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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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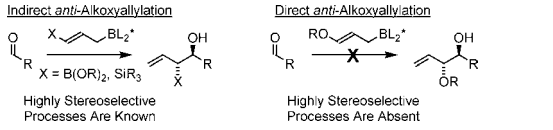
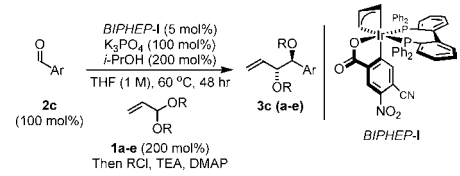
Enantioselective carbonyl allylation represents an important class of C−C bond-forming reactions that have found broad use in organic synthesis.[1] Among allylation protocols, enantioselective aldehyde α-alkoxyallylation provides an efficient means of generating allylic vicinal diol substructures. To date, asymmetric *syn*-additions of this type have employed chirally modified alkoxy-substituted allylmetal reagents based on boron,[2] aluminum,[3] titanium,[4] indium,[5] or 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.[7−9] For direct methods, stereocontrolled access to *anti*-alkoxyallylation products is problematic because of difficulties encountered in the synthesis of the requisite *E*-configured allylmetal reagents.[10] This fact has motivated alternate approaches to the *anti*-1-ene-2,3-diol functional group 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 allyltitanium reagent[4] has been employed in direct enantioselective *anti*-alkoxyallylation; however, only a single highly stereoselective example was reported, and use of this allylmetal reagent is attended by considerable "preactivation".[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 *tert*-prenylation[15d,f] under transfer hydrogenation conditions employing an *ortho*-cyclometalated iridium *C*,*O*-benzoate catalyst. Here, using the *ortho*-cyclometalated 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 enantioenrichment.

In an initial experiment, acrolein *gem*-diacetate **1a** was subjected to isopropyl alcohol-mediated transfer hydrogenation in the presence of aldehyde **2c** employing the ortho-cyclometalated iridium *C*,*O*-benzoate derived from $[Ir(cod)Cl]_2$, 4-cyano-3-nitrobenzoic acid, allyl acetate, and 2,2′-bis(diphenylphosphino)biphenyl (BIPHEP). To our delight, the product of reductive coupling (**3c**(**a**), R = Ac) was obtained in 74% yield with complete branched regioselectivity 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 the diastereoselectivity, a series of acrolein *gem*-dicarboxylates were assayed under identical conditions. It was hoped that a sufficiently large carboxy group would direct the 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 structure[17] would deliver the *anti*-diastereomer. Indeed, *gem*-dicarboxylates **1a**−**d**, which incorporate acetyl, propionyl, isobutyryl, and pivaloyl moieties, respectively, delivered products of alkoxyallylation with increasing levels of *anti*-diastereoselectivity. However, decreasing conversion in response to the increased steric demand of the carboxy moiety was observed. As earlier studies suggest that 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 was observed using *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).

Table 1. Optimizing Anti Diastereoselectivity in the Alkoxyallylation of Aldehydes Employing *gem*-Dicarboxylates Derived from Acrolein[a]



entry	*gem*-dicarboxylate	yield of **3c** (**a**−**e**)	dr (anti/syn)
1	**1a**, R = COMe	74%	4:1
2	**1b**, R = COEt	65%	5:1
3	**1c**, R = CO^{i}Pr	32%	8:1
4	**1d**, R = CO^{t}Bu	15%	10:1
5	**1e**, R = COPh	82%	11:1

[a] Yields are of material isolated by silica gel chromatography. See the Supporting Information for further details.

After identification of acrolein *gem*-dibenzoate **1e** as an effective reagent for *anti*-diastereoselective alkoxyallylation, enantioselective variants of this process were explored. Accordingly, representative C_2-symmetric phosphine ligands were used to prepare a small set of chiral iridium *C*,*O*-benzoate complexes that 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 the reaction scope. It was found that aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldehydes **2a**−**i** were converted to the corresponding alkoxyallylation products **3a**−**i** in good isolated yields (63−82%) with good to excellent diastereoselectivities

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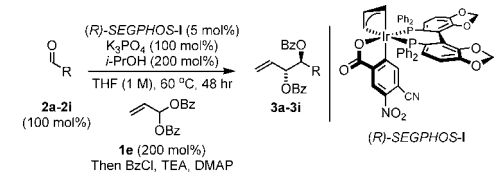
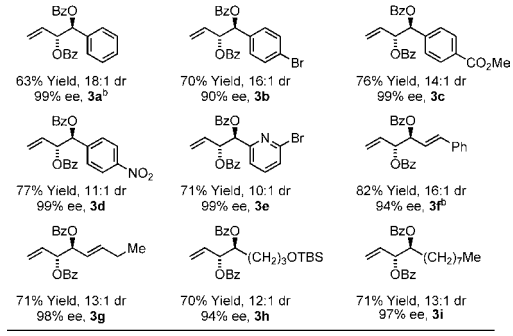
Table 2. *anti*-Diastereo- and Enantioselective Alkoxyallylation of Aldehydes Employing *gem*-Dibenzoate **1e** Derived from Acrolein[a]

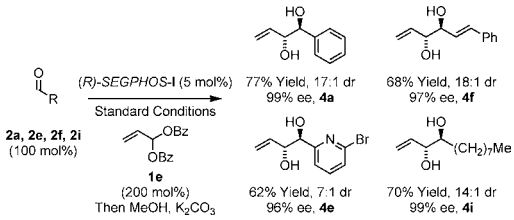


2a, R = Ph; **2b**, R = *p*-BrPh; **2c**, R = *p*-(CO$_2$Me)Ph
2d, R = *p*-NO$_2$Ph; **2e**, R = 6-Br-2-Pyr; **2f**, R = CH=CHPh
2g, R = CH=CHCH$_2$Me; **2h**, R = (CH$_2$)$_3$OTBS; **2i**, R = (CH$_2$)$_7$Me



[a] Yields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. See the Supporting Information for further details. [b] Reaction time 72 h.

Table 3. *anti*-Diastereo- and Enantioselective Alkoxyallylation of Aldehydes To Furnish Diol Products **4a**, **4e**, **4f**, and **4i**[a]



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

(10:1 to 18:1 dr) and exceptional enantioselectivities (90−99% ee) (Table 2). Generation of the cyclometalated catalyst in situ, as previously reported,[15a−c] led to poor isolated yields of product. In the absence of isopropyl alcohol, primary alcohols were 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** were exposed to the standard reaction conditions employing *gem*-dibenzoate **1e** as the allyl donor. Upon complete consumption of the aldehyde, methanol and potassium carbonate were added to the reaction mixture. The diol-containing products **4a**, **4e**, **4f**, and **4i** were obtained in good isolated yields and with *anti*-diastereo- and enantioselectivities roughly equivalent 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 isopropyl alcohol as the terminal reductant, *gem*-dibenzoate **1e** reductively couples to aldehydes **2a**−**i** to furnish products of *anti*-alkoxyallylation with excellent relative and absolute stereocontrol. This protocol provides an alternative to the use of premetalated 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.

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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.

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