Published in final edited form as:

Angew Chem Int Ed Engl. 2013 March 11; 52(11): . doi:10.1002/anie.201209863.

Site-Selective Primary Alcohol Dehydrogenation Enables Protecting Group-Free Diastereoselective C-C Coupling of 1,3-Glycols and Allyl Acetate**

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Keywords

Iridium; Allylation; Polyketide; Diastereoselectivity; Transfer Hydrogenation

The ability to discriminate between like functional groups, so as to transform organic molecules in a “site-selective” or “chemoselective” manner,^[1] precludes the requirement of protecting groups and, hence, carries the potential to dramatically enhance synthetic efficiency.^[2] Though an exceptionally daunting challenge, systematic efforts toward catalytic methods for the site-selective transformation of polyfunctional molecules have begun to emerge. For example, Miller^[3] and Taylor^[4] report catalytic methods for the site-selective manipulation of diols and higher polyols. Site-selective metal catalyzed cross-couplings have been catalogued.^[5] Further, in what is perhaps the most formidable theatre for site-selectivity, impressive advances in catalytic methods for C-H functionalization have been achieved, as illustrated in the seminal work of Barton,^[6a] Murai and Kakiuchi,^[6b] and in more recent studies by Davies,^[6c] Sanford,^[6d] Yu,^[6e] Daugulis,^[6f] Baran^[6g] and others.

Although methods for the site-selective diol oxidation have been reported, including iridium catalyzed methods,^[7,8] merged redox-C-C bond construction events involving chemoselective polyol oxidation are unknown.^[9] In connection with ongoing studies of C-C bond forming hydrogenation, we recently found that certain iridium and ruthenium complexes catalyze hydrogen exchange between primary alcohols and α -unsaturated reactants to generate organometal-aldehyde pairs that combine to form products of carbonyl addition.^[10] In these transformations, primary alcohol reactants are subject to oxidation, yet the secondary alcohol products are not. This fact, and the ability to perform certain transfer hydrogenative couplings in aqueous organic media, suggested unprotected polyols might engage in site-selective carbinol CH-functionalization. Here, we report that the cyclometallated α -allyliridium *C*,*O*-benzoate complex derived from (*R*)- or (*S*)-SEGPHOS and 4-cyano-3-nitro-benzoic acid catalyzes the redox-triggered allylation^[11,12] of unprotected diols and higher polyols with a pronounced kinetic preference for primary alcohol dehydrogenation. In this way, chemo- and stereoselective carbinol CH-allylation of polyols is achieved in the absence of protecting groups, chiral auxiliaries, premetallated reagents and discrete alcohol-to-aldehyde oxidation (Scheme 1).

** Acknowledgment is made to the Robert A. Welch Foundation (F-0038) and the NIH-NIGMS (RO1-GM093905) for partial financial support. The Cancer Prevention Research Institute of Texas (CPRIT) is acknowledged for Postdoctoral Fellowship support (D.C.S.). Dr. Taichiro Touge of Takasago is thanked for the generous donation of SEGPHOS ligands.

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In an initial set of experiments, a series of chromatographically isolated η^5 -allyliridium complexes modified by (*S*)-SEGPPOS and 4-substituted-3-nitro-*C,O*-benzoate moieties were assayed in the allylation of diol **1** (Figure 1). The iridium complexes (*R*)-Ir-b-NO₂ and (*S*)-Ir-a-CN, displayed roughly equal efficiency, with the latter providing the 1,3-*syn*-diol **2a** in 67% yield with complete levels of catalyst-directed diastereoselectivity^[13] and without any detectable oxidation of the unprotected secondary alcohol. Similarly, using the enantiomeric catalyst (*R*)-Ir-CN, diol **1** was transformed to the 1,3-*anti*-diol **2b** in 59% yield without any detectable over-oxidation. Inspired by these results, diols **3**, **5**, and **7** were subjected to the enantiomeric catalysts (*S*)- and (*R*)-Ir-CN. In each case, the corresponding products of allylation **4a** and **4b**, **6a** and **6b**, and **8a** and **8b**, respectively, were formed in good to excellent yields with exceptional control of diastereoselectivity and without oxidation of the unprotected secondary hydroxyl moieties. Notably, the preparation of **4b** in four steps through iterative redox-triggered allylation represents a synthesis of the C11-C18 fragment of the oxopolyene macrolide RK-397, which was previously prepared in 7 steps from the same starting material (Scheme 2).^[14] Finally, even the unprotected triol **9** is converted to adducts **10a** and **10b** using the enantiomeric catalysts (*S*)- and (*R*)-Ir-CN, respectively, in good yields and complete levels of catalyst directed diastereoselectivity (Table 1).

An even more challenging class of substrate is represented by the unprotected chiral η^5 -stereogenic alcohols **11** and **13**. Exposure of 1,3-glycol **11** to the catalyst (*S*)-Ir-NO₂ under standard conditions delivers the product of allylation **12a** as a 9:1 mixture of diastereomers. In this case, the diastereofacial bias of the catalyst matches the preference of the transient aldehyde for Felkin-Anh addition.^[15] In the mismatched case using the enantiomeric catalyst (*R*)-Ir-NO₂, the diastereomeric product **12b** is formed as a 3:1 mixture of diastereomers. Similarly, the 1,3-glycol **13** is converted to diastereomeric allylation products **14a** (5:1 dr) and **14b** (3:1 dr) using (*S*)-Ir-NO₂ and (*R*)-Ir-NO₂, respectively. For the allylation of unprotected chiral η^5 -stereogenic alcohols **11** and **13**, the minor diastereomer obtained principally stems from epimerization of the transient η^5 -stereogenic aldehyde (Table 2). Although the levels of catalyst-directed diastereoselectivity are modest, these results are significant in view of the intractability of η^5 -hydroxy- η^5 -substituted aldehydes. Whereas substrate-directed allylation of unprotected η^5 -hydroxyaldehydes is possible with allylindium reagents to provide *anti*-1,3-diols,^[16a] the corresponding 1,3-*syn*-allylation is only possible with stoichiometric allyltitanium-TADDOL complexes.^[16b]

It has been posited, and generally appreciated, that an ideal synthesis would be composed solely of construction events.^[9,17] As organic compounds, by their very definition, are compounds composed of carbon and hydrogen, catalytic C-C bond constructions that occur through the addition, transfer or removal of hydrogen potentially provides a direct means of accessing native molecule structure in a highly atom efficient manner. Site-selectivity further enhances efficiency by dispensing with the need to install and remove protecting groups. The site-selective redox-allylations described in this account, which occur by virtue of the strong kinetic preference of the iridium catalyst for primary alcohol dehydrogenation, allow chemo- and stereoselective carbinol CH-allylation in the absence of protecting groups, chiral auxiliaries, premetallated reagents and discrete alcohol-to-aldehyde redox manipulations, thus representing one step toward fulfillment of these ideals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Cyclometallated iridium catalysts for site-selective allylation.

Scheme 1.

Site selective dehydrogenation enables protecting group-free allylation of diols.

Scheme 2. Synthesis of the C11-C18 fragment of RK-397.^a^aAs described for Table 1.

Table 1

Protecting group-free catalyst-directed diastereoselective C-C coupling of chiral diols **1**, **3**, **5**, **7** and **9** with allyl acetate.^a

^a Cited yields are of diastereomeric mixtures isolated by silica gel chromatography. Stereoisomeric ratios were determined by ¹H NMR analysis of crude reaction mixtures (major diastereomer:sum of two minor diastereomers). See Supporting Information for further experimental details.

Table 2

Protecting group-free catalyst-directed diastereoselective C-C coupling of chiral , -stereogenic alcohols **11** and **13** with allyl acetate.^a

^a As described for Table 1.