Tetrahedron Letters 59 (2018) 1073–1079

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Digest paper

Base metal-catalyzed alcohol C–C couplings under hydrogen transfer conditions

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ARTICLE INFO

Article history:
Received 24 October 2017
Revised 23 January 2018
Accepted 25 January 2018
Available online 31 January 2018

Keywords:
Hydrogen transfer
Base metal
C–C coupling
Dehydrogenation and hydrogenation

ABSTRACT

Comparing to classical Grignard-type carbonyl additions, transfer hydrogenative C–C bond-forming reactions using alcohols as carbonyl precursors have shown remarkable advantages from the perspective of atom economy, step economy and redox economy. The significant drawbacks of conventional method, such as the use of multi-step reactions, the premetalated reagents, and stoichiometric oxidants and reductants, can be avoided by using hydrogen transfer processes. Moreover, the development of reactions employing earth-abundant and eco-friendly base metal as catalysts is an important objective in modern sustainable chemistry. In this review, we summarized recent advances in base metal-catalyzed C–C coupling of alcohols under hydrogen transfer conditions.

Contents

Introduction

Construction of carbon–carbon bond represents a fundamentally important transformation in organic synthesis. Accordingly, a number of Nobel Prizes in Chemistry have been awarded in the past century for reactions that construct carbon chains and rings, including the Grignard, Diels-Alder, and Wittig reactions. With the development of modern chemical science, safety and environment protection have become principal concerns, leading to an increased interest in green synthesis. Several conceptually novel principles, such as Trost's atom economy, Wender's step economy and Baran's redox economy, have emerged as measures of the "greenness" of a reaction and have subsequently been widely adopted by chemical community.[1] In the most recent decades, chemists have devoted substantial efforts toward the development of reactions that are not only green but also employ starting materials, solvent, reagents, and catalysts that are sustainable from the perspective of cost and availability.

Among many efficient strategies for sustainable chemical synthesis, the metal-catalyzed C–C coupling of alcohols through hydrogen transfer (HT) pathways constitutes one exceptionally promising approach (Scheme 1).[2] It typically commences with the activation of a starting alcohol with a transition-metal through a reversible hydrogen transfer to form a metal hydride and an aldehyde (or a ketone). The in situ generated metal-hydride species

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https://doi.org/10.1016/j.tetlet.2018.01.077
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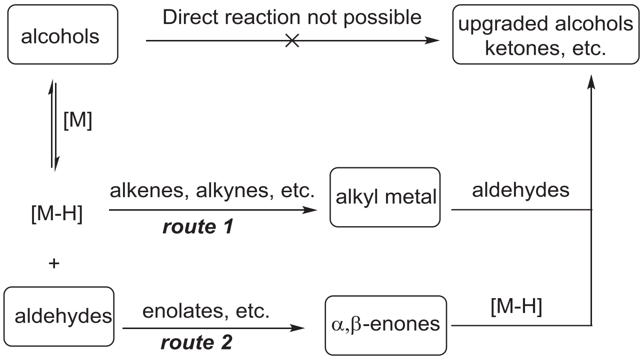
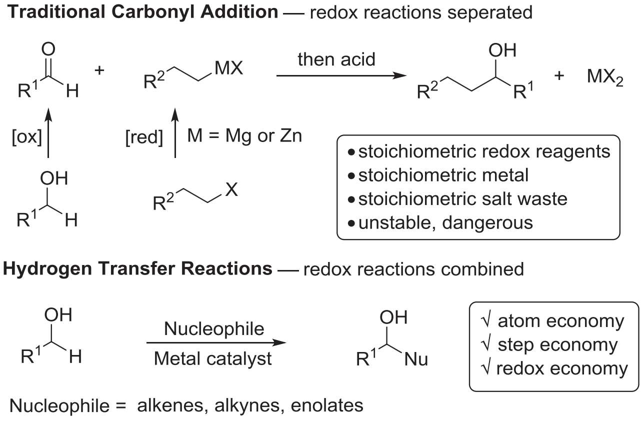


Scheme 1. Alcohol C–C coupling under hydrogen transfer conditions.

subsequently inserts into an unsaturated C–C bond to form an alkyl metal nucleophile, which in turn attacks the aldehyde to deliver the upgraded alcohol product (route 1). Alternatively, the aldehyde from alcohol dehydrogenation may first react with an enolate nucleophile to give a transient α,β-enone, which is reduced by the metal-hydride species to furnish the final product (route 2). Compared to the traditional Grignard reaction, the HT processes are exceptionally atom-economical since there may be no stoichiometric byproduct, or the only byproduct produced is an innocuous compound like water. Furthermore, these HT reactions have excellent step- and redox-economy, since the redox reactions occur simultaneously in single operation, while the traditional carbonyl additions require preformed nucleophiles and electrophiles that are separately generated via redox chemistry (Scheme 2). Apart from reaction efficiency, the use of alcohols as starting materials has the following benefits: a) alcohols can be obtained from abundantly available, but difficult to process and underutilized biomass; b) alcohols can be easily dehydrogenated to aldehyde by many transition metals; and c) alcohols can replace relative expensive reagents. For instance, they could take the place of alkyl halides in α-alkylation reactions of ketone. Taken together, the use of alcohols as substrates present substantial advantages in terms of various measures of reaction economy, compared to conventional multi-step reactions and stoichiometric metals, rendering C–C coupling more efficient, easier and safer.

Most of the HT reactions developed to date, however, rely on the use of noble metals, mainly ruthenium and iridium, which, as precious metals, are of considerable economic and environment cost, and the use of which may be unsustainable in the long run. To make HT reactions greener and more sustainable, it is desirable to develop efficient methods that replace noble metal with earth-abundant base metals. Base metals, including copper, iron, cobalt, nickel and manganese, are far more prevalent, readily obtained, and economically feasible for large scale chemical synthesis. Considering the fascinating features and potential applications of HT strategy, recent advances in base-metal catalyzed C–C coupling of alcohols under hydrogen transfer conditions are reviewed herein. Three types of reactions in which alcohols function as precursors to electrophiles are included: the coupling of alcohol and unsaturated hydrocarbons, α-alkylation of carbonyl compound, and the β-alkylation of alcohols.

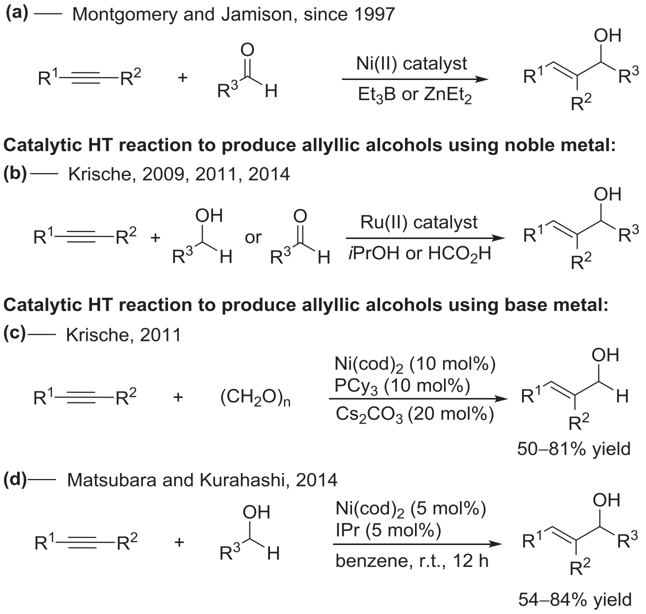


Scheme 2. Comparisons between traditional carbonyl addition and hydrogen transfer reactions.

Coupling of alcohol and unsaturated hydrocarbons

Allylic alcohols are found in a number of biologically active molecules. They are traditionally synthesized by the nucleophilic addition of vinylmetal reagents to carbonyl compounds. However, Grignard reagents and organolithium reagents are usually reactive to air and moisture, and are easily ignited or even pyrophoric. Moreover, these reagents lead to the generation of stoichiometric metal salts as waste products. Since 1997, Montgomery and Jamison have pioneered the development of nickel-catalyzed reductive coupling of easily accessible alkynes and aldehydes.[3] This chemistry provided an effective access to allylic alcohols without the use of preformed vinyl metal reagents, although stoichiometric reductants, like Et_3B and $ZnEt_2$, are normally still needed (Scheme 3a). In elegant works using noble metal catalysts, Krische has developed an array of coupling reactions of alkynes and alcohols (or aldehydes) catalyzed by ruthenium in the presence of an external, environmentally benign hydrogen source (e.g., *i*PrOH or HCO_2H) as another straightforward and powerful method to prepare diverse allylic alcohols (Scheme 3b).[4]

Although considerable effort has been devoted to developing base-metal catalyzed HT C–C coupling reactions, successful examples using alkynes as coupling partners are particularly rare. In 2011, an important breakthrough was made by Krische and coworkers, who developed the first nickel-catalyzed hydrohydroxymethylation of alkynes with paraformaldehyde to form allylic alcohols in 50–81% yield and with excellent regioselectivity (Scheme 3c).[5a] In this reaction, paraformaldehyde is used not



Scheme 3. Metal-catalyzed alkyne C–C coupling to form allylic alcohols.