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Metal Catalyzed Reductive C-C Bond Formation

A Departure from Preformed Organometallic Reagents

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Volume Editor: Michael J. Krische

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Preface

The prototypical catalytic reductive C–C bond formations, the Fischer-Tropsch reaction [1] and alkene hydroformylation [2], were discovered in 1922 and 1938, respectively [3,4]. These processes, which involve reductive coupling to carbon monoxide, have long been applied to the industrial manufacture of commodity chemicals [5]. Notably, alkene hydroformylation, also known as the oxo-synthesis, has emerged as the largest volume application of homogeneous metal catalysis, accounting for the production of over 7 million metric tons of aldehyde annually. Despite the impact of these prototypical reductive C–C bond formations, this field of research lay fallow for several decades. Eventually, the increased availability of mild terminal reductants, in particular silanes, led to a renaissance in the area of catalytic reductive C–C bond formation. For example, the first catalytic reductive C–C couplings beyond hydroformylation, which involve the hydrosilylative dimerization of conjugated dienes [6–12], appeared in 1969 – approximately 16 years after the first reported metal-catalyzed alkene hydrosilylation [13]. Following these seminal studies, the field of catalytic reductive C–C bond formation underwent explosive growth, culminating in the emergence of an ever growing body of research encompassing a powerful set of transformations.

To our knowledge, no thematic volumes devoted solely to metal-catalyzed reductive C–C bond formation have been assembled. For the first time, in this issue of *Topics in Current Chemistry*, we present a compilation of monographs from several leaders in this burgeoning area of research. This collection of reviews serves to capture the diversity of catalytic reductive C–C couplings presently available and, in turn, the remarkable range of reactivity embodied by such transformations. There is no indication that this field has reached its zenith and it is the hope of the present author that this volume will fuel further progress.

Of greatest significance, many of the reductive couplings described in this account involve the use of carbonyl compounds and imines as coupling partners. Hence, catalytic reductive additions to such conventional electrophiles herald a departure from the use of preformed organometallic reagents. For example, the catalytic reductive aldol couplings described in the volume employ metallo-enolates generated transiently in substoichiometric quantities under catalytic conditions, representing an alternative to stoichiometrically

preformed metallo-enolates and related enol derivates. Metal catalyzed reductive C–C bond formation promises to take organic chemistry beyond stoichiometric metallic reagents, thus fortifying a cornerstone of synthetic organic chemistry – the broad areas of carbonyl and imine addition.

University of Texas at Austin, April 2007 Michael J. Krische

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Nickel-Catalyzed Reductive Couplings of Aldehydes and Alkynes

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Abstract The nickel-catalyzed coupling of aldehydes and alkynes has evolved into a broadly useful procedure for the preparation of allylic alcohols. An overview of the many variants of the process, illustrations of complex synthetic applications, and a discussion of mechanism is provided. Additionally, a brief summary of mechanistically related nickel-catalyzed processes as well as a description of alternate strategies for the reductive coupling of aldehydes and alkynes using other metals is provided.

Keywords Allylic alcohol · Nickel · Reductive coupling · Reductive cyclization · Reductive cycloaddition

Abbreviations

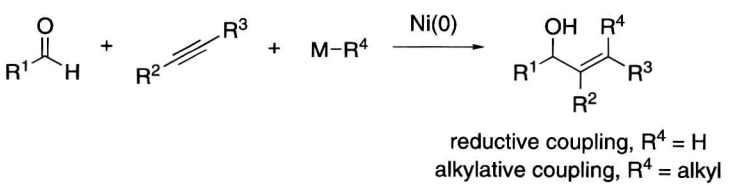
COD	1,5-Cyclooctadiene
Cyp	Cyclopentyl

IMes	*N*,*N*′-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPr	*N*,*N*′-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene
MOM	Methoxy methyl
NHC	*N*-Heterocyclic carbene
TBS	*t*-Butyldimethylsilyl
TES	Triethylsilyl
TIPS	Triisopropylsilyl
TMEDA	Tetramethylethylene diamine

1 Introduction

Allylic alcohols are useful substructures as key subunits embedded within bioactive natural products as well as versatile precursors for a variety of synthetic transformations. The range of transformations that rely on allylic alcohol derivatives include diverse processes such as metal π-allyl chemistry [1], directed epoxidations [2] and cyclopropanations [3, 4], cationic cyclization processes [5], S_N2' allylic displacement processes [6], and various sigmatropic processes including Claisen rearrangements and related variants [7]. A number of classical procedures allow efficient synthesis of allylic alcohols, with the most widely used procedures involving 1,2-reduction of enones or addition of vinyl organometallics to aldehydes or ketones. In a more contemporary strategy, the Hiyama–Nozaki–Kishi coupling [8, 9], which involves the nickel-catalyzed addition of vinyl halides to aldehydes, has become a benchmark procedure that is widely used.

An alternative to these procedures is the direct union of aldehydes and alkynes in a reductive coupling process (Scheme 1). The primary advantage of the reductive coupling of aldehydes and alkynes is that the olefin stereochemistry, the configuration of the hydroxyl-bearing stereocenter, and the central carbon–carbon single bond of the product allylic alcohol are all established in a single operation. The widely used methods described in the previous paragraph, while very powerful in many applications, each require two or more steps to establish these key structural features. This review will focus specifically on the development of nickel-catalyzed reductive couplings of aldehydes



Scheme 1 Reductive coupling of aldehydes and alkynes

and alkynes [10–13]. Concluding sections will briefly describe mechanistically related nickel-catalyzed processes as well as summarize methods for alkyne/aldehyde reductive couplings involving other transition metals.

2
Aldehyde/Alkyne Couplings

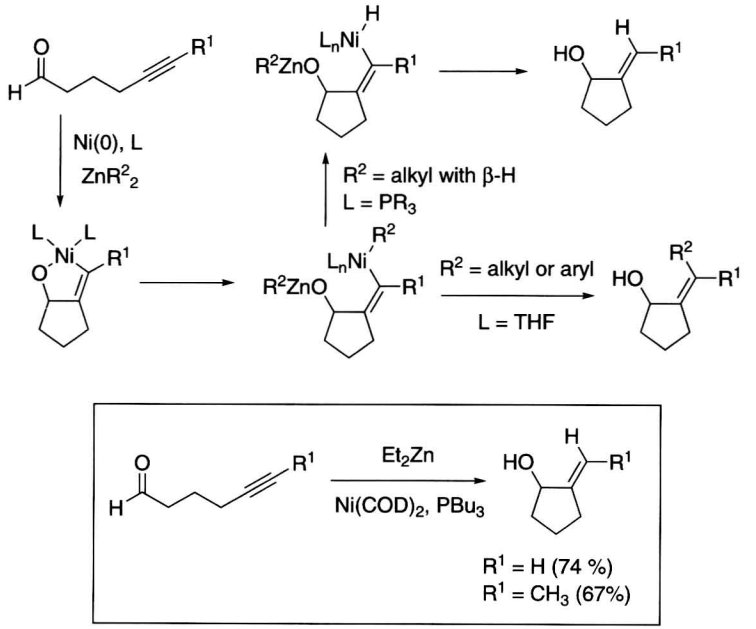
The nickel-catalyzed coupling of aldehydes and alkynes was first described in 1997, and many variants of the process are now known (Scheme 1) [14]. The processes may proceed intermolecularly or intramolecularly to assemble rings ranging from five-membered up to macrocyclic ring systems. Both alkylative and reductive processes may be performed, with the distinction involving whether a carbon substituent (alkylative coupling) or hydrogen substituent (reductive coupling) is installed from the reducing agent. Catalyst systems involving low valent nickel species stabilized by COD, phosphines, or *N*-heterocyclic carbenes (NHCs) are known, with phosphines and NHCs typically being monodentate. Reducing agents (MR^4) typically employed include silanes, organozincs, organoboranes, or vinylzirconium reagents.

2.1
Reductive Cyclizations

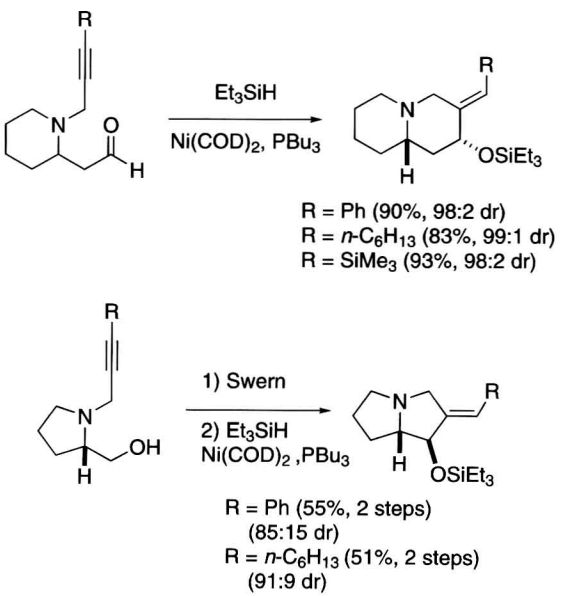
The first examples of nickel-catalyzed reductive couplings of aldehydes and alkynes involved organozincs as reducing agents (Scheme 2) [14]. In five-membered ring cyclizations, reductive couplings are effective with a $Ni(COD)_2/PBu_3$ catalyst system, whereas phosphine-free catalyst formulations favored the alkylative variant. In the phosphine-free conditions, reactions are rapid and favor the alkylative manifold, even with organozincs that are sp^3-hybridized and possess β-hydrogens. Alternatively, with $Ni(COD)_2/PBu_3$ (1 : 4) as catalyst, reactions are slower and favor the reductive manifold with Et_2Zn as reducing agent. A metallacycle that may serve as a common intermediate for both alkylative and reductive manifolds is depicted, and mechanistic issues are described in more detail in Sect. 3.

Subsequent studies illustrated that Et_3SiH and Et_3B are more effective reducing agents than Et_2Zn in promoting the reductive cyclization pathway. A number of bicyclic heterocycles were prepared employing the Et_3SiH variant, and the approach proved general for a number of different quinolizidine, indolizidine, and pyrrolizidine skeletal frameworks (Scheme 3) [15, 16].

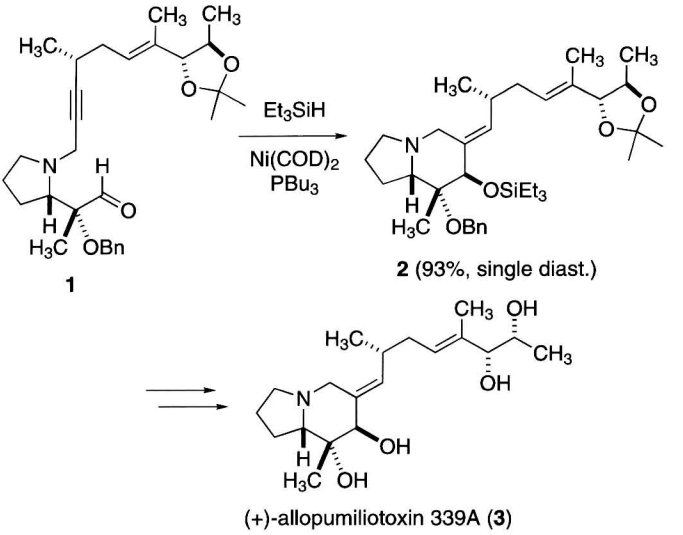
In addition to the methodological advances noted above, the Et_3SiH variant was utilized in the total synthesis of three members of the allopumiliotoxin family [15, 16]. In one of the more complex examples, ynal substrate **1** was converted to product **2** in 93% isolated yield as a single diastereomer (Scheme 4). Simple removal of the protecting groups allowed completion of



Scheme 2 Organozinc-mediated reductive cyclizations



Scheme 3 Triethylsilane-mediated reductive cyclizations



Scheme 4 Total synthesis of pumiliotoxin 339A

the synthesis of allopumiliotoxin 339A (**3**). This rapid approach to the pumiliotoxin framework provides an illustration of the complexity that can be installed in a single catalytic operation utilizing the ynal reductive cyclization method.

The Et_3B/PBu_3 and the NHC/Et_3SiH variants have largely been applied in intermolecular approaches, although both variants have been demonstrated to be useful in macrocyclizations. Elegant total syntheses of amphidinolides T1 and T4 were illustrated utilizing a complex macrocyclization involving the Et_3B variant (Scheme 5) [17, 18]. Cyclization of ynal **4** with $Ni(COD)_2/PBu_3$ with Et_3B as reducing agent allowed the efficient preparation of allylic alcohol **5**, which was converted to amphidinolide T1 (**6**). A key feature of the approach was the use of an aromatic alkyne, which directed the regiochemistry to favor the desired exocyclization process. An attempt to accomplish an endocyclic macrocyclization in the total synthesis of terpestacin was not successful since the exocyclic pathway predominated in that case as well. However, an intermolecular reductive coupling ultimately proved successful in that strategy (see Sect. 2.2.1).

The complementary regioselectivity of the NHC/Et_3SiH and PBu_3/Et_3B variants was demonstrated as a strategy for favoring either endocyclic or exocyclic macrocyclizations selectively in a ligand-controlled approach [19]. With ynal **7** for example, reductive macrocyclization with the very bulky IPr ligand and Et_3SiH as the reducing agent favored exocyclization product **8**, whereas cyclization with PMe_3 as the ligand and Et_3B as the reducing agent favored endocyclization product **9** (Scheme 6). A steric model was presented, suggesting that the bulky IPr ligand positions the alkyne in complex **10** such