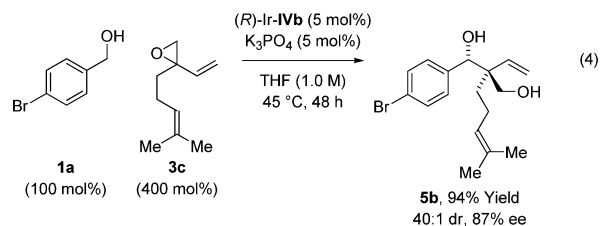
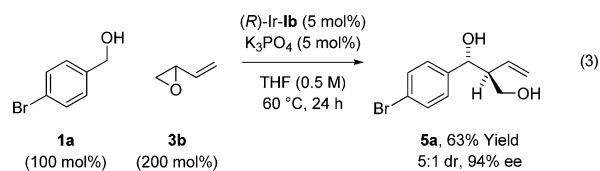
2a (Scheme 1), *anti*-diastereoselectivity was found to increase with decreasing concentration. This effect suggests a Curtin–Hammett scenario is operative wherein the relative thermodynamic stabilities of the (*Z*)- and (*E*)- σ -allyliridium intermediates do not solely determine diastereoselectivity. Rather, rate-determining carbonyl addition occurs more rapidly from the (*E*)- σ -allyliridium intermediate, requiring lower concentrations to retard the rate of carbonyl addition with respect to (*E*/*Z*)-isomerization of the allyliridium intermediate, which is required to replenish the (*E*)- σ -allyliridium intermediate from the unreacted (*Z*)- σ -allyliridium isomer.¹⁴ This effect is especially pronounced in reactions conducted from the aldehyde oxidation level, as the aldehyde concentration is higher throughout the course of the reaction, accelerating carbonyl addition. Concentration dependent kinetic resolution in the ionization of isoprene oxide **3a**, a chiral racemic material, can be excluded as recovered **3a** displays low levels of enantiomeric enrichment. Carbonyl addition by way of the (*E*)- σ -allyliridium intermediate may be faster due to minimization of dipole–dipole interactions. Reaction by way the (*Z*)- σ -allyliridium intermediate may be slow due to internal coordination of the hydroxyl group to iridium.

To further probe the scope of this process, the unprotected malic acid derived diol **1j** was reacted with isoprene oxide **3a**. As observed in related C–H allylations of glycols and higher polyols,^{2f} primary alcohol dehydrogenation is kinetically preferred. Thus, using (*R*)-Ir-IVb and (*S*)-Ir-IVb as catalysts, site-selective dehydrogenation enables *tert*-(hydroxy)-prenylation of **1j** to form **4j** and *iso*-**4j**, respectively, with excellent levels of diastereoselectivity, as determined by ¹H NMR analysis (eqs 1 and 2).

Vinyl epoxides beyond isoprene oxide also participate in redox-triggered C–C coupling. For example, the reaction of butadiene oxide **3b** with *p*-bromobenzyl alcohol **1a** delivers the product of (hydroxymethyl)-allylation **5a** in 63% yield, 5:1 *anti*-diastereoselectivity, and 94% enantiomeric excess (eq 3). The reaction of myrcene oxide **3c**¹⁵ with *p*-bromobenzyl alcohol **1a**



delivers the product of *tert*-(hydroxy)-geranylation **5b** in 94% yield, 40:1 *anti*-diastereoselectivity, and 87% enantiomeric excess (eq 4).



In summary, we report the *anti*-diastereo- and enantioselective redox-triggered C–C coupling of vinyl epoxides and alcohols to form products of carbonyl *tert*-(hydroxy)-prenylation. This process enables formation of an all-carbon quaternary center in the absence of stoichiometric byproducts

with uniformly high levels of *anti*-diastereo- and enantioselectivity, even in the case of unprotected diols. This methodology, used in combination with recently reported iron catalyzed reductive diene cyclizations,¹⁶ should broaden access to the >2000 terpenoid natural products incorporating the *tert*-(hydroxy)-prenylation motif. Studies of this type are underway and will be reported in due course.

■ ASSOCIATED CONTENT

● Supporting Information

Experimental procedures and spectral data for new compounds, including scanned images of ¹H and ¹³C NMR spectra. Single crystal X-ray diffraction data for **4a**-acetone. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

mkrische@mail.utexas.edu

Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) For a recent review on C–C bond forming hydrogenation and transfer hydrogenation, see: Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Gao, X.; Itoh, T.; Krische, M. J. *Nat. Prod. Rep.* **2014**, *31*, 504.
- (2) Allylation of alcohol C–H bonds: (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340. (b) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891. (c) Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5018. (d) Hassan, A.; Lu, Y.; Krische, M. J. *Org. Lett.* **2009**, *11*, 3112. (e) Schmitt, D. C.; Dechert-Schmitt, A.-M. R.; Krische, M. J. *Org. Lett.* **2012**, *14*, 6302. (f) Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 3195.
- (3) *anti*-Crotlylation of alcohol C–H bonds: (a) Kim, I. S.; Han, S. B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2514. (b) Gao, X.; Townsend, I. A.; Krische, M. J. *J. Org. Chem.* **2011**, *76*, 2350. (c) Gao, X.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 12795. (d) Zbieg, J. R.; Yamaguchi, E.; McInturff, E. L.; Krische, M. J. *Science* **2012**, *336*, 324.
- (4) *syn*-Crotlylation of alcohol C–H bonds: (a) Zbieg, J. R.; Moran, J.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 10582. (b) McInturff, E. L.; Yamaguchi, E.; Krische, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 20628.
- (5) Propargylation of alcohol C–H bonds: (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.
- (6) (a) Leung, J. C.; Geary, L. M.; Chen, T.-Y.; Zbieg, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 15700. (b) Han, S. B.; Kim, I. S.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 6916.
- (7) Reported *tert*-(hydroxy)-prenylation with allylboron reagents provides racemic mixtures of diastereomers: (a) Yamamoto, Y.; Takahashi, M.; Miyaura, N. *Synlett* **2002**, 128. (b) Crotti, S.; Bertolini, F.; Macchia, F.; Pineschi, M. *Org. Lett.* **2009**, *11*, 3762.
- (8) Reported *tert*-(hydroxy)-prenylations with vinyl epoxide-aldehyde reductive coupling provide racemic mixtures. Regio- and diastereomers are often observed: (a) Fujimura, O.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1990**, *55*, 1705. (b) Masuyama, Y.; Nakata, J.; Kurusu, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2598. (c) Aurrecoechea, J. M.; Iztueta, E. *Tetrahedron Lett.* **1995**, *36*, 7129. (d) Araki, S.; Kameda, K.

Tanaka, J.; Hirashita, T.; Yamamura, H.; Kawai, M. *J. Org. Chem.* **2001**, *66*, 7919.

(9) For a recent review on vinyl epoxides in organic synthesis, see: He, J.; Ling, J.; Chiu, P. *Chem. Rev.* **2014**, *114*, DOI: 10.1021/cr400709j.

(10) For palladium catalyzed allylic alkylation with vinyl epoxides and oxygen nucleophiles: (a) Trost, B. M.; McEachern, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 12702. (b) Trost, B. M.; Brown, B. S.; McEachern, E. J.; Kuhn, O. *Chem.—Eur. J.* **2003**, *9*, 4442.

(11) For cobalt catalyzed allylic alkylation with vinyl epoxides and oxygen nucleophiles: Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.

(12) For selected recent examples of catalytic allylic alkylation with vinyl epoxides in combination with various nucleophiles, see: (a) Thies, S.; Kazmaier, U. *Synlett* **2010**, 137. (b) Shaghafi, M. B.; Grote, R. E.; Jarvo, E. R. *Org. Lett.* **2011**, *13*, 5188. (c) Liu, Z.; Feng, X.; Du, H. *Org. Lett.* **2012**, *14*, 3154. (d) Zhang, Q.; Nguyen, H. M. *Chem. Sci.* **2014**, *5*, 291.

(13) For a review on the metal catalyzed ring expansion of vinyl epoxides, see: Ilardi, E. A.; Njardarson, J. T. *J. Org. Chem.* **2013**, *78*, 9533.

(14) Such Curtin–Hammett effects are evident in the ruthenium catalyzed C–C couplings of primary alcohols and allenes: Zbieg, J. R.; McInturff, E. L.; Leung, J. C.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 1141.

(15) (a) Fauchet, V.; Arreguy-San Miguel, B.; Taran, M.; Delmond, B. *Synth. Commun.* **1993**, *23*, 2503. (b) Löbermann, F.; Weisheit, L.; Trauner, D. *Org. Lett.* **2013**, *15*, 4324.

(16) (a) Lo, J. C.; Yabe, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 1304. (b) Iwasaki, K.; Wan, K. K.; Oppedisano, A.; Crossley, S. W. M.; Shenvi, R. A. *J. Am. Chem. Soc.* **2014**, *136*, 1300.