

Ketone-Based Transition-Metal-Catalyzed Carbon–Carbon and Carbon–Hydrogen Bond Activation: Exploratory Studies

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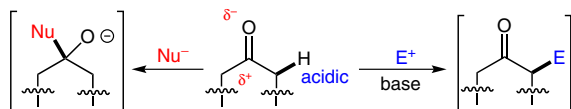
Dedicated to Professor Barry M. Trost

Abstract: The importance and ubiquity of ketone functional groups in organic synthesis has always been a driving force for discovering new modes of reactivity. Stimulated by the challenges of fused-ring synthesis and ketone alkylation, we summarize here our exploratory studies on ketone-based transition-metal-catalyzed carbon–carbon and carbon–hydrogen bond activation.

Key words: catalysis, cyclizations, alkylations, ketones, rhodium

Ketones are among the most important and ubiquitous functional groups found in a diversity of molecules ranging from natural products to materials. They also serve as key intermediates for many transformations in organic chemistry.¹ Selective reactions mediated by ketones have made a significant impact on organic synthesis in the past. Most of these reactions are generally driven by either the electrophilic character of the carbonyl carbon or the acidity of the α -hydrogen (Scheme 1). Thus, methodologies based on new modes of reactivity of ketones, particularly those that can provide high atom-economy,² are important and highly sought after.

Our research has been inspired by two long-standing ketone-related synthetic challenges: (1) finding a unified strategy to access fused rings using simple cyclic ketones as precursors and (2) the alkylation of ketones using simple unactivated olefins. Here, we summarize our recent progress towards these goals using transition-metal-catalyzed carbon–carbon and carbon–hydrogen bond functionalization.



Scheme 1 General reactivity of ketones

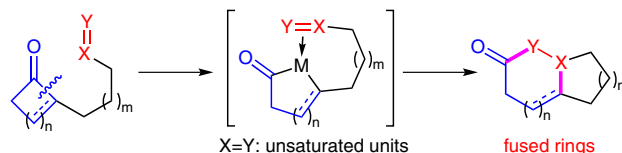
Ketone-Based Carbon–Carbon Bond Activation

Fused ring systems are widely found in natural products and drugs. Aiming towards a unified strategy for their synthesis, we conceived a catalytic ‘cut and sew’ approach using simple cyclic ketones as precursors (Scheme



Guangbin Dong received his B.S. degree from Peking University and completed his Ph.D. degree in chemistry at Stanford University, where he was a Larry Yung Stanford Graduate Fellow working with Professor Barry M. Trost. In 2009, he began research with Professor Robert H. Grubbs at the California Institute of Technology as a Camille and Henry Dreyfus Environmental Chemistry Fellow. In 2011, he joined the Department of Chemistry and Biochemistry at the University of Texas at Austin as an assistant professor and a CPRIT (Cancer Prevention Research Institute of Texas) Scholar. His research interests lie in the development of powerful chemical tools for addressing questions of biological importance.

2).³ In this approach, the transition-metal catalyst first ‘cuts’ the α -carbon–carbon bond of the ketone through oxidative addition, and then ‘sews’ to give fused rings via the migratory insertion of an unsaturated unit followed by reductive elimination. It is expected that by changing ring sizes, linker lengths, and unsaturated unit types, a great diversity of fused-ring scaffolds, which are difficult to access by conventional methods, will be afforded using a single approach.



Scheme 2 A ‘cut and sew’ strategy for the synthesis of fused rings

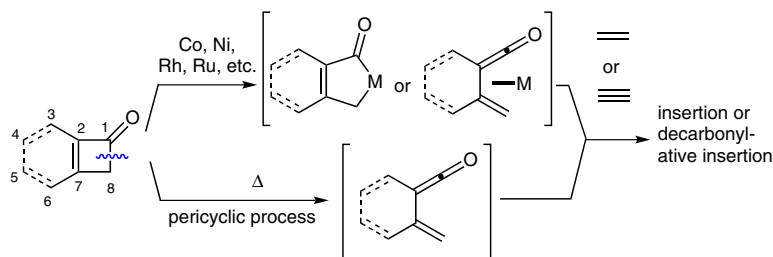
To prove the feasibility of this ‘cut and sew’ strategy, we initially focused on a benzocyclobutenone system. Also known as ‘vinylketene’ equivalents, cyclobutenones can undergo ring opening followed by the insertion of alkenes

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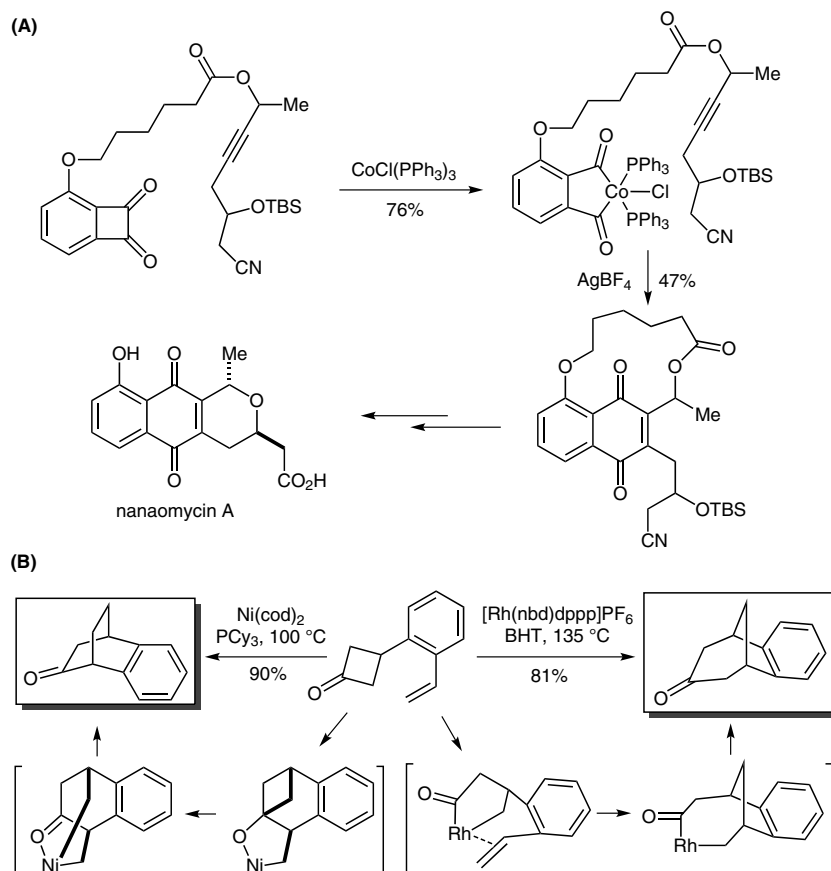
Scheme 3 Carbon–carbon bond cleavage of cyclobutenones

or alkynes under thermal conditions (Scheme 3).⁴ Higher reactivity and a broader scope have been shown using transition-metal catalysts. Pioneering work by Huffman and Liebeskind demonstrated that the insertion of alkynes into cyclobutenones can be catalyzed using a nickel catalyst.⁵ Contributions from Kondo and Mitsudo and co-workers enabled electron-deficient olefins norbornene and ethene to react intermolecularly using rhodium or ruthenium as catalysts.⁶ Decarbonylative insertions have also been developed.⁷ More recently, the insertion of alkynylboronates into cyclobutenones has been reported by Auvinet and Harray.⁸ It is noteworthy that in these transformations, cleavage of the less-hindered C-1–C-8 bond is generally observed.

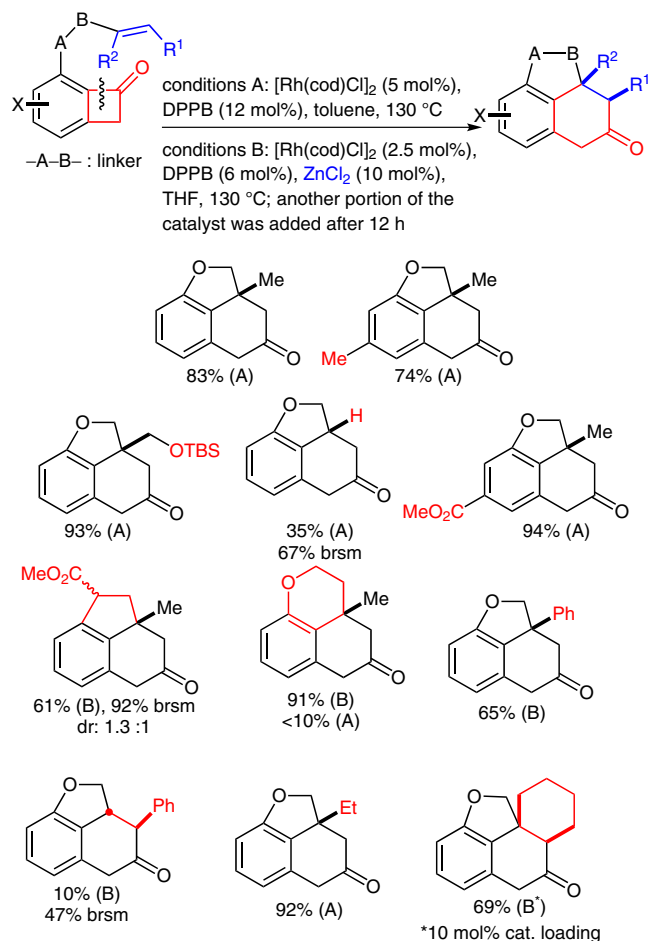
The intramolecular version of the aforementioned transformation was also reported by South and Liebeskind, where a cobalt-mediated cyclization occurred between a

benzocyclobutenedione and an alkyne. This method has been utilized in the total synthesis of nanaomycin A (Scheme 4, part a).⁹ Seminal work by Murakami et al. illustrated the catalytic intramolecular insertion of styrene-type olefins into cyclobutanones to give bridged ring systems, where complementary reaction pathways were achieved using different catalysts (Scheme 4, part b).¹⁰

We recently developed an olefin-directed, rhodium-catalyzed carboacylation using benzocyclobutenones, in which the more-hindered C-1–C-2 bonds are selectively activated (Scheme 5).³ A broad range of olefins can undergo this ‘cut and sew’ sequence including mono-, di-, and even trisubstituted olefins with both alkyl or aryl substituents. In addition, all-carbon quaternary centers can be efficiently generated and a number of functional groups are tolerated under the reaction conditions.



Scheme 4 Seminal examples of intramolecular cyclization; cod = cycloocta-1,5-diene; nbd = norbornadiene; dppp = 1,3-bis(diphenylphosphino)propane; BHT = butylated hydroxytoluene



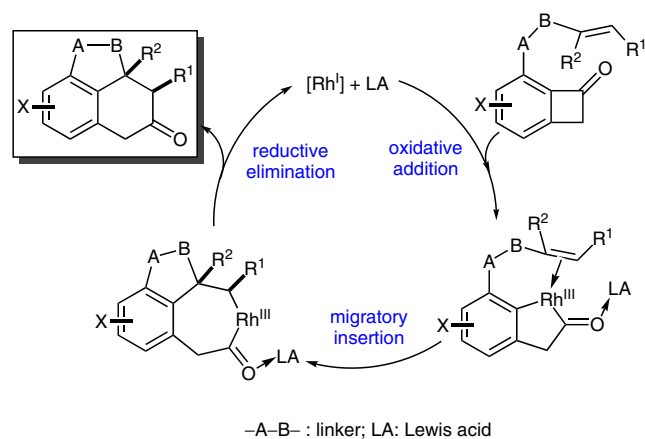
Scheme 5 ‘Cut and sew’ to access fused rings; dppb = 1,4-bis(diphenylphosphino)butane; brsm = based on recovered starting material

Furthermore, Lewis acid catalysts, such as zinc(II) chloride, were found to greatly enhance the overall reactivity; its usage was critical for more-challenging substrates, such as trisubstituted olefins and those that form hydropyran rings. We postulate that the role of the Lewis acid, zinc(II) chloride, in this catalytic cycle is twofold: it promotes both oxidative addition and reductive elimination through coordination with the carbonyl group of the substrate and the rhodacycle intermediate, respectively. This interaction makes both the substrate and the rhodacycle intermediate electron deficient.³ The proposed catalytic cycle is depicted in Scheme 6.

We expect this carbon–carbon bond activation method to serve as an important preliminary study towards our long-term goal of developing a unified strategy for fused-ring synthesis.

Ketone-Based Carbon–Hydrogen Bond Activation

As one of the most significant ways to generate carbon–carbon bonds, the alkylation of ketones has had long-standing interest.¹¹ Classical ways to alkylate ketones generally require strong bases (such as LDA) and halogen-based agents (Scheme 7, part a). The formation of stoichiometric byproducts and the difficulty associated in controlling monoalkylation/regioselectivity have been



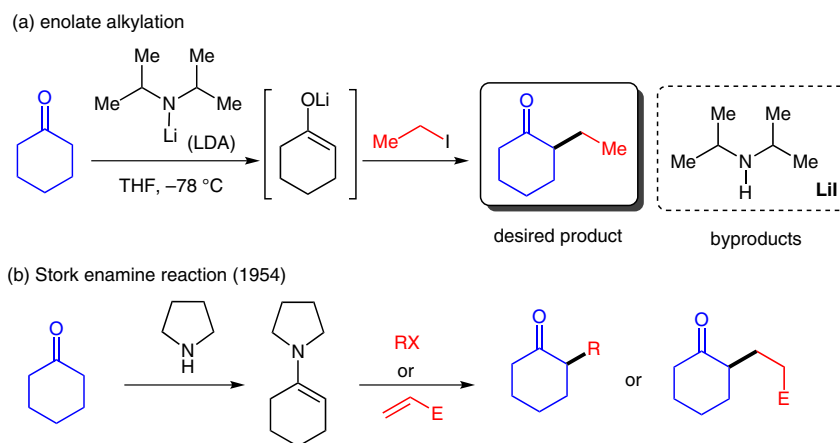
Scheme 6 Proposed catalytic cycle

concerns using such reactions.¹² The Stork enamine reaction is considered a breakthrough for the alkylation of ketones owing to its excellent regioselectivity and obviation of multiple alkylations (Scheme 7, part b); however, reactive alkylating agents are generally needed (i.e., methyl or allylic halides or Michael acceptors).¹³

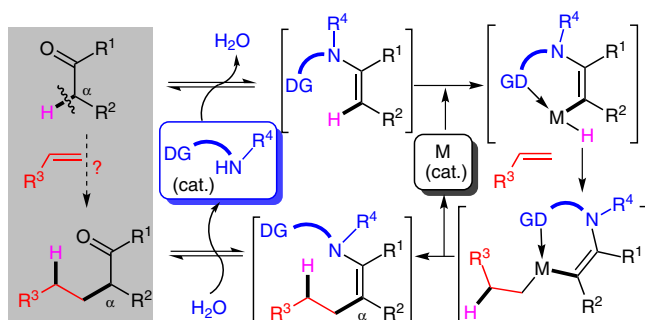
In search for a ‘green’ method to prepare alkylated ketones, we have been intrigued by the idea of using ‘simple unactivated olefins’ as alkylating agents through catalytic carbon–hydrogen bond and olefin coupling.

Intramolecular coupling between ketones and unactivated olefins has been well documented as the Conia-ene reaction.¹⁴ Generally, this reaction proceeds at high temperatures (>250 °C) and with moderate yields, and only a few functional groups are tolerated under the reaction conditions. Further seminal work on catalytic intramolecular cyclizations by Toste and co-workers¹⁵ and others^{16,17} involves Lewis acid metal-catalyzed coupling of activated methylene groups with alkynes. In addition, an intramolecular palladium-catalyzed ketone addition to olefins for accessing various cyclohexanone derivatives was first reported by Widenhoefer.¹⁸ Fewer efforts have been made on catalytic intermolecular ketone–olefin couplings. A potassium *tert*-butoxide catalyzed addition of ketones to styrenes was developed by Knochel and co-workers,¹⁹ and a manganese/cobalt-initiated radical process for the addition of ketones across nonaromatic olefins was reported by Ishii and co-workers, albeit requiring a large excess of ketone.²⁰ Hence, a general method for the addition of ketone α -carbon–hydrogen bonds across olefins remains underdeveloped.

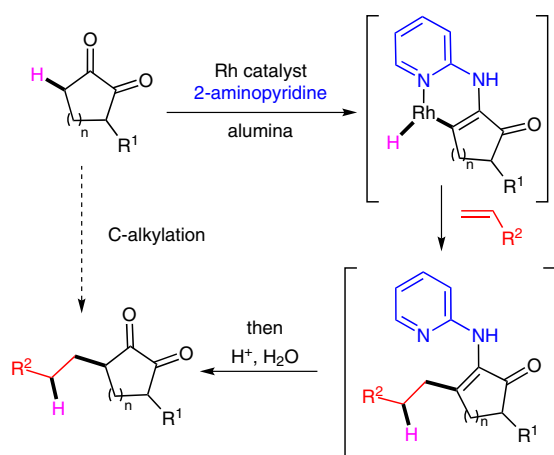
Inspired by the Stork enamine reaction, we conceived a carbon–hydrogen bond functionalization strategy to achieve the desired ketone–olefin coupling. We envisaged that *enamine formation would convert the ketone α - sp^3 -carbon–hydrogen bonds into sp^2 -carbon–hydrogen ones, thus enhancing their reactivity towards oxidative addition by a low-valent transition metal (Scheme 8). Meanwhile, if we incorporated a proper directing group (DG) in the amine agent, metalation would be directed to the α -car-*



Scheme 7 Classical methods for ketone alkylation



Scheme 8 A proposed strategy for ketone–olefin coupling

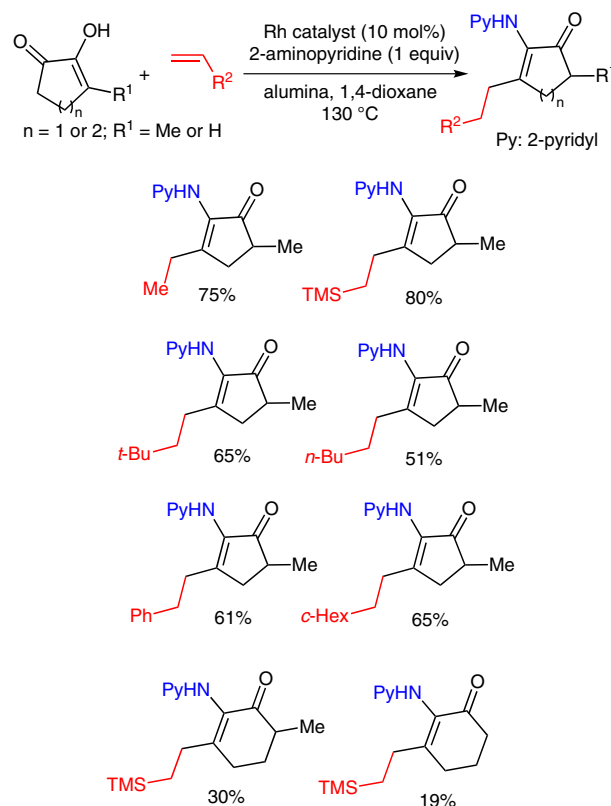


Scheme 9 Regioselective C-alkylation of cyclic 1,2-diketones

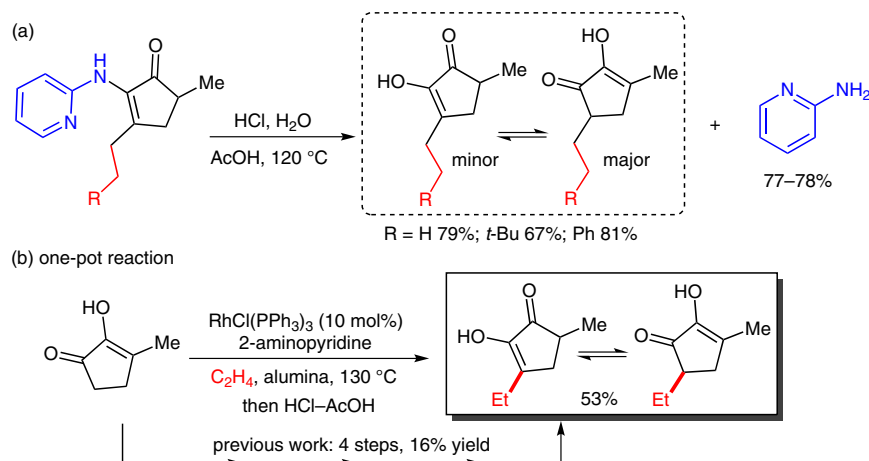
bon–hydrogen bonds upon enamine formation.²¹ Subsequent olefin insertion–reductive elimination and enamine hydrolysis would lead to the desired α -alkylation product. As documented in organocatalysis, enamine formation and hydrolysis can exist in an equilibrium, but the less-hindered ketone (starting material) forms the enamine faster than the hindered ketone (product).²² In addition, such an equilibrium is known to be compatible with the rhodium-catalyzed carbon–hydrogen bond/olefin coupling reaction.²³ Therefore, in principle, the amine DG can be employed catalytically.

Serving as an important proof of concept, we recently demonstrated the feasibility of such a strategy for a 1,2-diketone system (Scheme 9).²⁴ 2-Aminopyridine was employed as a traceless and removable DG.²⁵ Delightfully, after exploration of the reaction conditions, the desired enamine formation and subsequent carbon–hydrogen bond/olefin coupling proceed smoothly (Scheme 10). A range of terminal olefins undergo the coupling reaction providing the desired alkylated enamines in low to good yields.

Further, we also demonstrated the DG can be removed and recycled, providing the monoalkylated diketone (Scheme 11, part a). Finally, the enamine formation, car-



Scheme 10 C-Alkylation of cyclic 1,2-diketones through enamine formation



Scheme 11 Removal of the directing group and the one-pot reaction

bon–hydrogen bond/olefin coupling, and hydrolysis can all be operated in one pot (Scheme 11, part b). The efficiency of this method is also demonstrated in the synthesis of a natural flavoring compound (from roasted coffee), 3-ethyl-5-methylcyclopenta-1,2-dione (one pot, 53% vs 16% yield from a previous route of 4 steps from the same starting material).²⁶ We expect that this work will serve as a seminal study towards catalytic ketone α -alkylation with unactivated olefins.

In conclusion, our exploratory studies towards ketone-based carbon–carbon and carbon–hydrogen bond activation have been summarized. These include a ‘cut and sew’ strategy to prepare fused rings and a dual-activation strategy²⁷ for ketone alkylation using simple olefins. Although still in the very preliminary stage, efforts in these arenas should have a broad impact on the enhancement of synthetic efficiency.

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