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anti-Diastereo- and Enantioselective Carbonyl (Hydroxymethyl)allylation from the Alcohol or Aldehyde Oxidation Level: Allyl Carbonates as Allylmetal Surrogates

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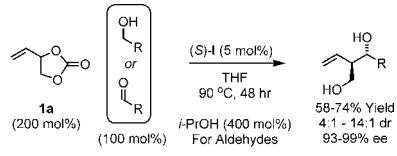
The hydroxymethyl 1,3-diol motif appears in numerous natural products,[1−4] yet asymmetric methods for carbonyl (hydroxymethyl)-allylation are largely unexplored.[5−7] In most cases, catalytic carbonyl hydroxymethylation has been accomplished through umpolung of palladium π-allyl complexes derived from 2-butene-1,4-diol carboxylates[5] or vinyl epoxides[6] in combination with metallic reductants, such as $SnCl_2$ or InI. However, control of regio- and diastereoselectivity has proven challenging. Nakajima as well as Cozzi and Umani-Ronchi each report a single example of catalytic *syn*-(hydroxymethyl)allylation, but only moderate enantioselectivities were observed.[7] To our knowledge, corresponding protocols for enantioselective *anti*-(hydroxymethyl)allylation are unknown.[8]

We have found that chiral *ortho*-cyclometallated iridium *C*,*O*-benzoates catalyze carbonyl allylation,[9a,b,e−h] crotylation,[9c,f] *tert*-prenylation[9d,f] and (alkoxy)allylation[9i] employing allyl acetate, α-methyl allyl acetate, 1,1-dimethylallene and allyl *gem*-dibenzoates as allyl donors, respectively. For such C−C bond forming transfer hydrogenations,[10] alcohols function as both hydrogen donors and carbonyl precursors, enabling identical sets of carbonyl addition products to be generated from either the alcohol or aldehyde oxidation level. In more recent work, it was found that use of the isolated iridium *C*,*O*-benzoate complex was essential for efficient reductive couplings of allylic *gem*-dibenzoates.[9i] This outcome prompted us to reexamine processes that failed using *in situ* generated catalysts, including reactions of allylic carbonates.

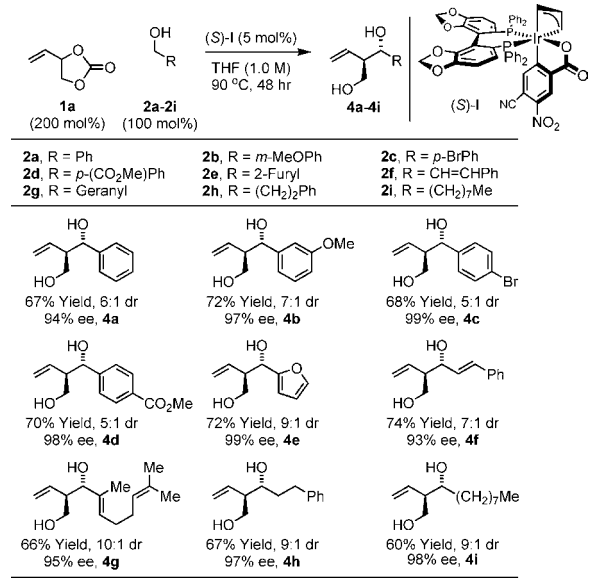
Here, we report that complex (*S*)-**I**, which is modified by the chiral phosphine ligand (*S*)-SEGPHOS,[12] serves as a single-component catalyst for the coupling of cyclic carbonate **1a** to alcohols **2a**−**2i** to furnish (hydroxymethyl)allylation products **4a**−**4i** in a highly enantiomerically enriched form. Under similar conditions in the presence of isopropanol, cyclic carbonate **1a** couples to aldehydes **3a**−**3i** to furnish an identical set of adducts **4a**−**4i** with comparable levels of selectivity. These studies represent the first general method for enantioselective carbonyl (hydroxymethyl)allylation, a process that has no highly stereoselective counterpart in conventional allylmetal chemistry.



Reactant Alcohols Dehydrogenate - Product Alcohols Do Not

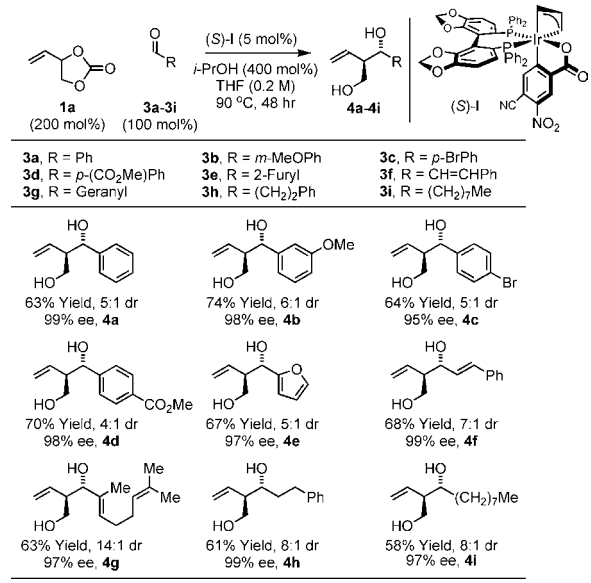
A principal concern regarding use of cyclic carbonate **1a** is the requirement that alcohols **2** selectively dehydrogenate in the presence of diol-containing products **4**. To probe this issue and to explore the feasibility of utilizing allylic carbonates as allyl donors, cyclic carbonate **1a** was exposed to benzyl alcohol **2a** in the presence of the cyclometalated complex derived from $[Ir(cod)Cl]_2$, 4-cyano-3-nitroben-

Table 1. Enantioselective (Hydroxymethyl)allylation from the Alcohol Oxidation Level[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.

Table 2. Enantioselective (Hydroxymethyl)allylation from the Aldehyde Oxidation Level[a]



[a] As described for Table 1.

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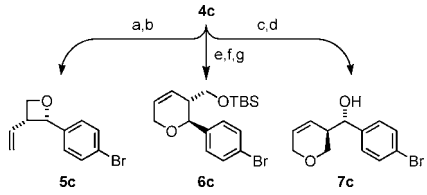
Scheme 1. Conversion of Diol **4c** to Compounds **5c**, **6c**, and **7c**[a]



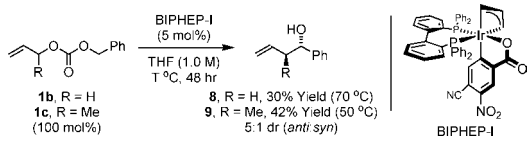
[a] Reagents: (a) NaH, TsCl, THF, 82%; (b) *n*-BuLi, THF, 92%; (c) NaH, $H_2C{=}CHCH_2Br$, THF, 82%; (d) Grubbs I, DCM, 90%; (e) TBSCl, Et_3N, DMAP, DCM, 88%; (f) NaH, $H_2C{=}CHCH_2Br$, THF, 90%; (g) Grubbs I, DCM, 91%. See Supporting Information for further details.

zoic acid, allyl acetate, and BIPHEP (2,2′-bis(diphenylphosphino)biphenyl). Remarkably, decarboxylative *anti*-(hydroxymethyl)allylation occurs smoothly to furnish the desired diol **4a** in good isolated yield. Dehydrogenation of the diol product is not observed as the homoallylic olefin of **4a** binds the single remaining coordination site essential for β-hydride elimination.[10d,11] Exclusive formation of the branched regioisomer and *anti*-diastereoselectivity are consistent with carbonyl addition from the primary (*E*)-σ-allyl iridium haptomer by way of a chairlike transition structure. Finally, unlike analogous reactions of allylic acetates which require added base,[9a−c,e−i] the decarboxylative process occurs in the absence of base or any additive.

This result prompted an assay of chiral iridium *C*,*O*-benzoates. Among the complexes screened, (*S*)-**I**, which is modified by the chiral phosphine ligand (*S*)-SEGPHOS,[12] was superior. By simply combining carbonate **1a** with alcohols **2a**−**2i** in the presence of (*S*)-**I** in THF solvent at 90 °C, products of (hydroxymethyl)allylation **4a**−**4i** are generated with good *anti*-diastereoselectivities (5:1−10:1 dr) and exceptional levels of enantiocontrol (93−99% ee). The isolated yields were moderate (60−74%) due to incomplete consumption of alcohols **2a**−**2i** (Table 1). Higher yields are obtained if the reaction time is extended.

Aldehydes **3a**−**3i** are converted to an equivalent set of adducts **4a**−**4i** under similar conditions employing isopropanol as the terminal reductant. Comparable isolated yields (58−74%), *anti*-diastereoselectivities (4:1−14:1 dr), and enantioselectivities (95−99% ee) are observed (Table 2). Thus, identical adducts **4a**−**4i** are produced with equal facility from the alcohol or aldehyde oxidation level. Construction of oxetane **5c** in two steps from adduct **4c** serves to illustrate the utility of the (hydroxymethyl)allylation process. Similarly, pyrans **6c** and **7c** are prepared in three and two steps from adduct **4c**, respectively (Scheme 1).

The ability of allylic carbonate **1a** to participate in intermolecular decarboxylative C−C bond forming transfer hydrogenation prompted us to investigate the decarboxylative C−C coupling of allyl-benzyl carbonates **1b** and **1c**. Remarkably, using the achiral iridium catalyst BIPHEP-**I**, the desired products of C−C bond formation **8** and **9** were produced in modest yield along with recovered benzyl alcohol. As a molar excess of allyl donor is required to enforce high conversion in the iridium catalyzed carbonyl allylations we describe, high-yielding decarboxylative C−C coupling of allyl carbonates will require improved second-generation catalysts.



In summary, we report the first general method for enantioselective carbonyl (hydroxymethyl)allylation. Future studies will focus on the development of related C−C couplings of alcohols and π-unsaturated reactants.

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Supporting Information Available: Experimental procedures, spectral data for new compounds, including scanned images of HPLC traces, as well as ^1H and ^{13}C NMR spectra. This material is available free of charge *via* the Internet at http://pubs.acs.org.

References

(1) Tedanolide, 13-deoxytedanolide, and the myriaporones incorporate the hydroxymethyl 1,3-diol motif. For total syntheses, see: (a) Pérez, M.; del Pozo, C.; Reyes, F.; Rodríguez, A.; Francesch, A.; Echavarren, A. M.; Cuevas, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 1724. (b) Taylor, R. E.; Fleming, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1728. (c) Julian, L. D.; Newcom, J. S.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 6186. (d) Ehrlich, G.; Hassfeld, J.; Eggert, U.; Kalesse, M. *J. Am. Chem. Soc.* **2006**, *128*, 14038. (e) Smith, A. B., III; Lee, D. *J. Am. Chem. Soc.* **2007**, *129*, 10957. (f) Dunetz, J. R.; Julian, L. D.; Newcom, J. S.; Roush, W. R. *J. Am. Chem. Soc.* **2008**, *130*, 16407. (g) Ehrlich, G.; Hassfeld, J.; Eggert, U.; Kalesse, M. *Chem.—Eur. J.* **2008**, *14*, 2232.

(2) Tylosin, its aglycone tylonolide, and *O*-mycinosyltylonolide incorporate the hydroxymethyl 1,3-diol motif. For total syntheses, see: (a) Tatsuta, K.; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. *Tetrahedron Lett.* **1981**, *22*, 3997. (b) Tatsuta, K.; Amemiya, Y.; Kanemura, Y.; Takahashi, H.; Kinoshita, M. *Tetrahedron Lett.* **1982**, *23*, 3375. (c) Masamune, S.; Lu, L. D.-L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc.* **1982**, *104*, 5523. (d) Grieco, P. A.; Inanaga, J.; Lin, N.-H.; Yanami, T. *J. Am. Chem. Soc.* **1982**, *104*, 5781. (e) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2030. (f) Tanaka, T.; Oikawa, Y.; Hamada, T.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 3651. (g) Tanaka, T.; Oikawa, Y.; Hamada, T.; Yonemitsu, O. *Chem. Pharm. Bull.* **1987**, *35*, 2219.

(3) The mycinamicins incorporate the hydroxymethyl 1,3-diol motif. For total syntheses, see: (a) Suzuki, K.; Matsumoto, T.; Tsuchihashi, G.-i. *Chem. Lett.* **1987**, 113. (b) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G.-i. *Tetrahedron Lett.* **1988**, *29*, 3575.

(4) For other natural products that incorporate the hydroxymethyl 1,3-diol motif, see Supporting Information.

(5) For (hydroxymethyl)allylation *via* palladium catalyzed reductive coupling of allylic carboxylates, see: (a) Masuyama, Y.; Takahara, J. P.; Kurusu, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4473. (b) Masuyama, Y.; Otake, K.; Kurusu, Y. *Tetrahedron Lett.* **1988**, *29*, 3563. (c) Takahara, J. P.; Masuyama, Y.; Kurusu, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2577.

(6) For (hydroxymethyl)allylation *via* palladium catalyzed reductive coupling of vinyl epoxides, see: (a) Araki, S.; Kameda, K.; Tanaka, J.; Hirashita, T.; Yamamura, H.; Kawai, M. *J. Org. Chem.* **2001**, *66*, 7919. (b) Gagliardo, M.; Selander, N.; Mehendale, N. C.; van Koten, G.; Klein Gebbink, R. J. M.; Szabó, K. J. *Chem.—Eur. J.* **2008**, *14*, 4800.

(7) For catalytic enantioselective (hydroxymethyl)allylation, see: (a) Bandini, M.; Cozzi, P. G.; Licciulli, S.; Umani-Ronchi, A. *Synthesis* **2004**, 409. (b) Nakajima, M.; Saito, M.; Hashimoto, S. *Chem. Pharm. Bull.* **2000**, *48*, 306.

(8) For selected reviews on enantioselective carbonyl allylation and crotylation, see: (a) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **1982**, *21*, 555. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23. (d) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732. (e) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (f) Yu, C.-M.; Youn, J.; Jung, H.-K. *Bull. Korean Chem. Soc.* **2006**, *27*, 463. (g) Marek, I.; Sklute, G. *Chem. Commun.* **2007**, 1683. (h) Hall, D. G. *Synlett* **2007**, 1644.

(9) For enantioselective carbonyl allylation, crotylation, and reverse prenylation *via* iridium catalyzed C−C bond forming transfer hydrogenation, see: (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) Kim, I. S.; Han, S. B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2514. (d) Han, S. B.; Kim, I. S.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 6916. (e) Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5018. (f) Itoh, J.; Han, S. B.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6316. (g) Lu, Y.; Krische, M. J. *Org. Lett.* **2009**, *11*, 3108. (h) Hassan, A.; Lu, Y.; Krische, M. J. *Org. Lett.* **2009**, *11*, 3112. (i) Han, S. B.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 1760. (j) For a recent application in total synthesis, see: Harsh, P.; O'Doherty, G. A. *Tetrahedron* **2009**, *65*, 5051.

(10) For recent reviews on C−C bond forming transfer hydrogenation, see: (a) Patman, R. L.; Bower, J. F.; Kim, I. S.; Krische, M. J. *Aldrichimica Acta* **2008**, *41*, 95. (b) Shibahara, F.; Krische, M. J. *Chem. Lett.* **2008**, *37*, 1102. (c) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34. (d) Han, S. B.; Kim, I. S.; Krische, M. J. *Chem. Commun.* **2009**, 7278.

(11) In response to a reviewers comment: the olefin moiety of homoallylic alcohol products **4a**−**4i** appears to bind the iridium center more strongly than the olefin moiety of allylic alcohols such as cinnamyl alcohol **2f** (five-membererd versus four-membered chelate). Thus, alcohol reactants **2a**−**2i** dehydrogenate whereas homoallylic alcohol products do not.

(12) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

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