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Asymmetric Iridium Catalyzed C-C Coupling of Chiral Diols via Site-Selective Redox-Triggered Carbonyl Addition

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Abstract

Cyclometalated π -allyliridium *C,O*-benzoate complexes modified by axially chiral chelating phosphine ligands display a pronounced kinetic preference for primary alcohol dehydrogenation, enabling highly site-selective redox-triggered carbonyl additions of chiral primary-secondary 1,3-diols with exceptional levels of catalyst-directed diastereoselectivity. Unlike conventional methods for carbonyl allylation, the present redox-triggered alcohol C-H functionalizations bypass the use of protecting groups, premetalated reagents, and discrete alcohol-to-aldehyde redox reactions.

Keywords

iridium; allylation; dehydrogenation; transfer hydrogenation; diastereoselectivity; enantioselectivity; green chemistry; polyketides

1. Introduction

As stated by Hendrickson, “*The ideal synthesis creates a complex skeleton... in a sequence only of successive construction reactions involving no intermediary refunctionalizations, and leading directly to the structure of the target, not only its skeleton but also its correctly placed functionality.*” [1]. This perspective elegantly captures many core aspects of synthetic efficiency, including the importance of merged redox-construction events (“redox-economy”) [2], regio-, chemo- and stereoselectivity [3, 4], as well as protecting group-free chemical synthesis [5, 6, 7]. A modernistic revision of this statement also would encompass considerations of atom-efficiency [8,9] and waste generation [10, 11, 12], overall process relevance [13, 14, 15, 16], and the minimization of preactivation: the degree of separation between reagent and feedstock [17]. Considerable progress toward these ideals has been made, especially in terms of controlling regio- and stereoselectivity. Indeed, 40 years have elapsed since the first industrial catalytic asymmetric synthesis was reported by Monsanto for the synthesis of L-DOPA, which utilizes a byproduct-free enantioselective hydrogenation [18, 19]. The design of chemoselective catalysts capable of discriminating between like functional groups, so as to transform organic molecules in a “site-selective” manner, poses a more formidable challenge, but offers the benefit of removing steps from a synthetic route otherwise required for the installation and removal of protecting groups. As demonstrated in the work of Kawabata [20, 21, 22, 23, 24, 25, 26], Miller [27, 28, 29, 30, 31, 32, 33, 34, 35], and Taylor [36, 37, 38, 39, 40, 41], the site-selective modification of

carbohydrates and other natural polyols directly delivers compounds that would normally require lengthy stepwise preparations, or may be entirely inaccessible by other means.

By exploiting the native reducing ability of alcohols, we have developed a broad, new family of redox-triggered carbonyl additions where hydrogen transfer from alcohols to π -unsaturated reactants results in the formation of electrophile-nucleophile pairs, which combine to give products of formal alcohol C-H functionalization [42, 43, 44, 45, 46, 47, 48]. These processes are redox-efficient as they merge alcohol oxidation and C-C bond construction events, bypassing discrete alcohol-to-aldehyde redox reactions, as well as manipulations required for the stoichiometric formation of premetalated reagents. One of the most useful processes based on this pattern of reactivity is the enantioselective iridium catalyzed coupling of primary alcohols with allyl acetate to form secondary homoallylic alcohols (Scheme 1) [49, 50, 51, 52, 53]. Such primary alcohol C-allylations have been applied to the syntheses of diverse polyketide natural products, resulting in the most concise routes reported, to date [54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64].

As documented in the review literature [65], iridium catalysts are remarkably sensitive to the steric environment of reactants and, in the context of diol oxidation, display a pronounced kinetic preference for dehydrogenation of the more accessible alcohol [66, 67, 68, 69, 70, 71, 72, 73, 74]. As illustrated in the context of oxidative lactonization, nearly complete levels of discrimination between two primary alcohols are achieved on the basis of remote steric effects: beta- *versus* gamma-branching (Scheme 2, eq. 1) [71]. In the case of benzylic diols, the energetic barrier to dehydrogenation should be lower, potentially diminishing selectivity in the dehydrogenation event. Yet as illustrated in the oxidative lactonization of the enantiomerically enriched 1,4-diol, oxidation at the primary benzylic alcohol occurs with complete levels of selectivity even though it is more endothermic than oxidation of the secondary benzylic alcohol (Scheme 2, eq. 2) [73].

The exceptional levels of chemoselectivity displayed in iridium catalyzed diol oxidation led us to explore the feasibility of redox-triggered diol C-allylations that are both asymmetric and site-selective [75, 76]. Such transformations would represent a significant departure from classical protocols for carbonyl allylation [77, 78, 79, 80, 81, 82, 83], as they would forego the requirement of protecting groups, premetalated reagents, chiral auxiliaries and discrete alcohol-to-aldehyde oxidation, thus representing an additional step toward fulfillment of the “Hendricksonian ideal.” In this review, we summarize our progress on chiral diol C-H functionalization *via* asymmetric redox-triggered carbonyl addition.

2. Redox-Triggered Allylation of Diols

The redox-triggered carbonyl allylations developed in our laboratory are catalyzed by cyclometalated π -allyliridium C,O-benzoate complexes bearing chiral phosphine ligands. These reactions proceed in accordance with the indicated general catalytic mechanism (Scheme 3). Entry into the catalytic cycles occurs upon protonolytic cleavage of the π -allyliridium complex by the primary alcohol reactant. The resulting iridium alkoxide suffers β -hydride elimination to furnish an aldehyde and an iridium hydride. Competition experiments demonstrate rapid and reversible β -hydride elimination, that is, alcohol

hydrogenation-dehydrogenation, in advance of carbonyl addition [50]. Deprotonation of the iridium hydride provides an anionic iridium(I) intermediate, which undergoes oxidative addition with allyl acetate to regenerate the starting π -allyliridium *C,O*-benzoate complex. Now, with aldehyde present, carbonyl addition occurs, resulting in the formation of a homoallylic iridium alkoxide that exchanges with the primary alcohol reactant to close the catalytic cycle. Use of isotopically labeled allyl acetate with deuterium at the allylic position, intervention of symmetric iridium π -allyl intermediate was corroborated [50]. Interestingly, both catalytic efficiency and stereoselectivity is dramatically influenced by remote substituents at the 4-position of the *C,O*-benzoate moiety. As suggested by single crystal X-ray diffraction data of a series of π -allyliridium *C,O*-benzoate complexes (Scheme 3) [53], more electron deficient *C,O*-benzoate ligands enhance Lewis acidity at iridium, which may accelerate turnover limiting carbonyl addition with respect to protonolytic cleavage of the π -allyl and other competing processes.

Our initial studies focused on the catalyst-directed diastereo- and site-selective allylation of chiral 1,3-diols **1a–1c**. The feasibility of these processes was rendered uncertain by the well-documented instability of the β -hydroxy aldehyde intermediates, which under equilibrium conditions exist predominantly as dimers [84, 85, 86]. Nevertheless, the chromatographically isolated π -allyliridium *C,O*-benzoate complex derived from [Ir(cod)Cl]₂, (*S*)- or (*R*)-SEGPPOS, 4-cyano-3-nitro-benzoic acid and allyl acetate proved to be effective in these transformations (Scheme 4) [75]. Specifically, in aqueous THF solvent at 100 °C, 1,3-diols **1a–1c** (100 mol%) were exposed to the (*S*)- or (*R*)-SEGPPOS modified catalyst (5 mol%), allyl acetate (200 mol%), cesium carbonate (100 mol%), and 4-cyano-3-nitro-benzoic acid (10 mol%) to furnish diastereomers **2a–2c** and **3a–3c**, respectively. In each case, the homoallylic alcohols were obtained in good to excellent yields with high levels of catalyst-directed diastereoselectivity. Oxidation of the unprotected secondary alcohol of the reaction products **2a–2c** and **3a–3c** (or reactants **1a–1c**) was not observed. Notably, the synthesis of **3b**, which is accomplished in four steps through iterative redox-triggered allylation, was previously achieved through a 7-step sequence from the same starting material [87], illustrating the inherent step-economy of protecting group-free chemical synthesis.

To further assess scope and determine whether a 1,3-relationship between hydroxyl moieties is required to suppress over-oxidation, the 1,5-diol **1d** and 1,5-triol **1e** were exposed to the chromatographically isolated π -allyliridium *C,O*-benzoate modified by (*S*)- or (*R*)-SEGPPOS and 4-cyano-3-nitro-benzoic acid under the aforesaid conditions (Scheme 5) [75]. The corresponding homoallylic alcohols **2d**, **2e** and **3d**, **3e** were obtained in good to excellent yields with high levels of catalyst-directed diastereoselectivity. The site-selective C-C coupling of **1e** to form either **2e** or **3e**, where one of three unprotected alcohols undergoes modification, suggest this technology will be applicable to the late stage modification of even more complex polyhydroxylated compounds, such as type I polyketides.

The unprotected chiral β,γ -stereogenic alcohols **1f** and **1g** represent an especially challenging class of reactant, as branching adjacent to the transient chiral aldehyde is anticipated to retard the rate of carbonyl addition with respect to racemization (Scheme 6).

For **1f** and **1g**, the chromatographically isolated π -allyliridium *C,O*-benzoate complex derived from $[\text{Ir}(\text{cod})\text{Cl}]_2$, (*S*)- or (*R*)-Cl,MeO-BIPHEP, 3,4-dinitro-benzoic acid and allyl acetate provided the best results [75]. While site-selectivity proved uniformly high, good levels of diastereocontrol were observed only in cases where the diastereofacial bias of the catalyst matched the intrinsic diastereofacial bias of the transient aldehydes for Felkin-Anh addition [88], as in the formation of **2f** and **2g**. In the mismatched case, represented by the formation of **3f** and **3g**, epimerization of the transient aldehydes erodes diastereoselectivity.

While use of an isolable, single component catalyst offers certain advantages, generation of the catalyst *in situ* from commercial precursors is expedient and enables rapid evaluation of structurally diverse complexes. Using the commercially available malic acid derived diol **1h**, a screening of catalysts generated *in situ* quickly led to the identification of the π -allyliridium *C,O*-benzoate complex derived from $[\text{Ir}(\text{cod})\text{Cl}]_2$, (*S*)- or (*R*)-Cl,MeO-BIPHEP, 4-chloro-3-nitro-benzoic acid and allyl acetate as a highly efficient and selective system for diol *C*-allylation [76]. Under these conditions, diol **1h** is converted to the homoallylic alcohol **2h** in 79% isolated yield as a single diastereomer, as determined by ^1H NMR analysis of the crude reaction mixture (Scheme 7).

These conditions for *in situ* generation of the enantiomeric catalysts (*S*)- or (*R*)-Ir-**Id** were applied to chiral 1,3-diols **1h–1j** (Scheme 8) [76]. The respective diastereomeric products of *C*-allylation **2h–2j** and **3h–3j** were generated in good isolated yields with complete levels of catalyst-directed diastereoselectivity and high levels of site-selectivity. The catalytic C-C coupling of the benzylic diol **1j** is especially noteworthy, as dehydrogenation to form the acetophenone should be far less endothermic than aldehyde formation, yet only trace quantities of the over-oxidized ketone product were observed. Notably, the diastereoselectivities observed in connection with the protocol for *in situ* catalyst generation were consistently better than those observed previously using the chromatographically purified catalysts [75, 76].

Having established the feasibility of diastereo- and site-selectivity in redox-triggered allylations of unprotected diols, we have begun to explore site-selectivity in related catalytic asymmetric C-C couplings. For example, using the chromatographically purified π -allyliridium *C,O*-benzoate complex derived from $[\text{Ir}(\text{cod})\text{Cl}]_2$, (*S*)- or (*R*)-Tol-BINAP, 4-cyano-3-nitro-benzoic acid and allyl acetate, primary alcohols react with isoprene oxide to form aldehyde-allyliridium pairs *en route* to products of *tert*-(hydroxy)-prenylation [89]. To evaluate the feasibility of site-selective coupling, the unprotected malic acid derived diol **1h** was reacted with isoprene oxide using enantiomeric Tol-BINAP modified iridium catalysts. The diastereomeric products of *tert*-(hydroxy)-prenylation **4h** and **5h** were formed with excellent levels of diastereo- and site-selectivity. A remarkable feature of this transformation resides in the ability to form an all-carbon quaternary center with control of relative and absolute stereochemistry (Scheme 9).

More recently, related redox-triggered C-C couplings of primary alcohols and vinyl aziridines were developed, which furnish products of carbonyl (α -aminomethyl)allylation [90]. This transformation was applied to the unprotected 1,3-diols **1h**, **1i** and **1k** using the enantiomeric cyclometalated iridium *C,O*-benzoate catalysts derived from 4-cyano-3-nitro-

benzoic acid and either Cl₂MeO-BIPHEP or BINAP (Scheme 10). The respective diastereomeric products of *C*-allylation **6h**, **6i** and **6k** and **7h**, **7i** and **7k** were generated in good isolated yields with good levels of catalyst-directed diastereoselectivity and site-selectivity. As illustrated in the conversion of diol **1k** to adducts **6k** and **7k**, the iridium catalyst is tolerant of Lewis basic pyridyl-substituents. To illustrate the utility of this methodology, the diol coupling products **6h**, **6i** and **6k** and **7h**, **7i** and **7k** were exposed to Mitsunobu reaction conditions, directly providing the diastereomeric trisubstituted piperidines **8h**, **8i** and **8k** and **9h**, **9i** and **9k**, respectively (Scheme 11).

3. Summary and Outlook

Stereo- and site-selective methods for the assembly of organic molecules that occur with addition, acceptorless removal or redistribution of hydrogen are natural endpoints in the evolution of methods for process-relevant chemical synthesis. Toward this objective, we have merged the chemistry of transfer hydrogenation and carbonyl addition by harnessing the native reducing ability of alcohols for the redox-triggered generation of transient organometal-aldehyde pairs. Using chiral cyclometalated π -allyliridium *C,O*-benzoate complexes, primary alcohols dehydrogenate faster than secondary alcohols, enabling site-selective modification of chiral 1,3-diols with exceptional levels of catalyst-directed diastereoselectivity. This and related technologies for the direct, stereo- and site-selective C-C coupling of polyols streamlines *de novo* chemical synthesis, and offers new possibilities for late-stage modification of natural products, such as type I polyketides.

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Scheme 1.

Iridium catalyzed coupling of primary alcohols with allyl acetate to form secondary homoallylic alcohols.

Scheme 2.

Examples of site-selective diol oxidation involving discrimination between two primary alcohols (eq. 1) and discrimination between benzylic primary *versus* secondary alcohols (eq. 2).

Scheme 3.

General catalytic mechanism for redox-triggered carbonyl allylation and survey of selected bond lengths from a series of π -allyliridium *C,O*-benzoate complexes.

Scheme 4.

Catalyst-directed diastereo- and site-selectivity in the asymmetric C-allylation of unprotected 1,3-diols **1a-1c**.

Scheme 5.

Catalyst-directed diastereo- and site-selectivity in the asymmetric C-allylation of unprotected 1,5-diol **1d** and 1,5-triol **1e**.

Scheme 6.

Catalyst-directed diastereo- and site-selectivity in the asymmetric C-allylation of unprotected chiral β,γ -stereogenic diols **1f** and **1g**.

Scheme 7.

Generation of structurally diverse catalysts *in situ* enables screening and identification of a highly efficient and selective system for C-allylation of unprotected diol **1h**.

Scheme 8.

Catalyst-directed diastereo- and site-selectivity in the asymmetric C-allylation of unprotected 1,3-diols **1h–1j** using *in situ* generation of catalyst.

Scheme 9.

Catalyst-directed diastereo- and site-selectivity in the asymmetric *tert*-(hydroxy)-prenylation of unprotected diol **1h**.

Scheme 10.

Catalyst-directed diastereo- and site-selectivity in the asymmetric C-(α -aminomethyl)allylation of unprotected 1,3-diols **1h**, **1i** and **1k** using *in situ* generation of catalyst.

Scheme 11.

Direct conversion of **6h**, **6i** and **6k** and **7h**, **7i** and **7k** to trisubstituted piperidines **8h**, **8i** and **8k** and **9h**, **9i** and **9k**, respectively.