Synthetic Methods

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

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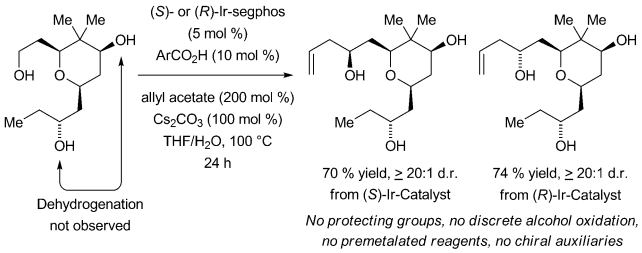
The ability to discriminate between like functional groups, so as to transform organic molecules in a site-selective or chemoselective manner,[1] precludes the requirement of protecting groups and, hence, carries the potential to dramatically enhance synthetic efficiency.[2] Though an exceptionally daunting challenge, systematic efforts toward catalytic methods for the site-selective transformation of polyfunctional molecules have begun to emerge. For example, the groups of 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,[6b] Murai and Kakiuchi,[6a] and in more recent studies by the groups of Davies,[6c] Sanford,[6d] Yu,[6e] Daugulis,[6f] Baran,[6g] and others.

Although methods for 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 π-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. Herein, we report that the cyclometallated π-allyliridium *C*,*O*-benzoate complex derived from (*R*)- or (*S*)-segphos (segphos = 5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole) 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).



Scheme 1. Site-selective dehydrogenation enables the protecting-group-free allylation of diols.

In an initial set of experiments, a series of chromatographically isolated π-allyliridium complexes modified by (*S*)-segphos and 4-substituted-3-nitro-*C*,*O*-benzoate moieties were assayed in the allylation of diol **1** (Figure 1). The iridium

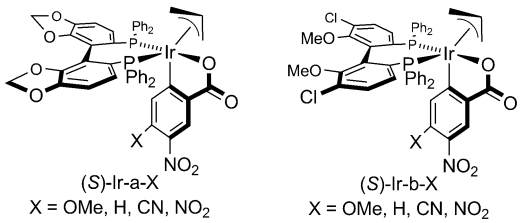


Figure 1. Cyclometallated iridium catalysts for site-selective allylation.

complexes (*R*)-Ir-b-NO_2 and (*S*)-Ir-a-CN, displayed roughly equal effectiveness, 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 into 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

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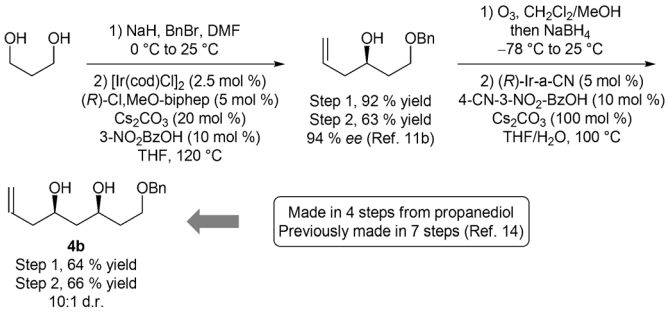
each case, the corresponding products of allylation, **4a** and **4b**, **6a** and **6b**, and **8a** and **8b**, respectively, were formed in good to excellent yields with exceptional control of diastereoselectivity and without oxidation of the unprotected secondary hydroxy moieties. Notably, the preparation 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 seven steps from the same starting material (Scheme 2).[14] Finally, even the unprotected triol **9** is converted into adducts **10a** and **10b** using the enantiomeric catalysts (*S*)- and (*R*)-Ir-CN, respectively, in good yields and with high levels of catalyst-directed diastereoselectivity (Table 1).

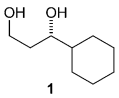
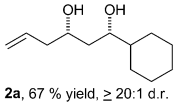
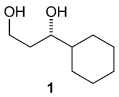
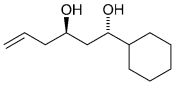
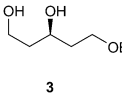
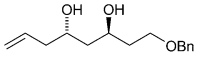
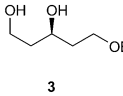
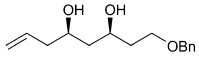
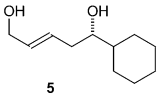
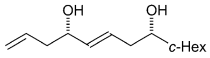
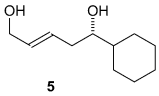
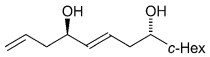
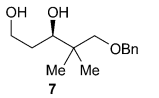
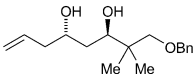
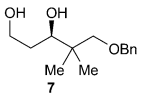
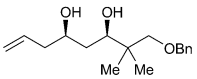
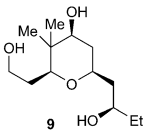
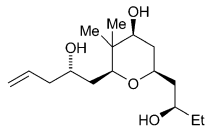
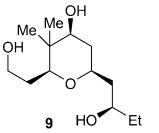
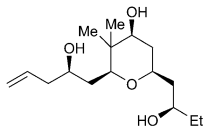


Scheme 2. Synthesis of the C11–C18 fragment of RK-397, as described in Table 1. Bn = benzyl, Bz = benzoyl, Cl,MeO-biphep = 2,2′-bis(diphenylphosphanyl)-5,5′-dichloro-6,6′-dimethoxy-1,1′-biphenyl, cod = 1,5-cyclooctadiene, DMF = dimethylformamide.

An even more challenging class of substrate is represented by the unprotected chiral β,γ-stereogenic alcohols **11** and **13**. Exposure of 1,3-glycol **11** to the catalyst (*S*)-Ir-NO_2 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-NO_2, the diastereomeric product **12b** is formed as a 3:1 mixture of diastereomers. Similarly, the 1,3-glycol **13** is converted into diastereomeric allylation products **14a** (5:1 d.r.) and **14b** (3:1 d.r.) using (*S*)-Ir-NO_2 and (*R*)-Ir-NO_2, respectively. For the allylation of unprotected chiral β,γ-stereogenic alcohols **11** and **13**, the minor diastereomer obtained principally stems from epimerization of the transient α-stereogenic aldehyde (Table 2). Although the levels of catalyst-directed diastereoselectivity are modest, these results are significant in view of the intractability of unprotected β-hydroxy-α-substituted aldehydes. Whereas substrate-directed allylation of unprotected β-hydroxyaldehydes is possible with allylindium reagents to provide *anti*-1,3-diols,[16a] the corresponding 1,3-*syn*-allylation is only possible using stoichiometric allyltitanium–taddol complexes.[16b]

In conclusion, 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,

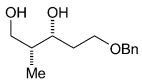
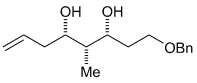
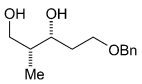
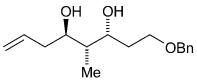
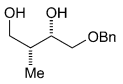
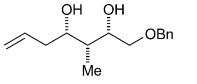
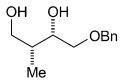
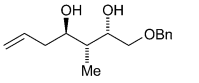
Table 1: Protecting-group-free catalyst-directed diastereoselective C–C coupling of chiral diols **1**, **3**, **5**, **7**, and **9** with allyl acetate.[a]

Entry	Diol	Ir catalyst	Product[b]
1	 **1**	(*S*)-Ir-a-CN	 **2a**, 67 % yield, ≥ 20:1 d.r.
2	 **1**	(*R*)-Ir-a-CN	 **2b**, 59 % yield, ≥ 20:1 d.r.
3	 **3**	(*S*)-Ir-a-CN	 **4a**, 73 % yield, 10:1 d.r.
4	 **3**	(*R*)-Ir-a-CN	 **4b**, 66 % yield, 10:1 d.r.
5	 **5**	(*S*)-Ir-a-CN	 **6a**, 74 % yield, 16:1 d.r.
6	 **5**	(*R*)-Ir-a-CN	 **6b**, 74 % yield, 19:1 d.r.
7	 **7**	(*S*)-Ir-a-CN	 **8a**, 69 % yield, 9:1 d.r.
8	 **7**	(*R*)-Ir-a-CN	 **8b**, 67 % yield, 18:1 d.r.
9	 **9**	(*S*)-Ir-a-CN	 **10a**, 70 % yield, ≥ 20:1 d.r.
10	 **9**	(*R*)-Ir-a-CN	 **10b**, 74 % yield, ≥ 20:1 d.r.

[a] Reaction conditions: allyl acetate (200 mol%), diol (100 mol%), Ir catalyst (5 mol%), 4-cyano-3-nitro-benzoic acid (10 mol%), and Cs_2CO_3 (100 mol%) in THF/H_2O (14:1, 0.4 M) at 100 °C for 24 h. [b] Cited yields are of diastereomeric mixtures isolated by silica gel chromatography. Stereoisomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures (major diastereomer/sum of two minor diastereomers). See the Supporting Information for further experimental details. Ac = acetyl, Bn = benzyl, *c*-Hex = cyclohexyl.

catalytic C–C bond constructions that occur through the addition, transfer, or removal of hydrogen potentially provide a direct means of accessing native molecule structure in an atom-efficient manner. Site selectivity further enhances synthetic efficiency by dispensing with the need to install and remove protecting groups. The site-selective redox-allylations described herein, which occur by virtue of the strong kinetic preference of the iridium catalyst for primary alcohol dehydrogenation, allow chemo- and stereoselective

Table 2: Protecting-group-free catalyst-directed diastereoselective C–C coupling of chiral β,γ-stereogenic alcohols **11** and **13** with allyl acetate.[a]

Entry	Diol	Ir catalyst	Product[b]
1	 **11**	(*S*)-Ir-b-NO_2	 **12a**, 75 % yield, 9:1 d.r.
2	 **11**	(*R*)-Ir-b-NO_2	 **12b**, 62 % yield, 3:1 d.r.
3	 **13**	(*S*)-Ir-b-NO_2	 **14a**, 76 % yield, 5:1 d.r.
4	 **13**	(*R*)-Ir-b-NO_2	 **14b**, 80 % yield, 3:1 d.r.

[a] Reaction conditions: allyl acetate (200 mol%), diol (100 mol%), Ir catalyst (5 mol%), 4-cyano-3-nitro-benzoic acid (10 mol%), and Cs_2CO_3 (100 mol%) in THF/H_2O (14:1, 0.4 M) at 100 °C for 24 h. [b] Cited yields are of diastereomeric mixtures isolated by silica gel chromatography. Stereoisomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures (major diastereomer/sum of two minor diastereomers). See the Supporting Information for further experimental details.

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 the fulfillment of these ideals.

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[1] The term chemoselectivity broadly refers to the ability to selectively act upon like or unlike functional groups: B. M. Trost, *Science* **1983**, *219*, 245 – 250. The term site-selectivity will be used in the more specific context of discrimination between like functional groups en route to constitutionally isomeric products.

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[4] a) D. Lee, M. S. Taylor, *J. Am. Chem. Soc.* **2011**, *133*, 3724 – 3727; b) L. Chan, M. S. Taylor, *Org. Lett.* **2011**, *13*, 3090 – 3093; c) C. Gouliaras, D. Lee, L. Chan, M. S. Taylor, *J. Am. Chem. Soc.* **2011**, *133*, 13926 – 13929; d) D. Lee, C. L. Williamson, L. Chan, M. S. Taylor, *J. Am. Chem. Soc.* **2012**, *134*, 8260 – 8267.

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