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Enantioselective Iridium Catalyzed Carbonyl Allylation from the Alcohol Oxidation Level *via* Transfer Hydrogenation: Minimizing Pre-Activation for Synthetic Efficiency

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Abstract

Existing methods for enantioselective carbonyl allylation, crotylation and *tert*-prenylation require stoichiometric generation of pre-metallated nucleophiles and often employ stoichiometric chiral modifiers. Under the conditions of transfer hydrogenation employing an *ortho*-cyclometallated iridium *C,O*-benzoate catalyst, enantioselective carbonyl allylations, crotylations and *tert*-prenylations are achieved in the absence of stoichiometric metallic reagents or stoichiometric chiral modifiers. Moreover, under transfer hydrogenation conditions, primary alcohols function dually as hydrogen donors and aldehyde precursors, enabling enantioselective carbonyl addition directly from the alcohol oxidation level.

1. Introduction: Significance of Hydrogenation

Because organic compounds are composed of carbon and hydrogen, the formation of C-C bonds under hydrogenation conditions is a natural endpoint in the evolution of strategies for the construction of carbon-containing molecules. Catalytic hydrogenation meets all criteria of synthetic efficiency set by the principles of atom-economy,¹ step-economy,^{2,3} and Green Chemistry.⁴ Hydrogen constitutes roughly 90% of the atoms present in the Universe, and with the advent of efficient catalysts for water-splitting, elemental hydrogen will become even more abundant.⁵ Catalytic hydrogenations are completely atom economic processes and the volatility of hydrogen trivializes its separation from other materials, virtually eliminating any waste stream. Catalytic hydrogenations such as the Haber-Bosch process,⁶ the Fischer-Tropsch reaction,⁷ alkene hydroformylation^{8,9} and enantioselective hydrogenation¹⁰ have improved our quality of life and are responsible for sustaining a large segment of the human population.

Presently, highly stereoselective variants of diverse carbonyl addition reactions are known, yet very few of these processes fulfill the aforementioned criteria of synthetic efficiency. This is especially true for carbonyl additions involving “non-stabilized carbanions”, which typically require stoichiometric quantities of pre-metallated nucleophilic reagents. However, just as classical carbanion chemistry is broad, so is the potential to create carbanion equivalents *via* hydrogenation and transfer hydrogenation. Indeed, the Grignard reaction and the catalytic hydrogenations developed by Sabatier are both reductive transformations, already suggesting a union between carbonyl addition chemistry and catalytic hydrogenation. Yet the emergence

of alkene hydroformylation in 1938 failed to stimulate systematic efforts toward related hydrogen-mediated C-C coupling processes. Reports of C-C bond forming hydrogenations beyond alkene hydroformylation were virtually absent until recent investigations from our laboratory established the progression from hydroformylation to the reductive C-C coupling of diverse unsaturates under hydrogenation and transfer hydrogenation conditions and, finally, to isohypsic¹¹ C-C couplings of alcohols and unsaturates where the redistribution of hydrogen embedded within reactants is accompanied by C-C bond formation (Scheme 1).^{12,13,14,15}

In this feature article, we describe how the union of hydrogenation and carbonyl addition chemistry has evoked a new suite of catalytic methods for enantioselective carbonyl allylation. Unlike classical methods for carbonyl allylation, the hydrogen-mediated variants occur in the absence of stoichiometric allylmatal reagents, minimizing or entirely excluding generation of stoichiometric byproducts. Additionally, under transfer hydrogenation conditions, primary alcohols serve dually as hydrogen donors and aldehyde precursors, enabling carbonyl addition directly from the alcohol oxidation level, which circumvents redox manipulations required for discrete generation of aldehyde electrophiles. These protocols are among the first methods available for direct catalytic C-H functionalization of alcohols at the carbinol position.^{12d,e,16,17}

2. Beyond Pre-Activation: Nucleophile-Electrophile Pairs *via* Transfer Hydrogenation

Classical protocols for carbonyl addition involving delivery of “non-stabilized carbanion equivalents” generally exploit pre-metallated nucleophiles. Such stoichiometric organometallic reagents mandate generation of stoichiometric byproducts in the form of metal salts. Additionally, considerable “pre-activation” in the form of redox manipulations (i.e. oxidative and reductive pre-activation)³ and isohypsic functional group interconversions (e.g. transmetallations) often attend their use. For example, the Oppolzer-Wipf method for enantioselective carbonyl vinylations require alkyne hydrozirconation (mediated by Cp_2ZrHCl) with subsequent transmetallation to zinc (mediated by ZnMe_2).^{18,19} Here, four stoichiometric organometallics are employed in advance of C-C coupling, not including reagents used for preparation of Cp_2ZrHCl and ZnMe_2 . A second example of direct relevance to the topic of this review involves Brown’s protocol for the crotylation of carbonyl compounds employing (*E*)- or (*Z*)-crotyldiisopinocampheylborane.²⁰ The Brown reagent is prepared through the potassiation of butene employing Schlosser’s base²¹ followed by transmetallation to boron. Here, multiple manipulations and stoichiometric reagents (*n*-BuLi, KC_4H_7 , Ipc_2BOMe) are required to prepare the desired crotylborane. Furthermore, for each crotyl moiety that is transferred, two equivalents of isopinocampheol are generated, meaning that the product, a secondary alcohol, must be separated from super-stoichiometric quantities of secondary alcohol byproduct (Scheme 2).²²

We have shown that the redistribution of hydrogen between alcohols and π -unsaturated reactants can result in the generation of nucleophile-electrophile pairs.^{12d,e} By exploiting “unactivated” reactants as redox pairs, pre-activation of the nucleophile and discrete generation of the electrophile are no longer required. Carbonyl addition is achieved directly from the alcohol oxidation level, simply by shuffling hydrogen between alcohols and unsaturates. Because stoichiometric organometallic reagents and transmetallation steps are avoided, molar equivalents of stoichiometric byproducts are not generated. This concept is applicable to diverse carbonyl addition reactions, including the aforementioned carbonyl vinylations and allylations. Such C-C bond forming transfer hydrogenations are inherently step-economic and redox-economic, as they dispense with discrete redox manipulations associated with nucleophilic and electrophilic pre-activation (Scheme 2).

3. Enantioselective Carbonyl Allylation, Crotylation and Reverse Prenylation from the Alcohol Oxidation Level

Enantioselective carbonyl allylation ranks among the most broadly utilized methods in asymmetric synthesis.²³ One major approach to asymmetric carbonyl allylation involves the use of chirally modified allyl metal reagents.²⁴ Additionally, chiral Lewis acids and chiral Lewis bases catalyze enantioselective carbonyl allylation employing achiral allylmetal reagents.²⁵ Other methods for catalytic carbonyl allylation include the reductive coupling of allylic alcohols and allylic carboxylates to aldehydes.^{26,27} With the exception of ruthenium-based catalysts,^{26k–m} these methods invariably require stoichiometric quantities of metallic reductants for catalytic turnover. Finally, enantioselective carbonyl allylation and crotylation may be achieved using asymmetric variants of the Nozaki-Hiyama reaction.^{28,29}

We have found that cyclometallated iridium *C,O*-benzoates modified by chiral phosphine ligands are effective catalysts for the enantioselective reductive coupling of allylic acetates and allenes to carbonyl electrophiles to furnish products of carbonyl allylation,^{30 a,b,e,f,g} crotylation^{29c,h} and reverse prenylation.^{30d,f,h} Unlike preexisting methods that exploit stoichiometric metallic reagents or reductants, the carbonyl allylation processes we report employ 2-propanol as terminal reductant in combination with non-metallic allyl donors, for example, allyl acetate, α -methyl allyl acetate and 1,1-dimethylallene. Of even greater significance, alcohols may serve dually as reductant and precursor to the carbonyl electrophile, enabling enantioselective carbonyl addition directly from the alcohol oxidation level. *Thus, identical products of asymmetric carbonyl allylation, crotylation and reverse prenylation are generated from alcohols or aldehydes.*

Our initial studies focused on allylations mediated by allyl acetate. It was found that under the conditions of transfer hydrogenation employing an iridium catalyst generated in situ from [Ir(cod)Cl]₂, the chiral phosphine ligands (*R*)-BINAP or (*R*)-Cl,MeO-BIPHEP and *m*-nitrobenzoic acid, allyl acetate couples to allylic alcohols, aliphatic alcohols and benzylic alcohols to furnish products of carbonyl allylation with excellent levels of optical enrichment. The very same set of optically enriched carbonyl allylation products are accessible from enals, aliphatic aldehydes and aryl aldehydes, using iridium catalysts ligated by (–)-TMBTP or (*R*)-Cl,MeO-BIPHEP under identical conditions, but employing 2-propanol as a hydrogen donor (Scheme 3).^{30a,b}

As corroborated by single crystal X-ray diffraction, the active catalyst is a cyclometallated *C,O*-benzoate complex, which arises upon *ortho*-*C-H* insertion of iridium onto *m*-nitrobenzoic acid (Fig. 1). The results of isotopic labeling are consistent with intervention of symmetric iridium π -allyl intermediate or rapid interconversion of σ -allyl haptomers through the agency of a symmetric π -allyl. Competition experiments demonstrate rapid and reversible hydrogenation-dehydrogenation of the carbonyl partner in advance of C-C coupling. Although the catalyst readily engages primary alcohols in rapid and reversible hydrogenation-dehydrogenation, the coupling products, which are homo-allylic alcohols, experience almost no erosion of optical purity by way of redox equilibration. This result is even more remarkable in light of the fact that 2-propanol, a secondary alcohol, is oxidized under coupling conditions. As indicated in the proposed catalytic mechanism (Scheme 4), coordination of the homoallylic olefin to the catalyst provides a hexa-coordinate, 18-electron complex that cannot engage in β -hydride elimination due to the absence of an open coordination site. Upon exchange of the homo-allyl alcohol product for a molecule of 2-propanol or a molecule of substrate, for example, cinnamyl alcohol, a penta-coordinate, 16-electron complex arises, which can engage in β -hydride elimination to generate acetone or the transient aldehyde electrophile.

A model accounting for the observed sense of absolute stereoinduction was proposed based on the coordination mode revealed in the crystal structure of the cyclometallated *C,O*-benzoate complex and the observed trends in substrate scope. Aldehyde binding by the α -allyl haptomer is postulated to occur such that the sterically less demanding allyl moiety is placed between the naphthyl and phenyl moieties of the ligand, allowing the aldehyde to reside in a more open environment. In the favored mode of addition, the aldehydic C–H bond projects into the π -face of a phenyl moiety of the ligand, possibly resulting in a weakly attractive aldehyde C–H- π -interaction,³¹ and the aldehydic “R-group” projects into an open quadrant, which accounts for the exceptional tolerance of aldehydes possessing methylene, methine and quaternary carbon centers adjacent to the carbonyl moiety. In the disfavored mode of addition, the aldehyde is bound such that the aldehydic “R-group” projects into the π -face of a phenyl moiety of the ligand, resulting in a severe nonbonded interaction (Fig. 2).

The ability to perform carbonyl allylation from the alcohol oxidation level enables allylation processes that cannot be performed from the aldehyde oxidation level. For example, whereas malondialdehyde is highly unstable, 1,3-propane diol is highly tractable. Under the conditions of C–C bond forming transfer hydrogenation, 2-substituted 1,3-propane diols and higher 1,*n*-diols are subject to the successive generation and capture of transient mono-aldehydes to provide *C*₂-symmetric adducts in good yield.^{30e,f} The minor enantiomer of the mono-adduct is transformed to the *meso*-stereoisomer, which dramatically amplifies the enantioselectivity of the process (Scheme 5).³²

Iterative one-directional and two-directional carbonyl allylations have been performed from the alcohol oxidation level.^{30e,g, 33} In the latter case, rapid construction of 1,3-polyols is achieved with complete levels of catalyst-directed diastereoselectivity.³⁴ To illustrate the utility of this approach, the 1,3-polyol substructure of the polyene macrolide (+)-roxaticin was prepared in a total of 9 steps from 1,3-propane diol (Scheme 6).³⁵

Employing an *ortho*-cyclometallated iridium catalyst generated in situ from [Ir(cod)Cl]₂, 4-cyano-3-nitrobenzoic acid and (*S*)-SEGPPOS, α -methyl allyl acetate couples to primary aliphatic, allylic and benzylic alcohols with complete levels of branched regioselectivity to furnish products of carbonyl crotylation. Good levels of *anti*-diastereoselectivity and exceptional levels of enantioselectivity are observed. The same set of products is accessible from the aldehyde oxidation level under identical conditions, but employing 2-propanol as the terminal reductant (Scheme 7).

Given the uniformly high levels of selectivity observed using the *ortho*-cyclometallated iridium *C,O*-benzoate as catalyst, an effort was made to extend the allylation methodology beyond the use of allylic acetates. Allenes and dienes, which are subject to hydrometallation by iridium hydride intermediates, represent an alternative source of nucleophilic iridium allyls.³⁶ Indeed, employing the cyclometallated iridium *C,O*-benzoate derived from allyl acetate, *m*-nitrobenzoic acid and (*S*)-SEGPPOS as catalyst, 1,1-dimethylallene participates in 2-propanol mediated reductive coupling to aromatic, α,β -unsaturated and aliphatic aldehydes to furnish products of reverse prenylation in good to excellent isolated yields and enantioselectivities. Enantioselective carbonyl reverse prenylation is achieved directly from the alcohol oxidation level in the absence of 2-propanol to provide an equivalent set of adducts with comparable yields and enantioselectivities (Scheme 8).

With new methods for carbonyl allylation, crotylation and reverse prenylation in hand, suitable applications toward the total synthesis of polyketide natural products were sought. Given the longstanding challenges associated with defining concise routes to the bryostatins,³⁷ this class of natural products was deemed an ideal vehicle to benchmark the utility of C–C bond forming hydrogenations and transfer hydrogenations developed in our laboratory. In prior work,

enantioselective hydrogen-mediated alkyne-carbonyl reductive coupling was applied to construction of the bryostatin C-ring.³⁸ Using two different C-C bond forming transfer hydrogenations, the double asymmetric carbonyl allylation of 1,3-propane diol and a subsequent catalyst-directed reverse prenylation, the synthesis of a known bryostatin A-ring fragment was achieved in less than half the steps previously required (Scheme 9).^{30f,37a}

5. Outlook

Given the current state-of-the-art in Organic Chemistry, the primary scientific challenge associated with complex molecule synthesis is no longer the question of whether a given compound can be prepared. Rather, it is the question of how one can dramatically simplify the syntheses of complex structures such that they better conform to the ideals of synthetic efficiency. Toward this end, processes that dispense with preactivation are highly desirable, as they are inherently step-economic and waste-minimizing. To the extent that a process is selective, the use of protecting groups and directing groups may be avoided, again conferring step-economy. Processes that embody new patterns of reactivity also are highly desirable, as these will open up new functional group interconversions, enabling new synthetic strategies. Ultimately, the transformations that we employ routinely in the academic lab or at the discovery level in the pharmaceutical industry should be directly transferable to the process level.

The nascent modes of reactivity illustrated by the reactions described in this review should serve as the basis for innumerable byproduct-free alcohol-unsaturate and amine-unsaturate coupling processes. And while we have only just begun to realize the potential of this novel reactivity mode, already one must question whether processes that traditionally have employed one or more stoichiometric metallic reagents can now be conducted catalytically under the conditions of hydrogenation or transfer hydrogenation. Many future outcomes can be envisioned. Carbonyl ethylation *via* ethylene-alcohol C-C coupling would dispense with the need for diethylzinc, a pyrophoric liquid. Related C-C couplings of α -olefin and alcohols would serve as an alternative to Grignard type additions. Indeed, Grignard additions mediated by hydrogen rather than magnesium, foreshadowed by Grignard and Sabatier's joint receipt of the 1912 Nobel prize, enter the realm of feasibility.

Biographies

Soo Bong Han

Soo Bong Han was born in Seoul, Korea in 1975. He received a B.S. degree in chemistry from Sogang University (2002) and an M.S. degree from KAIST (2004) under supervision of Professor Suk Bok Chang. After working as a senior researcher at LG Life Sciences, he began doctoral studies under the supervision of Professor Michael J. Krische at the University of Texas at Austin, where he has contributed to the development of numerous hydrogen-mediated C-C bond forming processes, including the work presented in this feature article.

In Su Kim

In Su Kim was born in 1975 in Gapyeong, Republic of Korea. He received B.S. (2001), M.S. (2003), and Ph.D. (2006) degrees from the College of Pharmacy, Sungkyunkwan University, where he conducted research under the supervision of Professor Young Hoon Jung. After working as a postdoctoral fellow of the BK21 program funded by the Korean Ministry of Science and Technology, he joined the research group of Professor Michael J. Krische at the University of Texas at Austin as a Korea Research Foundation postdoctoral fellow. In 2009, he was appointed Assistant Professor at the University of Ulsan.

Professor Michael J. Krische obtained a B.S. degree in chemistry from the University of California at Berkeley. After a year abroad as a Fulbright Fellow, he received a Ph.D. at Stanford University with Professor Barry Trost and then engaged in post-doctoral studies with Jean-Marie Lehn at the Université Louis Pasteur. In Fall 1999, Professor Krische joined the faculty at the University of Texas at Austin, where he presently resides as the Robert A. Welch Chair in Science. Professor Krische's research has led to the development of the first C-C bond forming hydrogenations beyond hydroformylation.

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X-Ray Crystal Structure
of Active Cyclometallated
 π -Allyl Complex
[Ln = (R)-BINAP]

Fig. 1.
Enantioselective carbonyl allylation from the alcohol or aldehyde oxidation level *via* iridium
catalyzed C-C bond forming transfer hydrogenation.

Favored Mode of Addition

Disfavored Mode of Addition

Fig. 2.
Proposed stereochemical model accounting for the observed sense of absolute stereinduction
(chiral ligand = (*S*)-Cl,MeO-BIPHEP).

Scheme 1.

Catalytic C-C coupling in the absence of stoichiometric byproducts *via* hydrogenation and transfer hydrogenation.

Scheme 2.

Pre-activation attends the use of established protocols for carbonyl additions involving non-stabilized carbanions, whereas transfer hydrogenation enables byproduct-free carbonyl addition in the absence of multi-step pre-activation.

The following chiral ligands were used: (A) = (*R*)-Cl,MeO-BIPHEP, (B) = (*R*)-BINAP, (C) = (-)-TMBTP

Scheme 3.

Enantioselective carbonyl allylation from the alcohol or aldehyde oxidation level *via* iridium catalyzed C-C bond forming transfer hydrogenation.

Scheme 4.

Postulated catalytic mechanisms for the iridium catalyzed transfer hydrogenative coupling from the alcohol or aldehyde oxidation level (chelating bis-phosphine ligand indicated schematically as P-P).

Scheme 5.

1,n-Glycols as dialdehyde equivalents in iridium catalyzed enantioselective carbonyl allylation from the alcohol oxidation level.

Scheme 6.

Synthesis of the 1,3-polyol substructure of the polyene macrolide (+)-roxaticin involving iterative two-directional carbonyl allylation.

^a(S)-C3-TUNEPHOS was used as ligand.

Scheme 7.

Enantioselective carbonyl crotylation from the alcohol or aldehyde oxidation level *via* iridium catalyzed C-C bond forming transfer hydrogenation.

Scheme 8.

Enantioselective carbonyl crotylation from the alcohol or aldehyde oxidation level *via* iridium catalyzed C-C bond forming transfer hydrogenation.

Scheme 9.
Synthesis of the bryostatin A-ring employing consecutive C-C bond forming transfer hydrogenations.