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Dimerization of Cyclopropyl Ketones and Crossed Reactions of Cyclopropyl Ketones with Enones as an Entry to Five-Membered Rings

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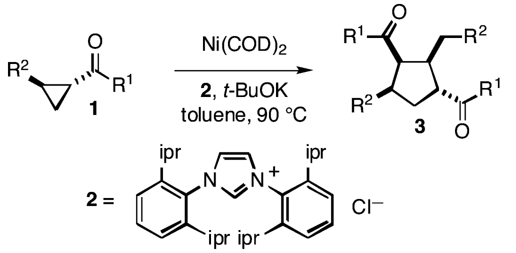
[3 + 2] Cycloadditions are among the most powerful strategies for the synthesis of five-membered carbocyclic and heterocyclic ring systems.[1] Among the reactions useful in the synthesis of cyclopentanes, trimethylene methane precursors,[2] activated cyclopropanes,[3] and allyl and propargylsilanes[4] are arguably the most useful three-carbon units in [3 + 2] cycloadditions. Methylene cyclopropanes are known to be versatile precursors in metal-catalyzed [3 + 2] cycloadditions involving either trimethylene methane intermediates or four-membered metallacycles, depending on whether the σ-bond proximal or distal to the exocyclic methylene undergoes oxidative addition with the low-valent transition metal.[3] Vinylcyclopropanes are also excellent substrates in metal-catalyzed cycloadditions and rearrangements in several contexts.[5] However, cyclopropanes that lack exomethylene or vinyl substituents have received relatively little attention as useful precursors in metal-catalyzed cycloaddition processes. Donor−acceptor cyclopropanes are highly versatile substrates in five-membered ring synthesis via Lewis acid catalysis.[6] However, Lewis acid-promoted [3 + 2] cycloadditions of simple cyclopropyl ketones are typically not efficient. Given the lack of utility of simple cyclopropyl ketones in both Lewis acid-catalyzed and transition metal-catalyzed cycloadditions, we have initiated an exploratory investigation of this potentially useful substrate class in nickel-catalyzed reactions.

In gauging the reactivity of cyclopropyl ketone **1a** with a catalyst derived from Ni(COD)$_2$, imidazolium chloride **2**, and potassium *tert*-butoxide,[7] we made the surprising observation that **1a** undergoes an efficient and highly diastereoselective dimerization to trisubstituted cyclopentane **3a** in 85% yield. A variety of aromatic ketones undergo the process efficiently (Table 1, entries 1−5), and aliphatic ketones were significantly less reactive in the process. Variation of the cyclopropyl unit was difficult since even a simple methyl substituent led to low yields of expected adduct **3f** along with 66% yield of 3-methyl-1-phenylbut-2-en-1-one (Table 1, entry 6). We reasoned that this remarkable transformation likely involves the oxidative addition of Ni(0) to **1** to afford metallacycle **4a** or **4b**,[8] which undergoes a sequence involving β-hydride elimination to afford enone **5a** or **5b** along with regeneration of Ni(0) (Scheme 1).[9] Enone **5a** then undergoes addition to another equivalent of **4b** to afford [3 + 2] cycloaddition product **3** (when R^2 = H, note that **4a** = **4b** and **5a** = **5b**, with alkene stereochemistry arbitrarily shown). The formation of an enone as the major product in reactions of substrate **1f** provided direct evidence for the **1** to **5b** conversion. Analysis of the overall mass balance of entry 6 (Table 1) illustrates that metallacycle **4b** is favored via oxidative addition to the least hindered carbon−carbon bond of **1**, although both **4b** and **5a** are required for the formation of **3f**.

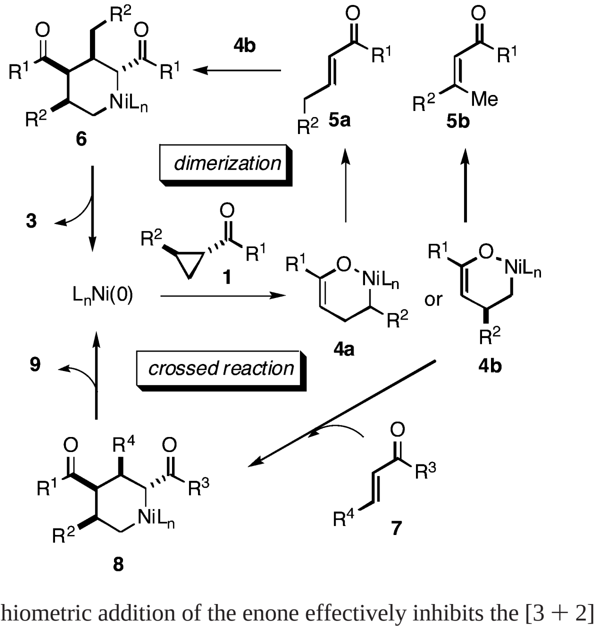
Table 1. Cyclopropyl Ketone Dimerizations



entry (substrate)	R^1	R^2	product (% yield, dr)
1 (**1a**)	Ph	H	**3a** (85, 98:2)
2 (**1b**)	4-MeO(C$_6$H$_4$)	H	**3b** (90, 99:1)
3 (**1c**)	4-F(C$_6$H$_4$)	H	**3c** (85, 98:2)
4 (**1d**)	thiophen-2-yl	H	**3d** (88, 99:1)
5 (**1e**)	furan-2-yl	H	**3e** (83, 90:10)
6 (**1f**)	Ph	Me	**3f** (24)[a]

[a] 3-Methyl-1-phenylbut-2-en-1-one was obtained in 66% yield.

Scheme 1. Proposed Mechanism



The crossed reaction of differentially substituted cyclopropyl ketones and enones was attempted in order to advance the synthetic utility of the process and to provide further evidence for the proposed reaction pathway. However, initial attempts failed since stoichiometric addition of the enone effectively inhibits the [3 + 2] process, presumably due to its π-acidity. However, keeping the enone concentration low by syringe drive addition over 2 h duplicates the slow release of enone suggested in the proposed mechanism, and crossed reactions now become possible (Table 2). Yields were typically modest to good, and the cyclopropyl ketone dimer **3** is nearly always observed as a component of the reaction mixture. While not strictly required, Ti(O-*i*Pr)$_4$ or Ti(O-*t*Bu)$_4$ as an additive improves yields and increases reaction rates. The crossed reactions of differentially substituted cyclopropyl ketones and

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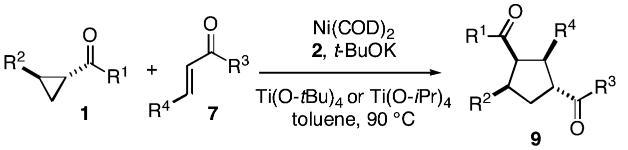
Table 2. Crossed Reactions of Cyclopropyl Ketones and Enones

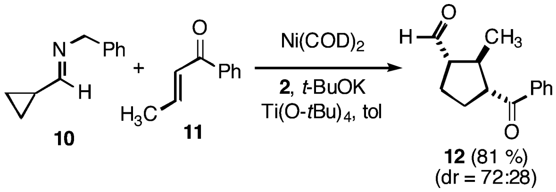


entry	R^1	R^2	R^3	R^4	product[a] (% yield, dr)
1	4-F(C_6H_4)	H	Ph	Me	**9a** (77, 94:6)
2	thiophen-2-yl	H	Ph	Me	**9b** (59, 97:3)
3	Ph	H	furan-2-yl	Me	**9c** (58, 96:4)
4	furan-2-yl	H	Ph	Me	**9d** (42, 90:10)
5	4-F(C_6H_4)	H	Ph	C_6H_{13}	**9e** (66, 93:7)
6	4-F(C_6H_4)	H	Ph	Ph	**9f** (59, 39:61)[b]
7	Ph	H	Ph	$SiMe_3$	**9g** (41, >97:3)
8	Me	H	Ph	Me	**9h** (47, 93:7)
9	Ph	Me	Ph	Me	**9i** (52, 75:25)
10	Ph	Me	furan-2-yl	Me	**9j** (41, 88:12)

[a] Typically, equimolar amounts of **1** and **7** were used. Most of the remaining mass balance was the dimer of **1**. See Supporting Information for details. [b] The major product is the trans/trans isomer of **9**.

enones that both possess aromatic substitution at the carbonyl proceed efficiently by this procedure (entries 1−4). Notably, a comparison of entries 3 and 4 illustrates that diastereoselectivities are kinetically controlled, and that either cis−trans diastereomer may be obtained by simply swapping the ketone substituents on the two reaction partners. Additionally, use of an enone reactant now allows additional flexibility in the R^4 functionality, as illustrated by incorporation of *n*-hexyl (entry 5), phenyl (entry 6), or trimethylsilyl (entry 7) substituents. Whereas dimerization of cyclopropyl methyl ketone was inefficient, a crossed reaction involving this substrate did proceed with modest efficiency (entry 8). Additionally, the use of disubstituted cyclopropanes allows the generation of tetrasubstituted cyclopentanes (entries 9 and 10). As noted above (Scheme 1), the dimerization of disubstituted cyclopropanes was inefficient since the formation of the desired cyclopentane required the formation of enone **5a** via oxidative addition of nickel into the more hindered cyclopropane carbon−carbon bond. However, with the syringe drive addition of enone **7**, cyclopentane **9** may be obtained solely from favored metallacycle isomer **4b** without requiring the production of **5a** from the less-favored metallacycle **4a**.

A significant limitation of the above reactions is that neither reaction partner bearing aldehyde or ester functional groups undergoes efficient cyclizations. For instance, cyclopropyl carboxaldehyde affords none of the desired cyclopentane products under conditions optimized for the dimerization or crossed reaction. However, aldimine **10**, when treated with enone **11** under the crossed reaction conditions, efficiently affords aldehyde **12** in 81% isolated yield as a 72:28 mixture favoring the trans/trans isomer. Formation of a diastereomer different than that observed in reactions of cyclopropyl ketones may be linked to the ease of epimerization of the aldehyde. Considering the decreased electrophilicity of cyclopropyl imines compared with cyclopropyl carboxaldehydes, the improved reactivity of the imine derivative is noteworthy. We suspect that prior coordination of the imine nitrogen to nickel may facilitate oxidative addition into the cyclopropane carbon−carbon bond.[10] Future studies will focus on further development of cyclopropyl imine cycloadditions and elucidation of the mechanistic basis for reaction acceleration with imine derivatives.



(1)

In summary, a new nickel-catalyzed cycloaddition process involving simple cyclopropyl ketones has been developed. An unexpected dimerization of cyclopropyl ketones was observed, and analysis of the reaction pathway led to development of a synthetically useful crossed reaction between cyclopropyl ketones and enones to afford densely functionalized cyclopentane products.

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Supporting Information Available: Full experimental details and copies of NMR spectral data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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