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Diastereo- and Enantioselective *anti*-Alkoxyallylation Employing Allylic *gem*-Dicarboxylates as Allyl Donors *via* Iridium Catalyzed Transfer Hydrogenation

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Abstract

Enantioselective transfer hydrogenation of *gem*-dibenzoate **1e** in the presence of aromatic, α , β -unsaturated or aliphatic aldehydes **2a–2i** mediated by isopropanol and employing a cyclometallated iridium *C,O*-benzoate derived from allyl acetate, 4-cyano-3-nitrobenzoic acid and (*R*)-SEGPHOS delivers products of alkoxyallylation **3a–3i**, **4a**, **4e**, **4f** and **4i** in good isolated yields (63–82%), good to excellent diastereoselectivities (10:1 – 18:1 dr) and exceptional enantioselectivities (90–99% ee). This protocol provides an alternative to the use of pre-metallated nucleophiles in carbonyl alkoxyallylation.

Enantioselective carbonyl allylation represents an important class of C-C bond forming reactions that have found broad use in organic synthesis.¹ Among allylation protocols, enantioselective aldehyde α -alkoxyallylation provides an efficient means of generating allylic vicinal diol substructures. To date, asymmetric *syn*-additions of this type have employed chirally modified alkoxy-substituted allylmethyl reagents based on boron,² aluminum,³ titanium,⁴ indium⁵ and tin.⁶ Indirect enantioselective aldehyde α -alkoxyallylation can be achieved using chirally modified reagents that promote aldehyde α -silylallylation or α -borylallylation followed by oxidation of the C-Si or C-B bond, respectively.^{7,8,9} For direct methods, stereocontrolled access to *anti*-alkoxyallylation products, is problematic due to difficulties encountered in the synthesis of the requisite (*E*)-configured allylmethyl reagents.¹⁰ This fact has motivated alternate approaches to the *anti*-1-ene-2,3-diol functional group

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Supporting information available: Experimental procedures, HPLC data, and spectral data for new compounds. This material is available free of charge *via* the internet at <http://pubs.acs.org>.

array. For example, enantioselective catalytic dihydroxylation of conjugated dienes was attempted,¹¹ but *syn*-1-ene-2,3-diols were formed. To our knowledge, only Duthaler's chiral allyl-titanium reagent⁴ has been employed in direct enantioselective *anti*-alkoxyallylation, however, only a single highly stereoselective example was established and use of this allylmetal reagent is attended by considerable "pre-activation".¹² To date, *catalytic* enantioselective methods for aldehyde *syn*- or *anti*- α -alkoxyallylation remain elusive.¹³

In connection with ongoing efforts to develop C-C bond forming hydrogenations beyond hydroformylation,¹⁴ we recently disclosed enantioselective protocols for carbonyl allylation, 15a,b,e-h crotylation 15c,f and reverse prenylation 15d,f under transfer hydrogenation conditions employing an *ortho*-cyclometallated iridium *C,O*-benzoate catalyst. Here, using the *ortho*-cyclometallated iridium catalyst generated from [Ir(cod)Cl]₂, 4-cyano-3-nitrobenzoic acid, allyl acetate and the chiral phosphine ligand (*R*)-SEGPHOS,¹⁶ we report that allylic *gem*-dibenzoate **1e** engages in reductive coupling to diverse aldehydes to furnish products of *anti*-alkoxyallylation with good levels of diastereocontrol and exceptional levels of enantio-enrichment.

In an initial experiment, acrolein *gem*-diacetate **1a** was subjected to isopropanol mediated transfer hydrogenation in the presence of aldehyde **2c** employing the *ortho*-cyclometallated iridium *C,O*-benzoate derived from [Ir(cod)Cl]₂, 4-cyano-3-nitrobenzoic acid, allyl acetate and BIPHEP (2,2'-bis(diphenylphosphino)biphenyl). To our delight, the product of reductive coupling (**1a**, R = Ac) was obtained in 74% yield with complete branched regioselectivity and as a 4:1 mixture of diastereomers favoring the *anti*-stereoisomer. Because partial migration of the acetyl moiety was observed under the reaction conditions, exhaustive acetylation was performed *in situ* upon complete consumption of **2c** and the product was isolated as the vicinal diacetate. In an effort to enhance diastereoselectivity, a series of acrolein *gem*-dicarboxylates were assayed under identical conditions. It was hoped that a sufficiently large carboxy group would direct partitioning of (*E*)- and (*Z*)- σ -allyl iridium intermediates to favor the (*E*)- σ -allyl isomer, which upon addition to the aldehyde through a Zimmerman-Traxler type transition structure¹⁷ would deliver the *anti*-diastereomer. Indeed, *gem*-dicarboxylates **1a–1d**, which incorporate acetyl, propionyl, isobutyryl and pivaloyl moieties, respectively, deliver products of alkoxyallylation with increasing levels of *anti*-diastereoselection. However, decreasing conversion in response to increased steric demand of the carboxy moiety is observed. As earlier studies suggest carbonyl addition is turnover-limiting,^{15b,c} it is likely that increased steric demand of the carboxy group impedes carbonyl addition. The best level of *anti*-diastereoselectivity and conversion is observed using the *gem*-dibenzoate **1e** (11:1 dr), perhaps because it is large enough to direct formation of the (*E*)- σ -allyl isomer yet does not impede approach of the aldehyde due to the flat topography of aromatic ring (Table 1).

Having identified acrolein *gem*-dibenzoate **1e** as an effective reagent for *anti*-diastereoselective alkoxyallylation, enantioselective variants of this process were explored. Accordingly, representative C₂-symmetric phosphine ligands were used to prepare a small set of chiral iridium *C,O*-benzoate complexes, which were assayed for their ability to promote efficient *anti*-diastereo- and enantioselective alkoxyallylation. The complex (*R*)-SEGPHOS-**I** proved superior to all others assayed and was used to establish reaction scope. It was found that aromatic, heteroaromatic, α , β -unsaturated and aliphatic aldehydes **2a–2i** are converted to the corresponding alkoxyallylation products **3a–3i** in good isolated yields (63–82%), good to

excellent diastereoselectivities (10:1–18:1 dr) and exceptional enantioselectivities (90–99% ee) (Table 2). Generation of the cyclometallated catalyst *in situ*, as previously reported, **15a–c** led to poor isolated yields of product. In the absence of isopropanol, primary alcohols are not suitable substrates due to benzoyl transfer.

To access the diol products directly, an alternate protocol involving saponification *in situ* was explored. Here, aldehydes **2a**, **2e**, **2f**, and **2i** are exposed to standard reactions conditions employing *gem*-dibenzoate **1e** as the allyl donor. Upon complete consumption of the aldehyde, methanol and potassium carbonate are added to the reaction mixture. The diol-containing products **4a**, **4e**, **4f**, and **4i** are obtained in good isolated yields and with *anti*-diastereo- and enantioselectivities consistent with those observed for the corresponding dibenzoates **3a**, **3e**, **3f**, and **3i** (Table 3).

In summary, under the conditions of iridium catalyzed transfer hydrogenation employing isopropanol as the terminal reductant, *gem*-dibenzoate **1e** reductively couples to aldehydes **2a–2i** to furnish products of *anti*-alkoxyallylation with excellent relative and absolute stereocontrol. This protocol provides an alternative to the use of pre-metallated nucleophiles and chiral auxiliaries in asymmetric carbonyl alkoxyallylation, providing direct stereocontrolled access to the *anti*-1-ene-2,3-diol functional group array under catalytic conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. For selected reviews on enantioselective carbonyl allylation, see: (a) Denmark SE, Fu J. Chem Rev 2003;103:2763. [PubMed: 12914480] (b) Yu CM, Youn J, Jung HK. Bull Korean Chem Soc 2006;27:463. (c) Marek I, Sklute G. Chem Commun 2007:1683. (d) Hall DG. Synlett 2007:1644. (e) Lombardo M, Trombini C. Chem Rev 2007;107:3843. [PubMed: 17713958]
2. For enantioselective aldehyde alkoxyallylation employing alkoxy-substituted allylboron reagents, see: (a) Wuts PGM, Bigelow SS. J Chem Soc, Chem Commun 1984:736. (b) Brown HC, Jadhav PK, Bhat KS. J Am Chem Soc 1988;110:1535. (c) Sebelius S, Szabó KJ. Eur J Org Chem 2005:2539.
3. For aldehyde alkoxyallylation employing alkoxy-substituted allyl aluminum reagents, see: Chika, J-i; Takei, H. Tetrahedron Lett 1998;39:605.
4. For aldehyde alkoxyallylation employing alkoxy-substituted allyl titanium reagents, see: Hafner A, Duthaler RO, Marti R, Rihs G, Rothe-Streit P, Schwarzenbach F. J Am Chem Soc 1992;114:2321.. To our knowledge, Duthaler's chirally modified allyl-titanium reagent is unique in its ability to promote highly stereocontrolled "direct" *anti*-alkoxyallylation of aldehydes. For an indirect method, see reference 8.
5. For aldehyde alkoxyallylation employing alkoxy-substituted allyl indium reagents, see: (a) Marshall JA, Hinkle KW. J Org Chem 1995;60:1920. (b) Marshall JA, Hinkle KW. J Org Chem 1996;61:105.
6. For aldehyde alkoxyallylation employing alkoxy-substituted allyl tin reagents, see: (a) Marshall JA, Gung WY. Tetrahedron Lett 1989;30:2183. (b) Marshall JA, Luke GP. J Org Chem 1991;56:483. (c) Yamamoto Y, Kobayashi K, Okano H, Kadota I. J Org Chem 1992;57:7003. (d) Roush WR, VanNieuwenhze MS. J Am Chem Soc 1994;116:8536. (e) Kadota I, Kobayashi K, Okano H, Asao N, Yamamoto Y. Bull Soc Chim Fr 1995;132:615.. (f) reference 5 cited above.
7. For an early example of indirect alkoxyallylation where M₁ = Li, M₂ = Si, see: Tamao K, Nakajo E, Ito Y. J Org Chem 1987;52:957.

8. For indirect enantioselective alkoxyallylation employing 1,3-bimetallic allyl transfer agents where $M_1 = M_2 = B$, see: Brown HC, Narla G. *J Org Chem* 1995;60:4686.
9. For indirect enantioselective alkoxyallylation employing 1,3-bimetallic allyl transfer agents where $M_1 = B$, $M_2 = Si$, see: (a) Roush WR, Grover PT, Lin X. *Tetrahedron Lett* 1990;31:7563. (b) Barrett AGM, Malecha JW. *J Org Chem* 1991;56:5243. (c) Roush WR, Grover PT. *Tetrahedron* 1992;48:1981. (d) Hunt JA, Roush WR. *Tetrahedron Lett* 1995;36:501. (e) Yamamoto Y, Miyairi T, Ohmura T, Miyaura N. *J Org Chem* 1999;64:296. [PubMed: 11674118] (f) Roush WR, Pinchuk AN, Micalizio GC. *Tetrahedron Lett* 2000;41:9413. (g) Lira R, Roush WR. *Org Lett* 2007;9:4315. [PubMed: 17867698]
10. Direct metallation of allyl ethers is (Z)-selective due to chelation. Hence, access to (E)-configured alkoxy-substituted allylmetal reagents and the resulting anti-1,2-diols has been problematic. For a more detailed discussion, see: Moriya T, Suzuki A, Miyaura N. *Tetrahedron Lett* 1995;36:1887. and references 8 and 9c
11. Upon exposure of cis, trans-2,3-hexadiene to conditions for osmium catalyzed asymmetric dihydroxylation, the trans-olefin reacts preferentially to provide the syn-diol: Xu D, Crispino GA, Sharpless KB. *J Am Chem Soc* 1992;114:7570.
12. As described in reference 14e, preactivation refers to the degree of separation between a reagent and the parent feedstock(s).
13. For catalytic enantioselective aldehyde alkoxyallylation *via* Nozaki-Hiyama coupling, see: Lombardo M, Licciulli S, Morganti S, Trombini C. *Chem Commun* 2003:1762.. This process employs 3-chloropropenyl pivalate as the allyl donor and only modest levels diastereo- and enantioselectivity are observed.
14. For selected reviews on C-C bond forming hydrogenation and transfer hydrogenation, see: (a) Ngai MY, Kong JR, Krische MJ. *J Org Chem* 2007;72:1063. [PubMed: 17288361] (b) Skucas E, Ngai MY, Komanduri V, Krische MJ. *Acc Chem Res* 2007;40:1394. [PubMed: 17784728] (c) Shibahara F, Krische MJ. *Chem Lett* 2008;37:1102. (d) Bower JF, Kim IS, Patman RL, Krische MJ. *Angew Chem Int Ed* 2009;48:34. (e) Han SB, Kim IS, Krische MJ. *Chem Commun* 2009:7278.
15. For enantioselective carbonyl allylation, crotylation and tert-prenylation via iridium catalyzed C-C bond forming transfer hydrogenation, see: (a) Kim IS, Ngai MY, Krische MJ. *J Am Chem Soc* 2008;130:6340. [PubMed: 18444616] (b) Kim IS, Ngai MY, Krische MJ. *J Am Chem Soc* 2008;130:14891. [PubMed: 18841896] (c) Kim IS, Han SB, Krische MJ. *J Am Chem Soc* 2009;131:2514. [PubMed: 19191498] (d) Han SB, Kim IS, Han H, Krische MJ. *J Am Chem Soc* 2009;131:6916. [PubMed: 19453190] (e) Lu Y, Kim IS, Hassan A, Del Valle DJ, Krische MJ. *Angew Chem Int Ed* 2009;48:5018. (f) Itoh J, Han SB, Krische MJ. *Angew Chem Int Ed* 2009;48:6313. (g) Lu Y, Krische MJ. *Org Lett* 2009;11:3108. [PubMed: 19586066] (h) Hassan A, Lu Y, Krische MJ. *Org Lett* 2009;11:3112. [PubMed: 19586067]
16. Saito T, Yokozawa T, Ishizaki T, Moroi T, Sayo N, Miura T, Kumobayashi H. *Adv Synth Catal* 2001;343:264.
17. Zimmerman HE, Traxler MD. *J Am Chem Soc* 1957;79:1920.

Table 1

Optimizing *anti*-diastereoselectivity in the alkoxyallylation of aldehydes employing *gem*-dicarboxylates derived from acrolein.^a

Entry	<i>gem</i> -Dicarboxylate	Yield 3c (a-e)	Diastereomeric Ratio
1	1a , R = COMe	74%	4:1 dr (<i>anti:syn</i>)
2	1b , R = COEt	65%	5:1 dr (<i>anti:syn</i>)
3	1c , R = CO ⁱ Pr	32%	8:1 dr (<i>anti:syn</i>)
4	1d , R = CO ⁱ Bu	15%	10:1 dr (<i>anti:syn</i>)
5	1e , R = CPh	82%	11:1 dr (<i>anti:syn</i>)

^aYields are of material isolated by silica gel chromatography. See Supporting Information for further details.

Table 2

anti-Diastereo and enantioselective alkoxyallylation of aldehydes employing *gem*-dibenzoate **1e** derived from acrolein.^a

2a , R = Ph	2b , R = <i>p</i> -BrPh	2c , R = <i>p</i> -(CO ₂ Me)Ph
2d , R = <i>p</i> -NO ₂ Ph	2e , R = 6-Br-2-Pyr	2f , R = CH=CHPh
2g , R = CH=CHCH ₂ Me	2h , R = (CH ₂) ₃ OTBS	2i , R = (CH ₂) ₇ Me

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

^b72 hr.

Table 3

anti-Diastereo and enantioselective alkoxyallylation of aldehydes to furnish diol products **4a**, **4e**, **4f** and **4i**.^a

^aYields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by chiral stationary phase GC analysis. See Supporting Information for further details.