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Umpolung of Michael Acceptors Catalyzed by *N*-Heterocyclic Carbenes

Christian Fischer, Sean W. Smith, David A. Powell, and Gregory C. Fu

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

As part of a program directed at the development of palladium- and nickel-catalyzed couplings of alkyl electrophiles,¹ we have been exploring the possibility of achieving a variant of the Heck reaction wherein an alkyl, rather than an aryl, electrophile is coupled with an olefin. In an initial study, we were pleased to discover that such a transformation can indeed be accomplished, albeit in very poor yield (1.2%; eq 1). Interestingly, however, control reactions established that carbon-carbon bond formation proceeds more efficiently in the *absence* of palladium (24%; eq 1)!

with 2.5% Pd₂(dba)₃ 1.2% yield (GC)
without Pd₂(dba)₃ 24% yield (GC)

Our mechanistic hypothesis for this unanticipated carbene-catalyzed cyclization is outlined in Figure 1.^{2,3} Thus, the catalyst (Nu:) adds to the electrophilic β carbon of the α, β-unsaturated ester, generating an enolate (**A**). Tautomerization then affords **B**,⁴ in which the β carbon is now nucleophilic (umpolung^{5,6}). An intramolecular S_N2 reaction provides **C**, which undergoes elimination to furnish the observed product and to regenerate the catalyst (Nu:).

For most of the previously described nucleophile-catalyzed reactions of Michael acceptors, the initial adduct (e.g., **A**) reacts with electrophiles in the α position (e.g., the Morita-Baylis-Hillman reaction⁷). Indeed, we have only been able to identify one previous report of a process wherein conjugate addition of a catalyst leads to the β carbon serving as a nucleophile.⁸ Furthermore, an interesting contrast is provided by the recent work of Krafft, who has established that enones/enals that bear pendant halides undergo cyclization in the α position when treated with stoichiometric PMe₃ or PBu₃ and then KOH (e.g., eq 2).⁹

We have optimized the carbene-catalyzed umpolung mode of β nucleophilicity for enoates (Figure 1) and determined that, through the appropriate choice of conditions, cyclization can be achieved with high efficiency (Table 1). Thus, *p*-methoxy-substituted variants of the Enders triazole-derived carbene^{10,11} have proved to be the best catalysts among those that we have examined to date, furnishing good yields of the target compounds (entries 1 and 2). The parent Enders carbene is somewhat less effective (entry 3), and IMes (entry 4), a thiazole derivative (entry 5), and a variety of amines (entries 6-8) and phosphines (entries 9-10), including PBu_3 , are essentially inactive as catalysts. With respect to the base, Cs_2CO_3 affords a somewhat lower yield than anhydrous K_3PO_4 (entry 11), whereas $\text{KO}t\text{-Bu}$ is not suitable (entry 12). Regarding the solvent, 1,4-dioxane and EtOAc may be employed (entries 13 and 14), whereas *N,N*-dimethylacetamide may not (entry 15). The reaction is sluggish at room temperature (entry 16), and no cyclization is observed if the carbene precursor or the base is omitted (entries 17 and 18).

We were pleased to determine that cyclizations of a range of substrates proceed smoothly under our standard reaction conditions (Table 2). With respect to the leaving group, not only bromides (entry 1), but also tosylates (entry 2) and even chlorides (entry 3; cf. eq 2), can be employed. Furthermore, α,β -unsaturated allyl esters (entry 4), Weinreb amides (entry 5), and nitriles (entries 6 and 7) cyclize with good efficiency. The method may be applied to the synthesis of an oxygen heterocycle (entry 8), as well as six-membered rings (entry 9). Interestingly, four-membered rings can even be generated, albeit in modest yield (entry 10).¹²

Clearly, tautomerization is a critical step in our proposed catalytic cycle, leading to nucleophilicity at the β carbon (Figure 1, **A@B**). In order to obtain insight into the origin of the difference in reactivity between the carbene derived from **1** and a phosphine (see above), we examined the deuterium-exchange process illustrated in eq 3. Scrambling occurs to a large extent with 10% **1**, whereas little exchange is observed in the presence of PBu_3 .¹³

In conclusion, we have demonstrated that, for a range of Michael acceptors, a nucleophilic catalyst can transiently transform the normally *electrophilic* β carbon into a *nucleophilic* site through an addition-tautomerization sequence. Specifically, we have established that an *N*-heterocyclic carbene can catalyze β -alkylations of a variety of α,β -unsaturated esters, amides,

and nitriles that bear pendant leaving groups. We anticipate that it will be possible to exploit this intriguing umpolung reactivity in a variety of contexts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- (12). Notes: (a) An α,β -unsaturated phenyl ketone can be cyclized, but a significant amount of the β,γ -unsaturated enone is produced. (b) We have not yet been able to achieve efficient seven-membered ring formation or *intermolecular* β -alkylation. (c) Substrates in which the olefin has a *Z*, rather than an *E*, configuration cyclize less rapidly. (d) Under our standard conditions, we have not been able to effectively cyclize α -substituted enoates.
- (13). In a competition experiment between the alkyl bromide and the alkyl chloride illustrated in entries 1 and 3 of Table 2, comparable reaction rates were observed, consistent with the hypothesis that cyclization may not be the turnover-limiting step for these substrates. In contrast, for the

homologous substrates (six-membered ring formation), the chloride is essentially unreactive under the conditions in which the bromide cyclizes.

Figure 1.
Possible mechanism for carbene-catalyzed β -alkylations of Michael acceptors.

Table 1Effect of reaction parameters on the carbene-catalyzed β -alkylation of a Michael acceptor

"standard conditions"

entry	change from the standard conditions	n = 1	yield (%) ^a n = 2
1	no change	92	85
2	10% 2 insted of 10% 1	88	85
3	10% 3 insted of 10% 1	91	37
4	10% IMes · HCl insted of 10% 1	5	5
5	10% 4 insted of 10% 1	<1	<1
6	10% DABCO insted of 10% 1	<1	<1
7	10% DMAP insted of 10% 1	<1	<1
8	10% quinidine insted of 10% 1	<1	<1
9	10% PBu ₃ insted of 10% 1	<1	<1
10	10% PPh ₃ insted of 10% 1	<1	<1
11	2.5 Cs ₂ CO ₃ insted of 2.5 K ₃ PO ₄	87	65
12	2.5 KO ^t -Bu insted of 2.5 K ₃ PO ₄	<1	<1
13	1,4-dioxane insted of glyme	91	70
14	EtOAc insted of glyme	89	60
15	<i>N,N</i> -dimethylacetamide insted of glyme	5	4
16	r.t. insted of 80 °C	16	2
17	no 1	<1	<1
18	no K ₃ PO ₄	<1	<1

Ar = *p*-anisyl.^aYield according to GC analysis versus a calibrated internal standard (average of two experiments).

Table 2Scope of the carbene-catalyzed β -alkylation of Michael acceptors

entry	starting material	reaction time (h)	yield (%) ^a
1 (X = Br)		8	94
2 (X = OTs)		16	94
3 (X = Cl)		8	89
4		8	88
5		16	68
6 (X = Br)		8	71
7 (X = OTs)		8	84
8		6	77
9		16	81
10		33	48 ^b

Ar = *p*-anisyl.^a Isolated yield (average of two experiments).^b 20% 1 was used, with dioxane as the solvent.