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Reductive C–C Coupling *via* Hydrogenation and Transfer Hydrogenation: Departure from Stoichiometric Metals in Carbonyl Addition

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Abstract

Metal catalyzed reductive couplings of π -unsaturated reagents with carbonyl compounds *via* hydrogenation or transfer hydrogenation has emerged as an alternative to the use of stoichiometric organometallic reagents in carbonyl addition.

Introduction

Carbonyl addition mediated by premetalated reagents has played an important role in synthetic chemistry for well over a century (Scheme 1, top).^{1,2} Despite their utility, the organometallic reagents commonly used in carbonyl addition pose safety issues and generate stoichiometric quantities of metallic byproducts, which complicates large-volume chemical manufacture.³ Metal-catalyzed reductive coupling of π -unsaturated reactants with carbonyl compounds represents an alternative to classical carbonyl addition.^{4–14} However, many frequently utilized terminal reductants (BEt_3 , ZnEt_2) are just as problematic as the organometallic reagents they replace. In contrast, recently developed reductive couplings under the conditions of catalytic hydrogenation or transfer hydrogenation preclude the use of such hazardous reagents and the metallic byproducts they generate (Scheme 1, middle).^{15–18} An even more ideal approach to carbonyl reductive coupling is represented by hydrogen auto-transfer reactions that exploit the native reducing ability of reactant alcohols (Scheme 1, bottom).^{19–27} Here, alcohols serve dually as reductants and proelectrophiles (carbonyl precursors). Consequently, exogenous reductants are not necessary and byproduct-free carbonyl addition is achieved directly from the alcohol oxidation level. These processes convert lower alcohols to higher alcohols and, consequently, may be distinguished from related “borrowing hydrogen” reactions that deliver products of formal alcohol substitution.^{28–34}

Reductive coupling vs classical carbonyl addition

Under the conditions of hydrogen-mediated reductive coupling, reactions that traditionally have employed premetalated reagents may now be conducted catalytically in the absence of stoichiometric byproducts. To illustrate how these features streamline chemical synthesis, it

is instructive to compare classical methods with the corresponding hydrogenative processes. For example, the Oppolzer-Wipf method for enantioselective carbonyl vinylation^{35,36} requires alkyne hydrozirconation mediated by Cp_2ZrHCl , a mass-intensive reagent, with subsequent transmetalation to zinc mediated by ZnMe_2 , a pyrophoric liquid. Stoichiometric quantities of two organometallic reagents, Cp_2ZrHCl and ZnMe_2 , are required to promote asymmetric carbonyl addition. In contrast, under hydrogenation conditions, alkyne- $\text{C}=\text{X}$ ($\text{X} = \text{O}, \text{NR}$) asymmetric reductive coupling can be achieved in the absence of stoichiometric byproducts (Scheme 2).³⁷

Similarly, as exemplified by Brown's method,^{38,39} carbonyl crotylation is typically conducted using crotylmetal reagents. The requisite (*E*)- or (*Z*)-crotyldiisopinocampheylboranes are prepared through potassiation of butene followed by transmetalation to boron. Multiple manipulations and stoichiometric reagents (*n*-BuLi, KC_4H_7 , Ipc_2BOMe) are involved, and for each crotyl moiety that is transferred two equivalents of isopinocampheol are generated. Corresponding transfer hydrogenative processes for carbonyl crotylation are achieved through the direct coupling of primary alcohols with butadiene, an abundant petrochemical feedstock, in the absence of stoichiometric byproducts (Scheme 3).^{40,41}

Enolates represent one of the most commonly utilized carbanions in chemical synthesis, and are frequently deployed in the context of asymmetric aldol addition for the construction of polyketide natural products.^{42–45} The control of relative and absolute stereochemistry in asymmetric aldol additions representing a longstanding challenge; one that is typically addressed through stereoselective enolization in combination with the use of chiral auxiliaries. Direct asymmetric reductive aldol addition is achieved upon hydrogenation of vinyl ketones in the presence of aldehydes using chiral rhodium complexes.⁴⁶ This methodology was used to great effect in the total synthesis of the marine macrodiolide swinholide A.⁴⁷ Notably, hydrogen-mediated aldol addition occurs in the presence of olefinic functional groups in a completely chemoselective fashion (Scheme 4).

Conclusion

To conclude, by merging the characteristics of hydrogenation and carbonyl addition, we have developed a new family of catalytic asymmetric reductive couplings.^{7–13} These processes offer an alternative to the use of stoichiometric carbanions in a range of classical carbonyl additions, bypassing the issues of safety, selectivity and waste generation posed by premetalated reagents. Of potentially greater importance, the new patterns of reactivity underlying the present hydrogen-mediated C–C bond formations are empowering processes beyond classical transformations, unlocking hitherto unavailable volumes of chemical space. Among the many possibilities for further growth in this area, the development of catalytic systems for the catalytic C–C coupling of alcohols or amines with simple α -olefins represents a significant unmet challenge.¹¹

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Highlights

- H₂-Mediated reductive coupling represents an alternative to classical carbonyl addition
- Circumvents use of stoichiometric metals
- Enhances efficiency by minimizing discrete redox and protecting group manipulations
- Direct use of feedstock chemicals as partners for C-C coupling

Classical C=O Addition - Metallic Byproducts

Metal Catalyzed C=O Reductive Coupling

Metal Catalyzed C=O Reductive Coupling

Scheme 1.
Carbonyl addition beyond stoichiometric metals.

Scheme 2.

Beyond stoichiometric metals in asymmetric C=X (X = O, NR) vinylation.

Scheme 3.

Beyond stoichiometric metals in asymmetric carbonyl crotylation.

Scheme 4.

Beyond stoichiometric metals in asymmetric aldol addition.