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Feedstock Reagents in Metal-Catalyzed Carbonyl Reductive Coupling: Minimizing Preactivation for Efficiency in Target-Oriented Synthesis

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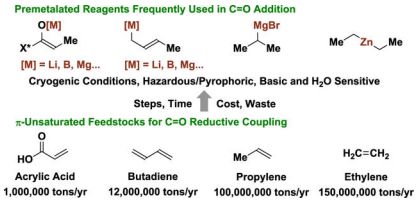
Abstract

Use of abundant feedstock pronucleophiles in catalytic carbonyl reductive coupling minimizes preactivation, enhancing efficiency in target-oriented synthesis. For reactions of this type, equally inexpensive reductants are desired or, ideally, corresponding hydrogen autotransfer processes may be enacted wherein alcohols serve dually as reductant and carbonyl proelectrophile.

Graphical Abstract



Keywords

Petrochemical Feedstocks; Atom-Efficiency; Enantioselective Catalysis; Carbonyl Addition; Hydrogenation; Transfer Hydrogenation

I. Introduction and Inspiration

The construction of complex small molecules often requires intervention of non-native structural elements to direct reactivity, regio- and stereoselectivity. For example, directing or protecting groups are frequently used to guide the site-selectivity of chemical processes, chiral auxiliaries are often required to direct the stereochemistry of covalent bond formations, and stoichiometric carbanion generation via halogenation-metalation-transmetallation sequences remains common. The additional manipulations required to prepare, install and remove such structural elements contribute to inefficiency.[1] More idealized views on chemical synthesis have been posited;[2] however, the relatively modest lexicon of synthetic methods available in the 20th century has necessitated a more arcane

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approach. For example, the commercial manufacturing route to eribulin, a skeletally and stereochemically complex chemotherapeutic agent used to treat breast cancer, demands a total of 65 steps, half of which are devoted to redox reactions and protecting group manipulations.[3] A vast number of "sacrificial reagents" are required. In contrast, dioctyl phthalate (an industrial plasticizer) is made through a 4-step sequence composed almost entirely of skeletal construction events with water as the sole byproduct.[4] This gap in efficiency, which may be quantified by the E-factor analysis,[5] should be viewed as a source of inspiration. While methods used in academic and discovery-related research are often poorly suited for large volume chemical manufacture, one may look to the largest volume applications of homogenous catalysis, hydroformylation[6] and methanol carbonylation,[7] and see that a principal characteristic of a scalable method resides in the ability to affect C-C bond formation between feedstock reactants in the absence of stoichiometric byproducts. Accordingly, one may narrow this gap in efficiency through the development of methods that enable complex molecule syntheses through routes composed exclusively of byproduct-free skeletal construction events (Scheme 1).

For both eribulin and dioctyl phthalate, the majority of the skeletal construction events exploit carbonyl addition, implicating the potential impact of developing catalytic methods for stereo- and site-selective carbonyl addition, especially processes that embody high levels of redox economy and exploit inexpensive feedstock reactants. In an effort to valorize carbonyl addition methodology for complex molecule synthesis, we have developed a broad, new class of metal-catalyzed carbonyl reductive C-C coupling reactions that occur through the addition or redistribution of hydrogen (Scheme 2).[8–10] These processes enable carbonyl addition from π-unsaturated pronucleophiles, bypassing the use of premetalated reagents and the attendant issues of safety, selectivity, and waste posed by their use. The terminal reductants utilized in these reactions are abundant, low molecular weight feedstocks (elemental hydrogen, 2-propanol and formic acid). This aspect is significant: metallic reductants (e.g. Mn, Zn) can be just as problematic as the organometallic reagents they are intended to replace,[8,9] and silane based reductants are orders of magnitude more expensive than the feedstocks they are used to activate.[11] Simply stated: *don't sacrifice something expensive to modify something cheap!* For this reason, carbonyl reductive couplings wherein alcohols serve dually as reductant and carbonyl proelectrophile are uniquely efficient. Such hydrogen autotransfer reactions directly convert lower alcohols to higher alcohols without exogenous reductants or discrete alcohol-to-carbonyl redox reactions.

In this mini-review, efforts to exploit π-unsaturated feedstocks as pronucleophiles and reductants in target-oriented synthesis via metal-catalyzed carbonyl reductive coupling and related hydrogen autotransfer reactions are surveyed.[5] For detailed discussions of reaction mechanism, the reader is referred to the primary literature. This review is not exhaustive, but utilizes case studies to illustrate how this new carbonyl addition chemistry streamlines chemical synthesis. Indeed, as organic molecules are compounds of carbon and hydrogen, we feel catalytic C-C bond formation via H_2-addition or H_2-redistribution are natural endpoints in the evolution of synthetic methods for efficient chemical synthesis.

II. From Feedstocks to Building Blocks in Target-Oriented Synthesis

Polyketides and their derivatives are used more frequently in human medicine than any other natural product class.[9,12] However, with the exception of eribulin,[3] all commercial polyketides are manufactured via fermentation or semi-synthesis, suggesting the present lexicon of synthetic methods does not adequately address the challenges that arise by the construction of such complex structures. Asymmetric aldol additions[13] and carbonyl allylations[14] are among the most commonly utilized methods for polyketide construction. However, to guide relative and absolute stereochemistry, most methods for asymmetric aldol addition and carbonyl allylation require multi-step syntheses of discrete enol(ate) or allylmetal derivatives that involve numerous sacrificial reagents and, consequently, generate numerous stoichiometric byproducts. For example, the vast majority of methods for asymmetric carbonyl crotylation exploit stereospecific reactions of (*E*)- or (*Z*)-crotylmetal reagents to form *anti*-or *syn*-configured propionate substructures, respectively. As exemplified by Leighton's reagent,[15] many of the requisite crotylmetal reagents derive from butadiene (12×10^6 tons/yr) through multi-step sequences (Scheme 3). Direct asymmetric butadiene-mediated carbonyl crotylation via hydrogen autotransfer would be significantly more efficient, as undesired degrees of separation between reagent and feedstock would be removed and the crotylation would be completely atom-efficient.

In 2008, aldehyde crotylations via ruthenium-catalyzed butadiene-carbonyl reductive coupling mediated by 2-propanol were developed, along with mechanistically related hydrogen autotransfer reactions involving primary alcohols.[16a] In these processes, alcohol dehydrogenation generates a ruthenium(II) hydride, which promotes butadiene hydrometalation to form a transient crotylruthenium(II) nucleophile. While the initially reported reactions displayed high levels of regioselectivity, diastereo- and enantioselective variants required use of 2-trialkylsilyl-substituted dienes.[16b] It was later found that ruthenium catalysts modified by chiral phosphate counterions could affect highly enantioselective butadiene-mediated carbonyl crotylations with access to either the *anti*- or *syn*-diastereomers depending on the choice of chiral counter-ion (Scheme 4).[16c,d] This method was used in a concise total synthesis of 6-deoxyerythronolide B.[17,18] As will be shown (*vide infra*, Scheme 5), the triketide stereopolyad spanning C1–C6 is created using a related two-directional transfer hydrogenative carbonyl crotylation of 2-methyl-1,3-propane diol.

The total synthesis of the marine macrodiolide swinholide A enables juxtaposition of classical carbonyl addition chemistry and corresponding hydrogenative and transfer hydrogenative carbonyl additions.[19–22] Rather than utilizing a chiral auxiliary-based asymmetric aldol addition, as exemplified by Evans-type aldol reagents (Figure 1),[19] an asymmetric vinyl ketone-aldehyde reductive coupling catalyzed by a chiral phosphinite-modified rhodium complex is employed.[24,25] Methyl vinyl ketone (MVK) is manufactured from acetone (1.56×10^6 tons/yr) and formaldehyde (8.7×10^6 tons/yr), and is of commercial significance due to its frequent use as a comonomer in photodegradable plastics. The reductant is elemental hydrogen (60×10^6 tons/yr). To construct the swinholide A substructure spanning C2–C18, MVK is hydrogenated at ambient pressure in the presence of the indicated C15 aldehyde to deliver the aldol product with excellent control of relative and

absolute stereochemistry. This method is completely atom-efficient, meaning no sacrificial reagents are required and no stoichiometric byproducts are generated. Furthermore, the hydrogen-mediated coupling is highly chemoselective and can be performed in the presence of olefins and diene functional groups without competing conventional hydrogenation (Scheme 5).

To prepare the C26-C32 trisubstituted pyran of swinholide A, an iridium-catalyzed stereo- and site-selective carbinol C-H allylation of (*S*)-1,3-butane diol was performed (Scheme 6, bottom).[26] Unlike conventional carbonyl allylation methodology,[14] which typically combines preformed allylmetal and aldehyde reactants, the analogous reactive species are generated *transiently* from abundant, tractable precursors: (*S*)-1,3-butane diol is commercially available and allyl acetate is a feedstock (7×10^4 tons/yr) prepared via palladium-catalyzed aerobic allylic acetoxylation of propylene (1×10^8 tons/yr) using acetic acid (8×10^6 tons/yr). The same C-C bond construction has been affected using the Brown reagent, which requires multiple cryogenic steps and sacrificial reagents (Scheme 6, top).[27] Alcohol-mediated carbonyl allylation methodology[28] is also used to prepare the triketide stereopolyad spanning C19-C25 of swinholide A. Here, α-methyl allyl acetate serves as a crotylmetal surrogate[29] in a two-directional chain elongation of 2-methyl-1,3-propane diol – a process that forms predominantly one of 16 possible stereoisomers.[30] Syntheses of closely related stereopolyads have required 15 steps (Scheme 6, right).[31] This “double crotylation” has dramatically simplified the syntheses of other polyketide natural products, such as 6-deoxyerythronolide B[17] and zincophorin.[32]

The catalytic enantioselective two-directional allylation of 1,3-propane diol (1.5×10^5 tons/yr) using allyl acetate (7×10^4 tons/yr) combines two abundant feedstocks to directly furnish a value-added C_2-symmetric diol (Scheme 7).[33] The same C_2-symmetric diol previously required a 7 step synthesis involving three protecting group manipulations, two separate alcohol oxidations and two separate carbonyl asymmetric allylborations.[34] As illustrated in concise total syntheses of (+)-roxaticin,[35,36] bryostatin 7,[37,38] cryptocaryol,[39,40] mandelalide (not shown),[41] and neopeltolide (not shown),[42,43] this C_2-symmetric diol serves as a powerful building block for polyketide construction. Neopentyl glycol (6.8×10^5 tons/yr) is used extensively in the paints and coatings industry. The two-directional enantioselective allylation of neopentyl glycol delivers a C_2-symmetric diol that served as a key intermediate in total syntheses of cyanolide A[44,45] and psymberin (irciniastatin A) (not shown).[46]

Acetylene (7×10^4 tons/yr) is a basic feedstock used in a variety of applications. Previously generated from calcium carbide (which is derived from coal), the majority of acetylene is now obtained as a side-product in the production of ethylene by hydrocarbon cracking. Hydrogenation of acetylene in the presence of aldehydes and imines using a chiral cationic rhodium catalyst results in 3-component reductive coupling to form enantiomerically enriched (*Z*)-butadienylated allylic alcohols and amines, respectively (Scheme 8).[47] Using this method, along with an alcohol-mediated crotylation to define the propionate-based stereotriad,[29] the triene-containing C17-benzene ansamycins, trienomycins A and F, were prepared in a short number of steps.[48,49] The hydrogen-mediated reductive coupling of

acetylene to L-glyceraldehyde acetonide displays high levels of catalyst-directed diastereoselectivity, enabling preparation of all eight L-hexoses (not shown).[47c]

In an effort to extend the concepts of hydrogen autotransfer-mediated carbonyl addition to the synthesis of terpenoid natural products, catalytic couplings of alcohols with isoprene oxide were developed.[50] This process converts primary alcohols to products of carbonyl *tert*-(hydroxy)-prenylation, generating an acyclic quaternary carbon stereocenter with excellent control of diastereo- and enantioselectivity.[51] No stoichiometric byproducts are generated, as each atom in the reactants is integrated in the reaction product. Isoprene oxide is obtained upon regioselective metal-catalyzed epoxidation of the feedstock diene isoprene (8×10^5 tons/yr). Using this method, concise total syntheses of oridamycin A, triptoquinones B and C and isoiresin were completed from a common intermediate in significantly fewer steps than previously required (Scheme 9).[52,53]

Beyond alkanes, which are so plentiful they are used as fuel, the most abundant petrochemical feedstocks are ethylene (1.5×10^8 tons/yr) and higher olefins such as propylene (1.0×10^8 tons/yr) and 1-octene (1×10^6 tons/yr). Use of these compounds as non-stabilized carbanion equivalents in metal-catalyzed reductive coupling to unactivated carbonyl partners and related hydrogen autotransfer additions remains an unmet challenge.[8h] Progress has been made; however, vicinal dicarbonyl proelectrophiles are required. For example, ruthenium(0) catalyzed couplings of 3-hydroxy-2-oxindole to ethylene, propylene and 1-octene occur in excellent yield with complete levels of branched regioselectivity (Scheme 10).[54] Styrene (2.5×10^7 tons/yr) is also a competent partner in these transformations, and in couplings with simple aliphatic alcohols (not shown).[55] Styrene also participates in reductive couplings to anhydrides mediated by elemental hydrogen.[56] These processes have yet to be deployed in target-oriented synthesis, but demonstrate important proof-of-concept vis-à-vis use of feedstock alkenes as non-stabilized carbanion equivalents.

III. Conclusion

The current dichotomy between transformations used routinely in academic and discovery-related research *vs* large volume chemical manufacture defines a technological gap and, most importantly, an opportunity to innovate.[57] To achieve more ideal chemical syntheses and fulfill the longstanding goal of enacting synthetic routes composed solely of skeletal construction events,[2,9b] it is necessary to minimize preactivation by eliminating the degree of separation between reactant/reagent and the parent feedstock.[58] Hence, the development of catalytic methods that employ feedstock pronucleophiles in combination with feedstock reductants in stereo- and site-selective (protecting group-free) C-C bond formations represents an important objective.[59] Even more efficient, however, are related hydrogen autotransfer processes wherein native structural elements serve dually as redox mediators and coupling partners, as in hydrogen autotransfer additions of alcohols and π-unsaturated reactants. As demonstrated by the catalytic processes highlighted in this account, many traditional transformations that exploit preformed carbanions already have catalytic counterparts that bypass stoichiometric organometallic reagents and the multi-step

sequences required for their preparation. We believe human ingenuity and economic-aesthetic selective pressure will cause this field to grow.

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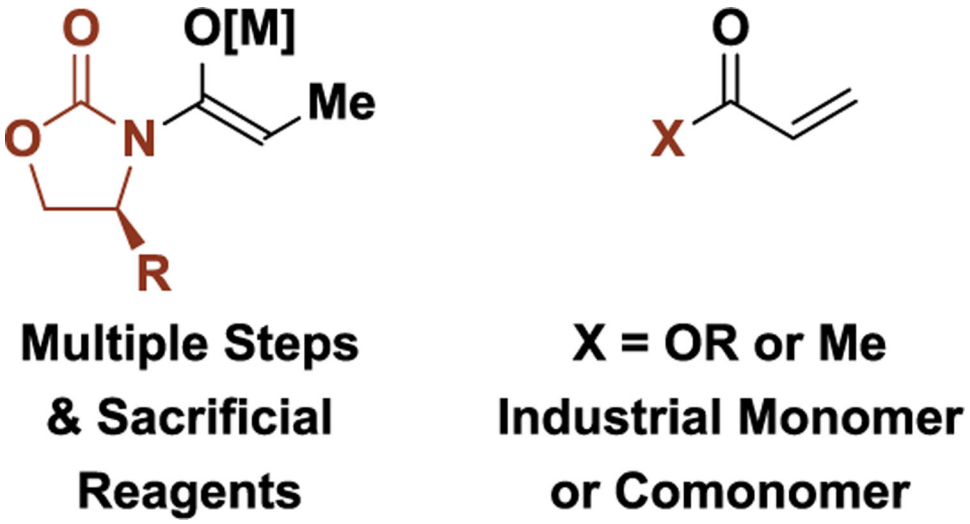
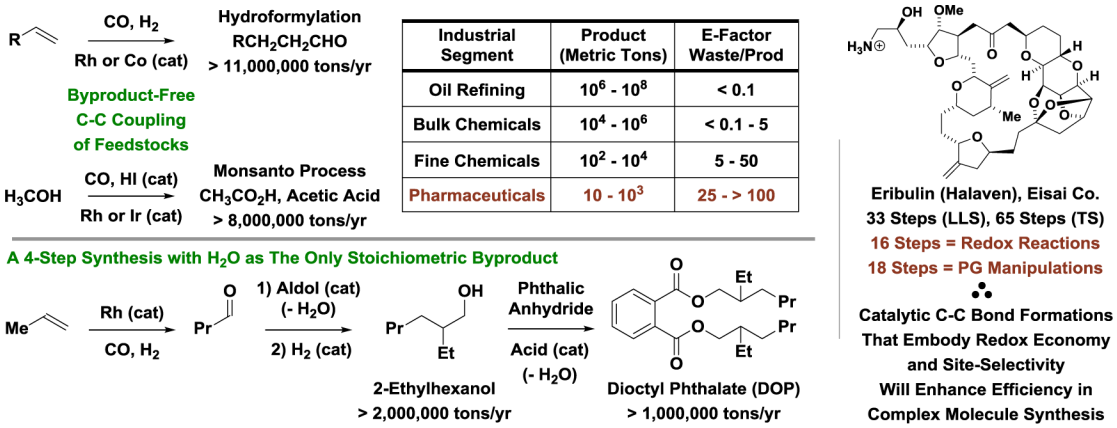
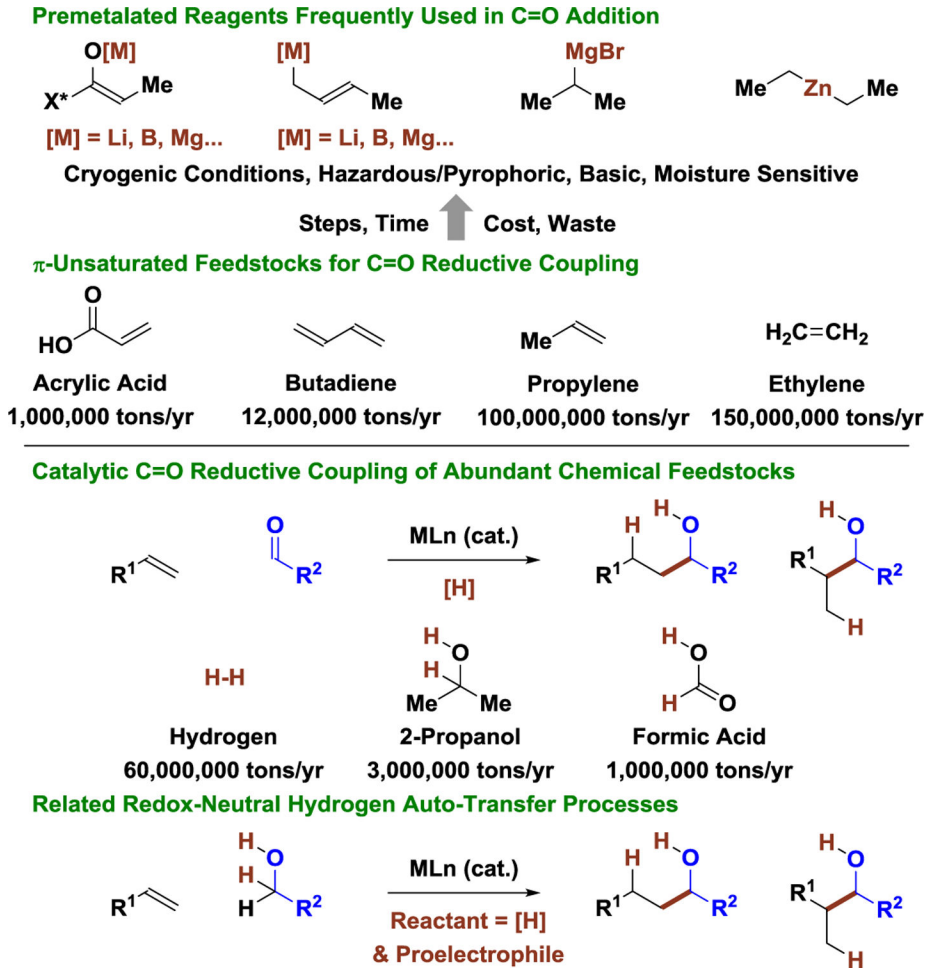


Figure 1.
Propionate synthons for polyketide construction.



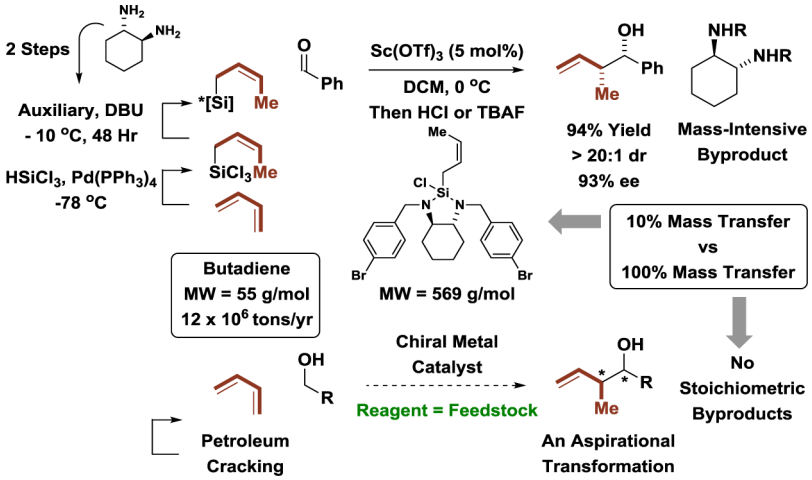
Scheme 1.

An inverse relationship between complexity and efficiency highlights the need for redox- and site-selective catalytic C-C bond formation.



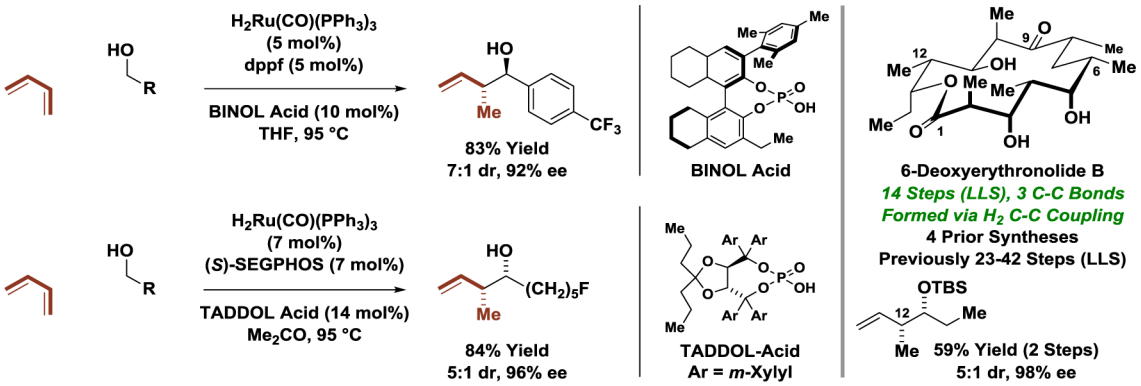
Scheme 2.

Catalytic reductive coupling of π-unsaturated feedstocks: beyond stoichiometric organometallic reagents. Production statistics shown here and elsewhere in this review are taken from the Kirk-Other Encyclopedia of Chemical Technologyor Ullmann's Encyclopedia of Industrial Chemistry.



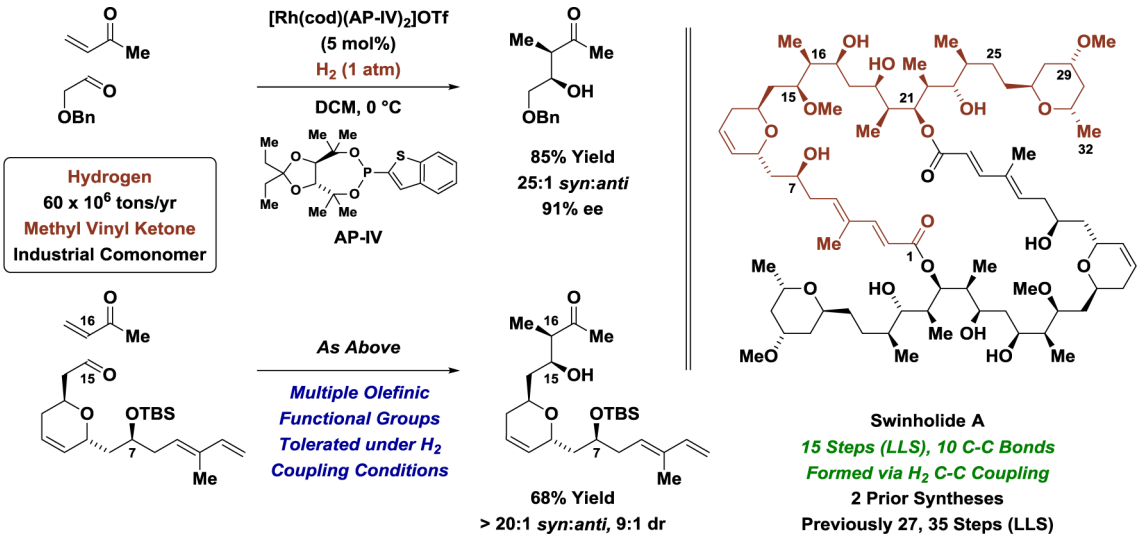
Scheme 3.

Removing degrees of separation between reagent and feedstock in asymmetric carbonyl crotylation.



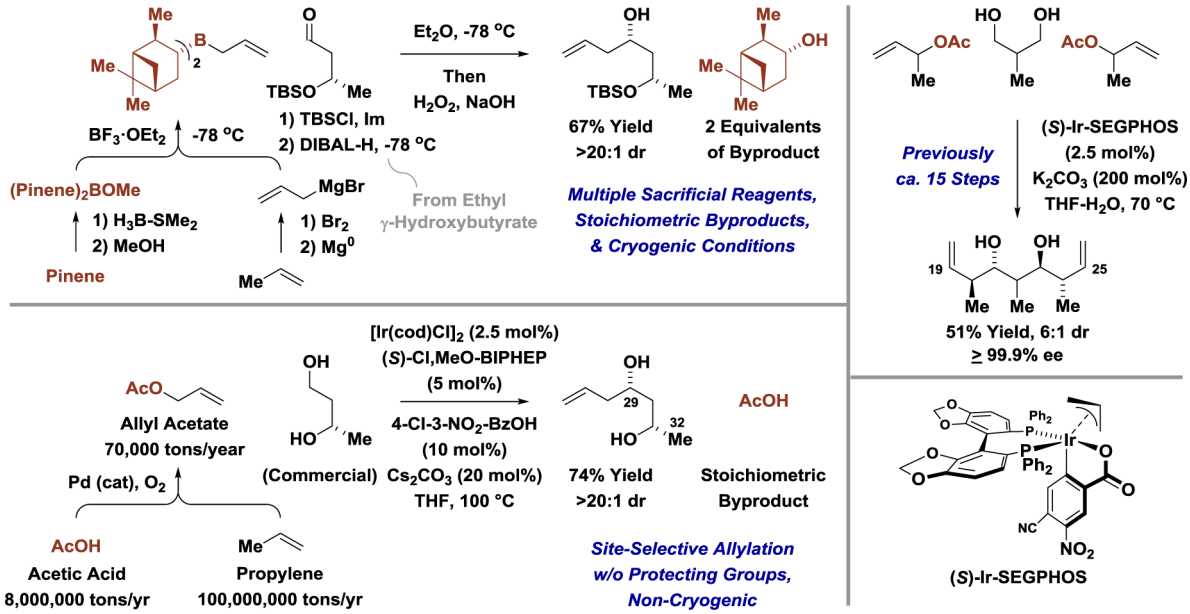
Scheme 4.

Direct butadiene-mediated carbonyl crotylation with chiral counterion-dependent stereoselectivity.



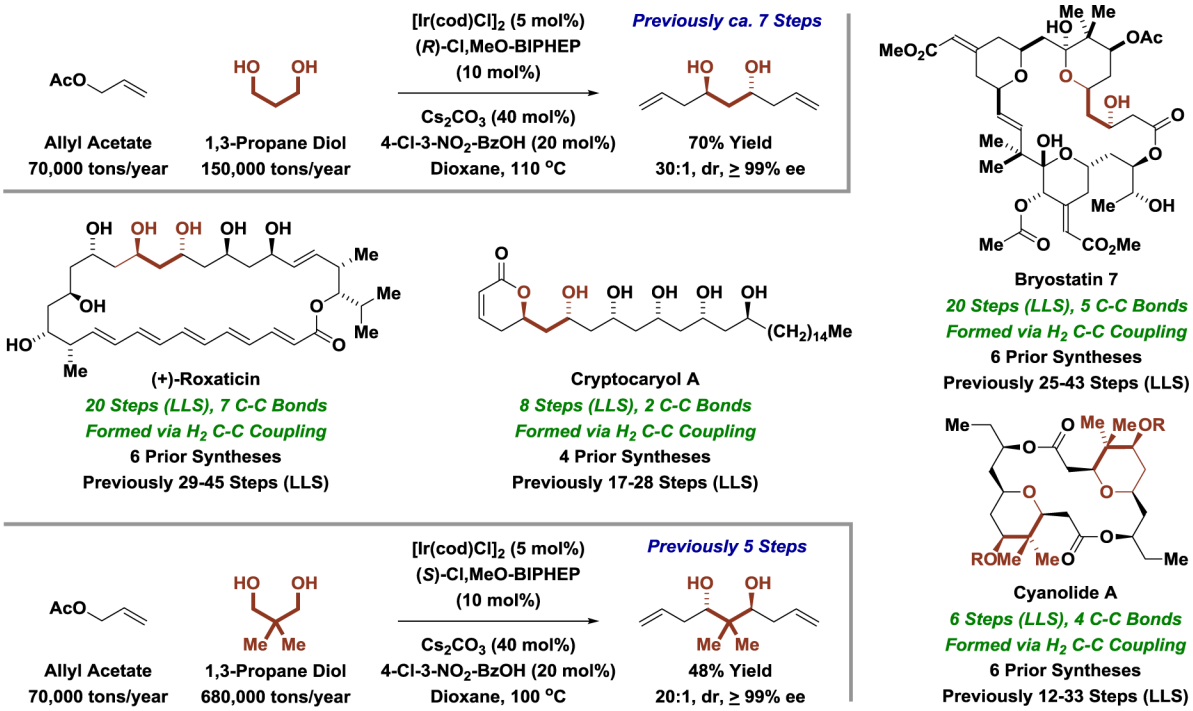
Scheme 5.

Hydrogen-mediated aldol reductive coupling for the total synthesis of swinholide A.



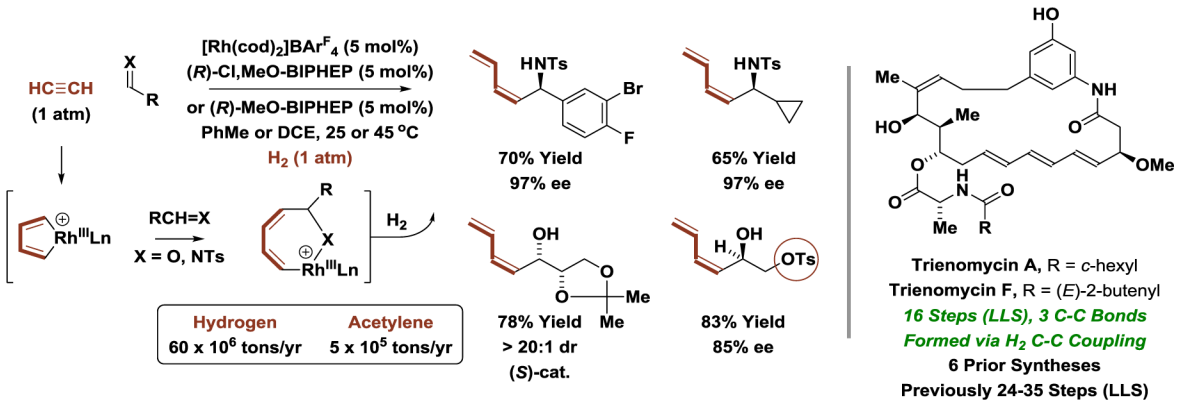
Scheme 6.

Stereo- and site-selective alcohol-mediated carbonyl allylation for the total synthesis of swinholide A.



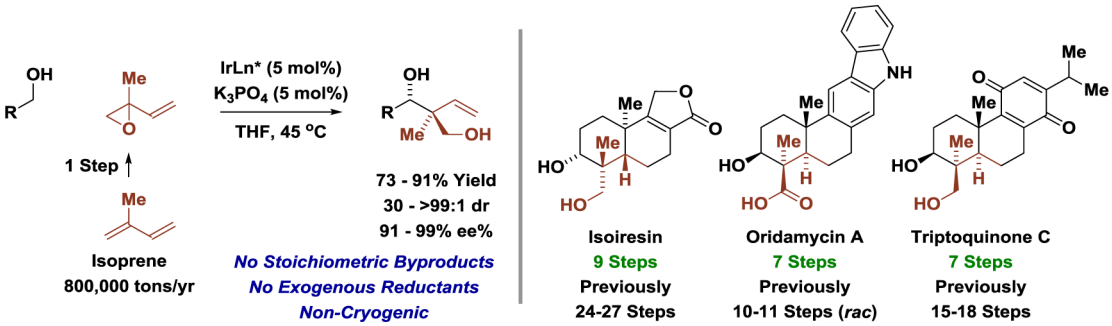
Scheme 7.

Polyketide construction via two-directional allylation of feedstock glycols using allyl acetate.



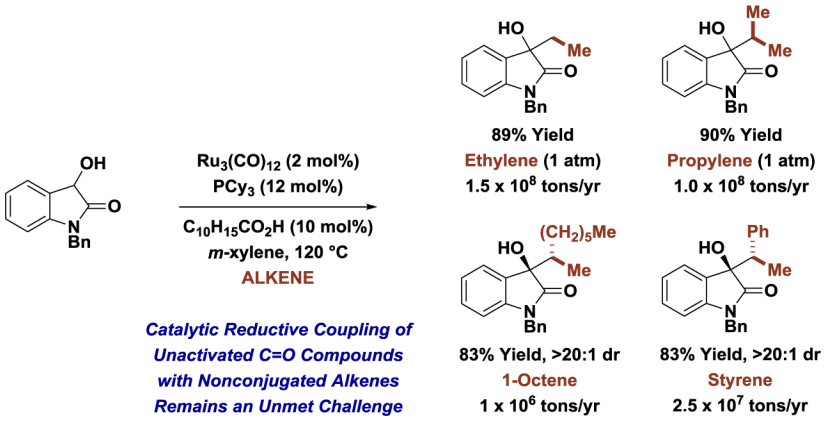
Scheme 8.

Hydrogen-mediated reductive coupling of acetylene with imines or aldehydes.



Scheme 9.

Synthesis of terpenoid natural products using a byproduct-free hydrogen auto-transfer addition.



Scheme 10.

Ethylene and higher feedstock olefins as non-stabilized carbanion equivalents.