C–C Coupling

DOI: 10.1002/ange.200601364

# Umpolung Reactivity of Alkenyl Fischer Carbene Complexes, Copper Enolates, and Electrophiles**

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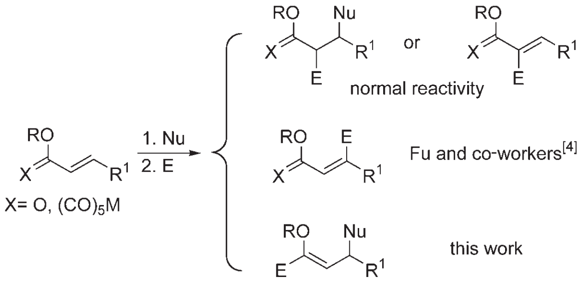
The umpolung of the "normal" reactivity of a functional group stands as a very interesting objective in synthetic organic chemistry.[1] For example, in general, α,β-unsaturated esters react with nucleophiles at the β-position through a conjugate addition to generate an enolate that further reacts with electrophiles at the α-position (Scheme 1).[2],[3] Fu and co-workers very recently reported an umpolung reactivity of α,β-unsaturated esters (Scheme 1).[4] In this interesting work, the normally electrophilic β-carbon atom is transformed into a nucleophilic site through an addition–tautomerization sequence.[5] Herein, we wish to report a new conjugate umpolung reactivity of Michael acceptors (Scheme 1).



***Scheme 1.*** Comparison of conjugate normal and umpolung reactivity of Michael acceptors. E = electrophile, Nu = nucleophile, M = metal.

Fischer carbene complexes,[6] and in particular α,β-unsaturated carbene complexes, have become very interesting tools in organic synthesis.[7] It is well known that these compounds, which may be considered as α,β-unsaturated ester equivalents, behave as Michael acceptors. Thus, in this context we recently reported the 1,4-addition of enolates to

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[**] This research was supported by the DGICYT (BQU-2001-3853). The authors thank the MEC (FPU predoctoral grant to A.M.), FICYT (predoctoral grant to A.D.), and the MEC and Fondo Social Europeo ("Ramón y Cajal" contract to F.R.).

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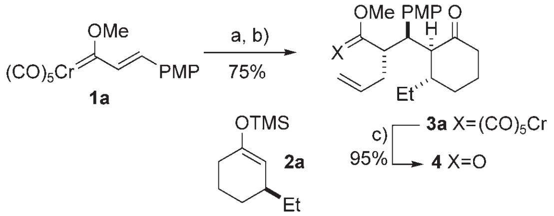
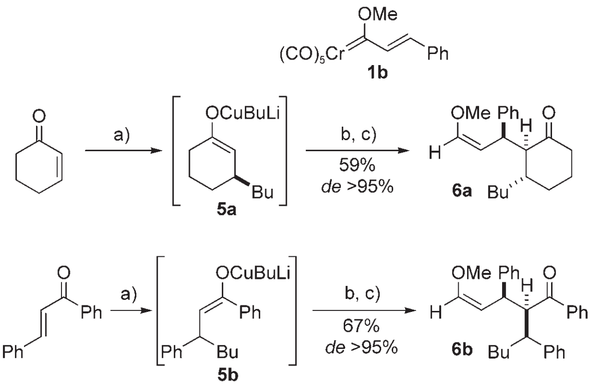
alkenyl carbene complexes.[8] Moreover, the α-position of Fischer carbene complexes is also known to become a nucleophilic position when these complexes are treated with bases.[9]

Taking all these facts into account, it is supposed that treatment of an alkenyl carbene complex with a ketone enolate would generate a new anionic species that would further react with an electrophile at the α-position (see Scheme 1, path 1). To test this hypothesis, carbene complex **1a** was sequentially treated with the lithium enolate derived from silyl enol ether **2a** and then with allyl bromide to obtain, as expected, the new carbene complex **3a** (Scheme 2). It is interesting to note that the reaction occurs with complete selectivity, and we only observed the formation of a single diastereoisomer of the final product **3a**.[10] Moreover, this carbene complex **3a** is readily transformed into the corresponding ester **4** by simple oxidation of the metal fragment.



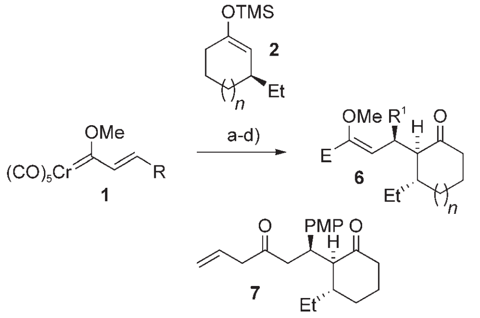
*Scheme 2.* Normal reactivity of alkenyl carbene complexes, lithium enolates, and allyl bromide. Reagents and conditions: a) **2a**, BuLi, THF, 0 °C, 30 min, then **1a**, THF, −78→−30 °C; b) allyl bromide, −78 °C→RT; c) pyridine-*N*-oxide, THF, RT. PMP = 4-MeOC$_6$H$_4$, TMS = trimethylsilyl.

In an attempt to find the optimal conditions to perform the sequence mentioned above, we decided to check the reaction by using copper enolates instead of lithium enolates. In an initial experiment, we generated the necessary copper enolate by simple 1,4-addition of lithium dibutylcuprate to cyclohexenone (Scheme 3). This reaction leads to the corresponding enolate **5a**, which was added to the carbene complex **1b**. The resulting solution was hydrolyzed with an aqueous saturated solution of ammonium chloride. To our surprise, this reaction did not produce the expected carbene complex from the 1,4-addition of the enolate to **1b** and protonation at the α-position of the carbene complex; instead, the enol ether **6a** was obtained in a totally regio- and diastereoselective manner.[10] This result indicates that the anionic species generated after the 1,4-addition of the copper enolate to the carbene complex **1b** did not react with electrophiles at the α-position, as could be anticipated (and as shown in Scheme 2), but at the initial carbene carbon atom.[11] This unexpected mode of reactivity of alkenyl Fischer carbene complexes can be considered to be a new umpolung of Michael acceptors. As shown in Scheme 3, the reaction could also be performed with open-chain copper enolates. Thus, enol ether **6b** could readily be obtained by reaction of the enolate **5b**, derived from chalcone, and carbene complex **1b**.



*Scheme 3.* Umpolung reactivity of alkenyl carbene complexes, copper enolates, and a proton as the electrophile. Reagents and conditions: a) Bu$_2$CuLi, Et$_2$O, −78 °C; b) **1b**, THF, −78 °C→RT; c) NH$_4$Cl (aq).

The scope of this new umpolung reaction of alkenyl Fischer carbene complexes has been investigated. We found that several carbene complexes, enolates, and electrophiles can be used (Scheme 4 and Table 1). Also, we found that the



*Scheme 4.* Synthesis of enol ethers **6** (or diketone **7**). Reagents and conditions: a) **2**, BuLi, THF, 0 °C, 30 min, then CuI, 0 °C and 15 min, RT; b) **1**, THF, −78→−30 °C; c) E$^+$, −30 °C→RT; d) NH$_4$Cl (aq).

*Table 1:* Enol ethers **6** (or diketone **7**) from alkenyl carbene complexes **1**, enolates **2**, and electrophiles.

| **1** | R$^1$ | **2**[a] | *n* | E$^+$ | **6** | E | Yield [%][b] | *de* [%][c] | *ee* [%][d] |
|---|---|---|---|---|---|---|---|---|---|
| **1a** | PMP[e] | **2a** | 1 | PhCOCl | **6c** | PhCO | 82 | > 95 | – |
| **1a** | PMP[e] | **2a** | 1 | H$_2$C=CHCH$_2$Br | **7**[f] | HC=CHCH$_2$ | 63 | > 95 | |
| **1c** | 2-Fu[e] | **2a** | 1 | PhCOCl | **6d** | PhCO | 80 | > 95 | – |
| **1b** | Ph | **2a**[g] | 1 | H$_2$O | **6e** | H | 70 | > 95 | > 95 |
| **1c** | 2-Fu[e] | **2a** | 1 | D$_2$O | **6f** | D | 73 | > 95 | – |
| **1a** | PMP[e] | **2a**[g] | 1 | H$_2$O | **6g** | H | 74 | > 95 | > 95 |
| **1a** | PMP[e] | **2a**[g] | 1 | MeCOCl | **6h** | MeCO | 68 | > 95 | > 95 |
| **1c** | 2-Fu[e] | **2a**[g] | 1 | HC≡CCH$_2$Br | **6i** | HC≡CCH$_2$ | 53 | > 95 | > 95 |
| **1d** | Fc[e] | **2a**[g] | 1 | H$_2$O | **6j** | H | 76 | > 95 | > 95 |
| **1e** | (*E*)-styryl | **2a**[g] | 1 | H$_2$O | **6k** | H | 78 | > 95 | 95 |
| **1a** | PMP[e] | **2b**[g] | 2 | H$_2$O | **6l** | H | 72 | > 95 | > 95 |
| **1b** | Ph | **2b**[g] | 2 | *t*BuCOCl | **6m** | *t*BuCO | 76 | > 95 | > 95 |

[a] Unless noted, racemic silyl enol ether **2** was used. [b] Yield of the isolated product based on starting carbene complex **1**. [c] Determined by $^1$H NMR spectroscopic analysis of the crude reaction product. [d] Determined by HPLC analysis on a chiral support. [e] PMP = 4-MeOC$_6$H$_4$, 2-Fu = 2-furyl; Fc = ferrocenyl. [f] The corresponding enol ether could not be isolated. [g] Enantiopure (> 95 % *ee*) silyl enol ether was used (see Ref. [12]).

reaction can be performed in a very simple way that starts from the readily available silyl enol ether **2**. Thus, **2** was treated with butyllithium to generate the corresponding lithium enolate. Treatment of these intermediates with solid CuI and addition to the corresponding carbene complex **1** generated the final enol ether **6**, after reaction with the corresponding electrophile, as a single regio- and diastereoisomer.[10] With allyl bromide as the electrophile, **6** could not be isolated and the diketone **7** was directly obtained. As exemplified by this result, this methodology allows the simple synthesis of chiral 1,5-diketone derivatives by simple hydrolysis of the enol ether functionality of **6**. The straightforward procedure described herein allowed us to synthesize enantiomerically pure products **6** when the reaction was carried out using readily available enantiopure silyl enol ethers **2**.[12] Interestingly, α,β,γ,δ-unsaturated carbene complex **1e** could also be used. Although a 1,6-addition of the cooper enolate to **1e** could be expected, we only observed the corresponding 1,4-addition and further reaction with the electrophile at the initial carbene carbon atom. Finally, it is important to remark that similar results were obtained when carbene complexes **1** were initially treated with the lithium enolates derived from **2** and CuI was added just before the reaction with the corresponding electrophile.

In summary, we have developed a new regio- and diastereoselective one-pot three-component coupling reaction of alkenyl carbene complexes, copper enolates, and several electrophiles. Highly functionalized enol ethers or 1,5-diketone derivatives are readily available from very simple starting materials in a straightforward manner. The process is amenable to the synthesis of enantiomerically pure compounds. As the process described herein is very simple, it could be easily adapted for diversity-oriented synthesis (DOS). Thus, a large range of structurally diverse compounds that are not readily available from traditional organic transformations could be obtained by following this straightforward multicomponent coupling reaction. Our study has shown for the first time a differential behavior between ketone lithium and copper enolates when they are treated with alkenyl carbene complexes. A conceptually new mode of reactivity of Michael acceptors and a clear example of umpolung reactivity is reflected.

Received: April 6, 2006

**Keywords:** C–C coupling · carbenes · multicomponent reactions · synthetic methods · umpolung

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