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[3+2] Cycloaddition Reactions of Cyclopropyl Imines with Enones

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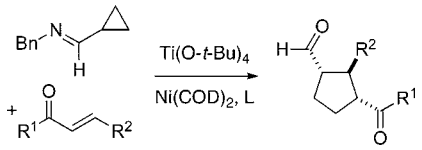
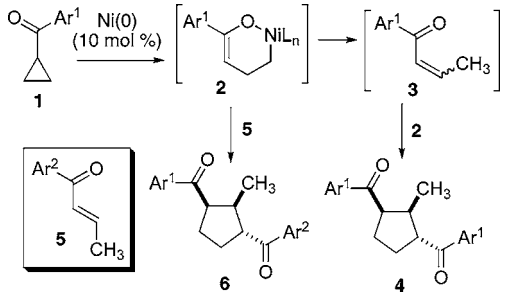
ABSTRACT



A nickel-catalyzed [3+2] cycloaddition of cyclopropyl aldimines and enones has been developed. The process provides direct access to trisubstituted cyclopentanes, and the scope exceeds that of the corresponding reactions involving cyclopropyl ketones. A basis for the improved performance of cyclopropyl aldimines compared with cyclopropyl ketones is provided.

Transition metal-catalyzed ring opening of cyclopropanes is a key step in a number of cycloaddition processes. The involvement of vinyl cyclopropanes[1] and methylene cyclopropanes[2] in metal-catalyzed cycloadditions is well established in a number of important contexts. However, cyclopropanes that lack either a methylene or vinyl substituent are generally unreactive in metal-catalyzed processes.[3,4] A strategy for overcoming this limitation was recently disclosed simultaneously by our group and by Ogoshi.[5] In an example of that work, cyclopropyl ketone **1** was demonstrated to be an effective participant in a [3+2] cycloaddition process, either in an unusual dimerization process to produce cyclopentane **4** or in a crossed reaction with enone **5** to produce cyclopentane **6** (Scheme 1). Six-membered metallacyclic enolate **2** was an intermediate in both pathways, and the dimerization sequence was shown to involve enone **3** generated from the rearrangement of metallacycle **2**.

Scheme 1. Cyclopropyl Ketone Dimerizations and Crossed Cycloadditions



Although cyclopropyl(phenyl)ketone cycloadditions proceeded in good yield, the corresponding reactions of cyclopropyl carboxaldehyde were completely ineffective. In our

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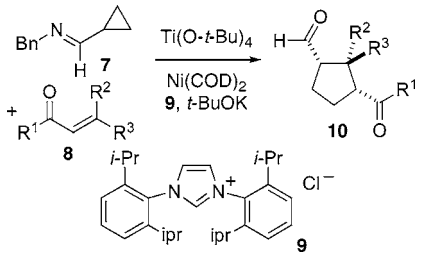
initial report,[5b] we illustrated a single example of a cyclopropyl aldimine participating in a ring-opening [3+2] cycloaddition reaction. Cyclopropyl imine derivatives thus have potential for improved reactivity relative to cyclopropyl ketones, and the generation of aldehyde products has considerably broader synthetic utility than phenyl ketone derivatives. To capitalize on these advantages of cyclopropyl imines, we now report an examination of the scope, stereoselectivity, and mechanism of cyclopropyl imine/enone cycloadditions.

Comparison of *N*-phenyl and *N*-benzyl imines in crossed reactions with enones illustrated minimal differences in yield and rate, and *N*-benzyl imines were thus used in our study. In analogy to our prior studies on the development of cyclopropyl ketone/enone cycloadditions, the corresponding cycloadditions of *N*-benzyl aldimines were effective by using 10 mol % each of $Ni(COD)_2$ and an *N*-heterocyclic carbene ligand with 2.0 equiv of $Ti(O\text{-}t\text{-}Bu)_4$ in toluene at 90 °C. Under these conditions, a variety of crossed reactions were possible in high yield (Table 1). Typically, enones were employed as the limiting reagent and were added by syringe drive over 1.5−2.0 h since enone accumulation inhibits the reaction.

Table 1. Scope of [3+2] Cycloadditions



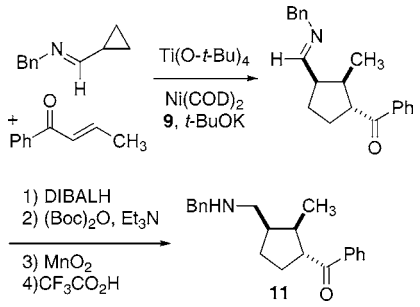
entry	R^1	R^2	R^3	% yield (dr)[a]
1	Ph	H	Ph	98 (92:8)[b]
2	Ph	H	Me	81 (72:28)
3	Ph	H	*n*-hexyl	93 (57:43)
4	Ph	H	*tert*-butyl	93 (>98:2)
5	Ph	H	Ph	94 (94:6)[b,c]
6	Ph	H	Me	71 (64:36)[c,d]
7	Ph	H	*n*-hexyl	67 (71:29)[c,d]
8	Ph	H	*tert*-butyl	69 (>98:2)[c,d]
9	Ph	H	CH=CHPh	62 (81:19)
10	Ph	Me	Me	87 (54:46)[e]
11	naphthyl	H	Me	87 (84:16)
12	Furan-2-yl	H	Me	78 (57:43)

[a] Reaction conditions: $Ni(COD)_2$ (10 mol %), **9** (10 mol %), *t*-BuOK (10 mol %), $Ti(O\text{-}t\text{-}Bu)_4$ (2.0 equiv), cyclopropylimine (1.5 equiv), enone (1.0 equiv, added over 1.5−2.0 h by syringe drive), toluene, 90 °C, 3−6 h, H_3O^+ workup, unless otherwise noted. Diastereoselectivities were determined by GC or NMR analysis of the crude reaction mixture. [b] 1.7 equiv of imine was used. [c] Reaction was carried out in the absence of $Ti(O\text{-}t\text{-}Bu)_4$. [d] Reaction time of 12 h was required. [e] 2.5 equiv of imine was used.

In examining couplings of an unsubstituted cyclopropyl aldimine **7** with aryl(alkenyl) ketones **8**, a variety of substrate variations at the enone β-position were tolerated (Table 1). Substitution patterns tolerated at the enone β-position included phenyl (entry 1), methyl (entry 2), *n*-hexyl (entry 3), and *tert*-butyl (entry 4). These four examples were compared with the corresponding reactions in the absence of $Ti(O\text{-}t\text{-}Bu)_4$, and lower yields were observed without this additive with longer reactions being required (entries 5−8). Other enone variations were examined, including an $\alpha,\beta,\gamma,\delta$-unsaturated substrate (entry 9), and a β,β-disubstituted enone, which allowed installation of a quaternary center (entry 10). Additionally, naphthyl and furanyl enones were effective participants in couplings (entries 11 and 12); however, enoates and alkyl(alkenyl) ketones failed to undergo coupling. Mixtures of two diastereomers were typically observed. Compound **10** was the major product in all cases, and the structure of the minor diastereomer was determined in three cases (entries 3, 10, and 12) to be epimeric to **10** at the formyl-bearing stereocenter.

An interesting difference in couplings of cyclopropyl imine **7** vs ketones **1** is that the imine variant produces the trans/trans cyclopentane stereoisomer **10** (R^2 = H) as the major product, whereas the ketone variant produces the cis/trans cyclopentane stereoisomer **6** selectively (which corresponds to the minor isomer in the current study). To determine the kinetic selectivity of an imine reaction, a coupling (entry 2, Table 1) was repeated, and DIBAL-H was directly injected into the reaction mixture upon disappearance of starting material (Scheme 2). Boc-protection of the resulting amine, followed by alcohol oxidation and Boc removal resulted in the production of compound **11** as a single diastereomer. This result illustrates that both the cyclopropyl ketone and cyclopropyl imine reactions favor kinetic production of the cis/trans isomer with high selectivity, and that the imine-derived aldehyde undergoes epimerization during imine hydrolysis.

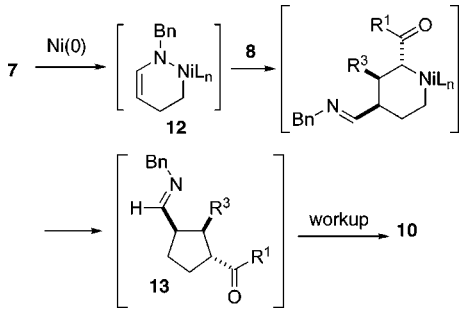
Scheme 2. Determination of Kinetic Selectivity



In analogy to the mechanism proposed for [3+2] reactions of cyclopropyl ketones,[5] we envision that the process is initiated by oxidative addition of cyclopropyl imine **7** to Ni(0) to afford metalloenamine **12** (Scheme 3).[6,7] Michael addition of **12** to enone **8**, followed by reductive elimination affords the cyclopentyl imine **13**, which undergoes hydrolysis and epimerization upon workup to afford the observed product **10**.

The basis for the improved yields of imine derivatives compared with cyclopropyl ketones is an interesting question. Prior coordination of the imine nitrogen to nickel likely directs oxidative addition into the strained C−C bond of the cyclopropyl aldimine derivatives.[8] Additionally, undesired side reactions may simply be less accessible for intermediates

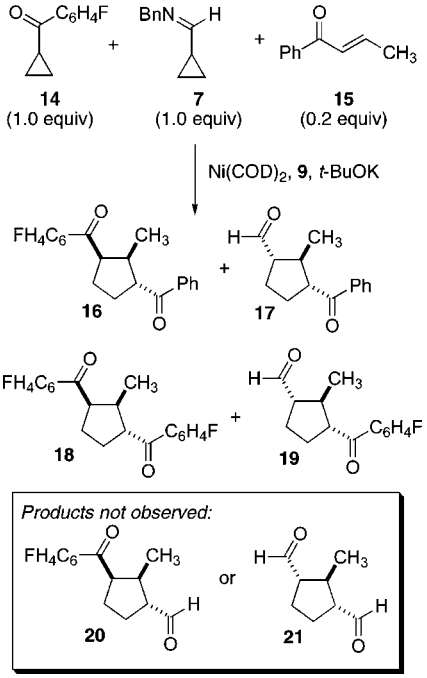
Scheme 3. Proposed Mechanism



in the cyclopropyl aldimine catalytic cycle in comparison with the corresponding catalytic cycle involving cyclopropyl ketone derivatives. Several observations shed light on the relative importance of these issues. First, treatment of a cyclopropyl imine to the reaction conditions in the absence of an added enone leads to none of the five-membered dimer analogues to the species **4** derived from cyclopropyl ketone dimerization. Second, the overall reaction times and rates of conversion for crossed cycloadditions of enones with cyclopropyl imines are only slightly faster than reactions of cyclopropyl ketones.

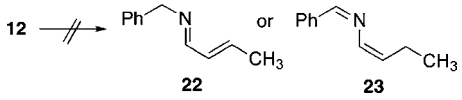
To gain more precise insight into these qualitative observations, a competition experiment between cyclopropyl ketone **14** and cyclopropyl aldimine **7** (1.0 equiv of each) was carried out with 20 mol % of enone **15** under the standard reaction conditions (Scheme 4). An initial burst of **16** is seen, followed by generation of a 1.5:1.0 ratio of **16**:**17** after 10−15 min. Upon further consumption of cyclopropane starting materials, significant amounts of products **18** and **19** were observed (via enone generation from **14** as described in Scheme 1), whereas no evidence for products **20** and **21** was obtained. The final ratio of products **16**:**17**:**18**:**19** was approximately 1:1:4:3. These observations suggest that, while substrate direction by the imine nitrogen likely plays a role in substrate activation, the improved performance of cyclopropyl imines compared with cyclopropyl ketones is not derived primarily from an increased rate of coupling reactions of cyclopropyl imines relative to cyclopropyl ketones. The better yields of reactions of cyclopropylimines are likely attributed to the failure of metalloenamine **12** to undergo conversion to unsaturated imines **22** or **23** (Scheme 5).[9] In crossed reactions of cyclopropyl imine **7** with enone

Scheme 4. Imine/Ketone Competition Experiments



15, less than 5% each of crotonaldehyde (derived from **22** via endocyclic β-hydride elimination of **12**) or benzaldehyde (derived from **23** via exocyclic β-hydride elimination of **12**) was observed by GC analysis. This suggests that β-hydride elimination of metalloenamine **12** to **22** or **23** is slow relative to productive addition of **12** to the enone.

Scheme 5. Evidence for Metalloenamine Stability



In summary, a nickel-catalyzed [3+2] cycloaddition reaction of cyclopropyl aldimines and enones has been developed. The scope and utility of the process exceeds that of the corresponding cycloaddition of cyclopropyl ketones and enones. Evidence is presented that suggests that the improved performance of cyclopropyl aldimines compared with cyclopropyl ketones is linked to the failure of imine-derived metalloenamine **12** to participate in undesired reaction pathways.

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Supporting Information Available: Experimental procedures and copies of spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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