Stereoselective Synthesis of Tri- and Tetrasubstituted α,β-Unsaturated Esters via Copper-catalyzed Coupling of Enol Triflates of β-Ketoesters with Grignard-based Zinc Ate Complexes

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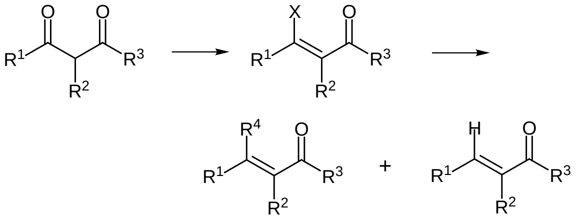
Received 30 July 2001

Abstract: Tri- and tetrasubstituted α,β-unsaturated esters were stereoselectively prepared via the copper-catalyzed couplings of the enol triflates of β-ketoesters with Grignard-based zinc ate complexes. Some insights into the mechanistic considerations are described.

Key words: stereoselective synthesis, enol triflates, copper catalysts, Grignard reagents, zinc ate complexes

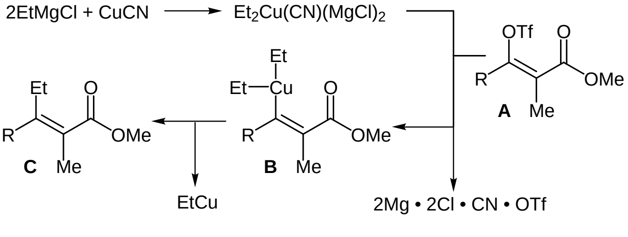
The stereoselective synthesis of tri- and tetrasubstituted α,β-unsaturated carbonyl compounds from β-functionalized α,β-unsaturated carbonyl compounds is an important objective in organic synthesis. Some synthetic methods have already been developed that include:(1) the couplings of β-alkylthio- or β-phenylthio-α,β-unsaturated carbonyl compounds with dialkylcopper lithium[1,2] or Grignard-based copper reagents,[3] (2) the couplings of the enol acetates or benzoates of β-ketocarbonyl compounds with dialkylcopper lithium,[4] (3) the couplings of β-halo-α,β-unsaturated ketones with dialkylcopper lithium,[5] (4) the couplings of the enol phosphates of β-ketocarbonyl compounds with dialkylcopper lithium[6] or Grignard-based copper reagents,[7] (5) the couplings of the enol triflates of β-ketoesters with organostannanes in the presence of a catalytic Pd/Cu,[8] with organocopper reagents,[9,10a] or with Grignard-based copper reagents.[8c,10b,c] A drawback of these transformations is that a reduction product (a hydrogen-incorporated product) is sometimes obtained as the major product or by-product (Scheme 1).[4a,c,10a,11] There have been some discussion about this phenomenon[4a,10a,11d] and about the same phenomenon in related reactions;[9,12] however, the actual species responsible for donating a hydrogen atom is still inconclusive. We report here a new methodology for the stereoselective synthesis of tri- and tetrasubstituted α,β-unsaturated esters via the copper-catalyzed couplings of the enol triflates of β-ketoesters with Grignard-based zinc ate complexes and some insights into the mechanistic considerations of this reaction.



Scheme 1

We chose 1[13,14] the enol triflates of β-ketoesters and ethyl magnesium chloride as the Grignard reagent (Table 1). First, the Gibbs conditions[10b,c,12e] were applied to these substrates to obtain the required product **2**. A 0.97 M THF solution of EtMgCl (4 equiv) was added to a 1.02 M THF solution of CuCN (2 equiv)-2LiCl at -78 °C. This was warmed to 0 °C over a 1 h period. To this pale yellow solution of $Et_2Cu(CN)(MgCl)_2$ was added at -30 °C a THF solution of **1** (1 equiv) and the mixture was warmed to r.t. over a 2 h period. After 1.5 h at r.t., the ethylated product **2**[14] (R = Et) was almost quantitatively obtained (Table 1, entry 1). CuI could also be used instead of CuCN (Table 1, entry 2). The use of equal amounts of EtMgCl and CuCN (i.e., EtCu(CN)MgCl) gave a much slower reaction and a lower yield of **2** (Table 1, entry 3). When the coupling reaction or the preparation of the copper reagent was conducted at -78 °C, the yield of **2** decreased (Table 1, entries 4 and 5). In these runs, neither the stereoisomer of **2** nor the reduction product **3** was produced.[15] No reaction occurred with EtMgCl in the absence of the copper salt (Table 1, entry 6).

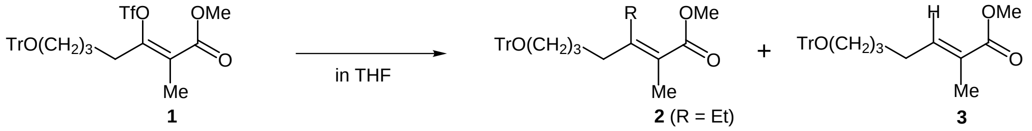
A plausible mechanism of this reaction is as follows (Scheme 2).[4a,10a,12e,f] The ate complex $[Et_2Cu(CN)(MgCl)_2]$, derived from a 2:1 mixture of EtMgCl and CuCN, is oxidatively added by the enol triflate **A**, giving the Cu(III) species **B**. The reductive elimination from **B** gives the desired alkylated product **C**.



Scheme 2

ISSN 0936-5214

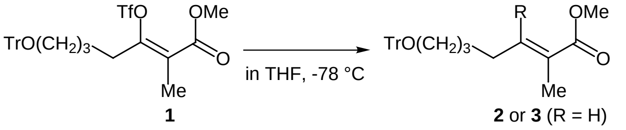
Table 1 Copper-promoted Ethylation of **1**



Entry	Reagents (equiv for **1**)	Conditions for copper reagents	Conditions for coupling	Yield (%) of **2**
1	EtMgCl (4), CuCN (2)-2LiCl	-78 °C to 0 °C, 1 h	-30 °C to r.t., 2 h; r.t., 1.5 h	98
2	EtMgCl (4), CuI (2)	-78 °C to 0 °C, 1 h	-30 °C to r.t., 2 h; r.t., 1.5 h	98
3	EtMgCl (2), CuCN (2)-2LiCl	-78 °C to 0 °C, 1 h	-30 °C to r.t., 2 h; r.t., 4 h	40[a]
4	EtMgCl (4), CuCN (2)-2LiCl	-78 °C to 0 °C, 1 h	-78 °C, 8.5 h	74[b]
5	EtMgCl (4), CuCN (2)-2LiCl	-78 °C, 15 min	-78 °C, 2.5 h	93[c]
6	EtMgCl (4)	-78 °C	-78 °C, 4.5 h	NR[d]

[a] The starting material **1** was recovered in ~60% yield.
[b] The starting material **1** was recovered in ~25% yield.
[c] The starting material **1** was recovered in ~5% yield.
[d] No reaction.

Table 2 Copper-catalyzed Alkylation of **1**

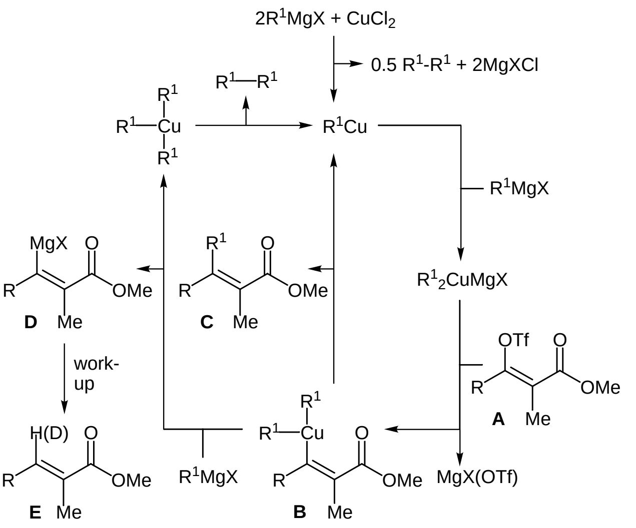


Entry	Reagents (equiv for **1**)	Time/h	Yield (%) of **2**	Yield (%) of **3**
1	EtMgCl (4), CuCN (20 mol%)-2LiCl	4.5	16 (R = Et)	80
2	EtMgCl (4), $CuCl_2$ (10 mol%)-2LiCl	0.5	17 (R = Et)	76
3	BuMgCl (4), $CuCl_2$ (10 mol%)-2LiCl	0.5	21 (R = Bu)	72
4	PhMgBr (4), $CuCl_2$ (20 mol%)-2LiCl	5	32 (R = Ph)	66
5	vinyl MgBr (4), $CuCl_2$ (20 mol%)-2LiCl	5	32 (R = vinyl)	68
6	*t*-BuMgCl (4), $CuCl_2$ (10 mol%)-2LiCl	5	4[a] (R = *t*-Bu)	0
7	MeMgCl (4), $CuCl_2$ (10 mol%)-2LiCl	0.5	86 (R = Me)	0

[a] The starting material **1** was recovered in ~95% yield.

We next investigated the use of catalytic amounts of copper in this reaction (Table 2). To a solution of **1** (1 equiv) in THF were added at -78 °C a 0.1 M THF solution of CuCN (20 mol%)-2LiCl and a 0.97 M THF solution of EtMgCl (4 equiv). After 4.5 h at -78 °C, the ethylated product **2** (R = Et) was obtained in only 16% yield together with the reduction product **3** in 80% yield (R = H, Table 2, entry 1). The use of $CuCl_2$ (10 mol%) instead of CuCN gave the same result (Table 2, entry 2). The reduction product **3** was also the major product when BuMgCl, PhMgBr and vinyl MgBr were used (Table 2, entries 3, 4, and 5). The yield of **2** was very low with *t*-BuMgCl (Table 2, entry 6). Interestingly, the methylated product **2** (R = Me) was obtained in 86% yield when MeMgCl was used (Table 2, entry 7).

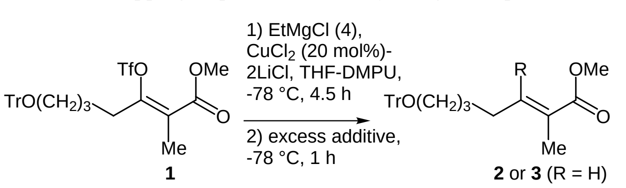
The mechanism in Scheme 3 is what we assume occurs to give the reduction product **3**. R^1Cu, obtained from a 2:1 mixture of R^1MgX and Cu(II), couples with R^1MgX to afford R^1_2CuMgX. This ate complex is oxidatively added by the enol triflate **A**, giving the Cu(III) species **B**. The reductive elimination from **B** furnishes the desired alkylated product **C**, and R^1Cu is regenerated. However, when this step is slow, transmetallation would occur between the excess R^1MgX and **B** to give the vinyl Grignard species **D** and R^1_3Cu. R^1Cu is regenerated from R^1_3Cu. The final work-up produces the reduction product **E** from **D**. For *t*-BuMgCl, the ate complex (*t*-Bu_2CuMgX) or Cu(III) species **B** is not effectively generated at -78 °C. In the case of MeMgCl, the reductive elimination step (**B** to **C**) is fast even at -78 °C, giving the methylated product **2** (R = Me).



Scheme 3

In order to support this assumption, the following reactions were examined (Table 3). To a THF-DMPU (10:1) solution of **1** (1 equiv) were added at -78 °C a 0.11 M THF solution of $CuCl_2$ (20 mol%)-2LiCl and a 0.97 M THF solution of EtMgCl (4 equiv). After 4.5 h at -78 °C, excess CD_3OD was added to the reaction mixture. After 1 h at -78 °C, the ethylated product **2** (R = Et) and the reduction product **3** (R = D, 95% deuterium incorporation) were obtained in 47% and 48% yields, respectively (Table 3, entry 1). This result indicates that no hydrogen source exists in the reaction medium at -78 °C and the hydrogen incorporation occurs during the quenching process. Moreover, quenching the reaction mixture with EtI increased the yield of **2** (R = Et) to 82% and decreased the yield of **3** (R = H) to 16% (Table 3, entry 2).[16] When the reaction mixture was quenched with MeI, the ethylated product **2** (R = Et) was obtained in 32% yield together with the 53% yield of the methylated product **2** (R = Me, Table 3, entry 3). In addition, when the reaction mixture was quenched with I_2, the ethylated product **2** (R = Et) and the vinyl iodide **2** (R = I) were produced in 28% and 72% yields, respectively (Table 3, entry 4).

Table 3 Trapping Experiments of Vinyl Grignard Species

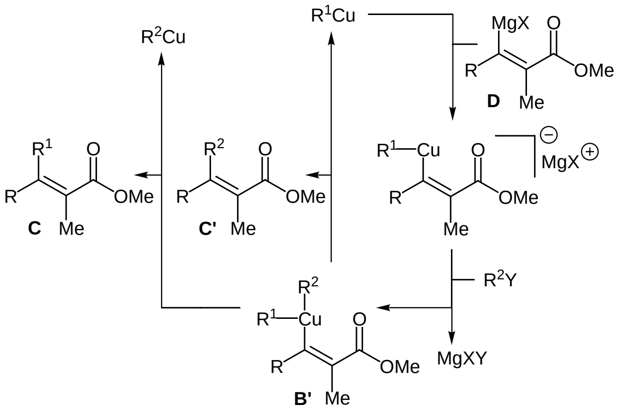


Entry	Additive (equiv for **1**)	Yield (%) of **2**	Yield (%) of **3**
1	CD_3OD (100)	47 (R = Et)	48[a]
2	EtI (100)	82 (R = Et)	16
3[b]	MeI (100)	32 (R = Et) 53 (R = Me)	5
4[b]	I_2 (10)	28 (R = Et) 72 (R = I)	0

[a] 95% Deuterium incorporation.

[b] DMPU was not used.

These results can be explained by the mechanism shown in Scheme 4. The vinyl Grignard species **D** instead of R^1MgX couples with R^1Cu to give the ate complex, to which oxidatively added R^2Y (EtI, MeI, or I_2), affording the new Cu(III) species **B'**. Two kinds of products, **C** and **C'**, were produced from **B'**. Therefore, we expected that, to prevent the transmetallation step (**B** to **D** in Scheme 3), less nucleophilic organometallic species than Grignard reagents would be preferable for this catalytic cycle. Therefore, we selected organozincates.[17]

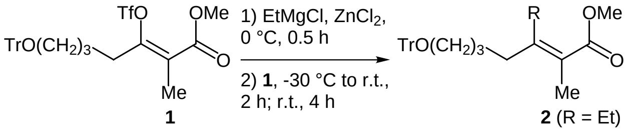


Scheme 4

To a 0.5 M THF solution of $ZnCl_2$ (1.5 equiv) was added at 0 °C a 1.02 M THF solution of EtMgCl (4.5 equiv); after 0.5 h at 0 °C, a 0.1 M THF solution of $CuCl_2$ (15 mol%)-2LiCl and **1** (1 equiv) in THF-DMPU (10:1) were added at -30 °C. The reaction mixture was warmed to r.t. over a 2 h period. After 4 h at r.t., the ethylated product **2** (R = Et) was obtained in 98% yield (Table 4, entry 1).[18] Neither the stereoisomer of **2** nor the reduction product **3** was produced. The use of a 2:1 or 1:1 mixture of EtMgCl and $ZnCl_2$ was less satisfactory (Table 4, entries 2 and 3). DMPU was essential for this coupling (Table 4, entry 4). In the absence of the copper salt, the reaction did not proceed (Table 4, entry 5).

We propose the reaction mechanism depicted in Scheme 5. $Et_3ZnMgCl$, obtained from a 3:1 mixture of EtMgCl and $ZnCl_2$, reduces Cu(II) to Cu(I). The resulting EtCu couples with $Et_3ZnMgCl$ to produce $Et_2CuMgCl$. The insertion of this ate complex to the enol triflate **A** affords the Cu(III) species **B**. The reductive elimination from **B** furnishes the desired alkylated product **C**, and EtCu is regenerated. It is noteworthy that the zinc ate complex ($Et_3ZnMgCl$) is less nucleophilic than the Grignard reagents; therefore, the transmetallation step is prevented and the reductive elimination step is preferred.

Table 4 Copper-catalyzed Ethylation of **1** with Ethylzincate

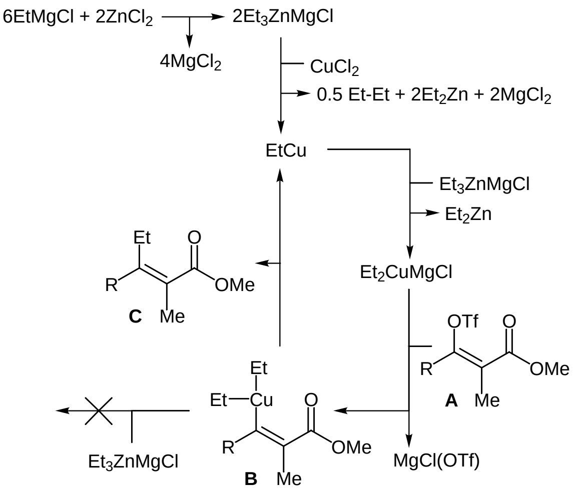


Entry	Reagents (equiv for **1**)	Solvent	Yield (%) of **2**
1	EtMgCl (4.5), $ZnCl_2$ (1.5), $CuCl_2$ (15 mol%)-2LiCl	THF-DMPU	98
2	EtMgCl (3.0), $ZnCl_2$ (1.5), $CuCl_2$ (15 mol%)-2LiCl	THF-DMPU	26[a]
3	EtMgCl (1.5), $ZnCl_2$ (1.5), $CuCl_2$ (15 mol%)-2LiCl	THF-DMPU	NR[b]
4	EtMgCl (4.5), $ZnCl_2$ (1.5), $CuCl_2$ (15 mol%)-2LiCl	THF	49[c]
5	EtMgCl (4.5), $ZnCl_2$ (1.5)	THF-DMPU	NR[b]

[a] The starting material **1** was recovered in ~70% yield.

[b] No reaction.

[c] The starting material **1** was recovered in ~50% yield.



Scheme 5

Under the above optimized conditions, other alkylated products were secured (Figure 1). In addition to the ethyl group, the Me (MeMgCl in ether), Bu (BuMgCl in THF), *i*-Pr (*i*-PrMgCl in THF) and *t*-Bu (*t*-BuMgCl in THF) groups were easily incorporated into **1** in high yields without the formation of the stereoisomer or the reduction product.[19]

Finally, the incorporation of the ethyl group into other enol triflates of β-ketoesters were examined (Figure 2).[13,14] In all the cases examined, satisfactory results were obtained. Neither the stereoisomer nor the reduction product, was produced.

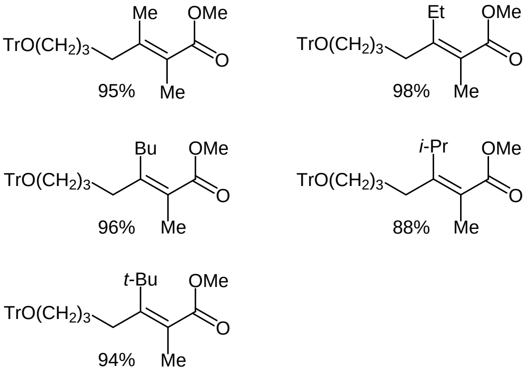


Figure 1

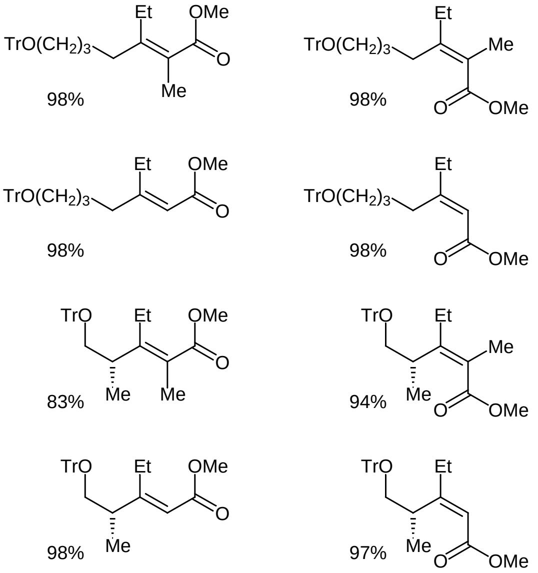


Figure 2

In summary, we have demonstrated that tri- and tetrasubstituted α,β-unsaturated esters were stereoselectively prepared via the copper-catalyzed couplings of the enol triflates of β-ketoesters with Grignard-based zinc ate complexes in high yields. The zinc ate complexes (R_3ZnMgX) are milder nucleophiles than Grignard reagents. This was critical for preventing hydrogen incorporation in the copper-catalyzed conditions. Moreover, from a synthetic point of view, the experimental procedures are easier than those of the stoichiometric copper-mediated reactions in both preparation of reagents and work-up.[20]

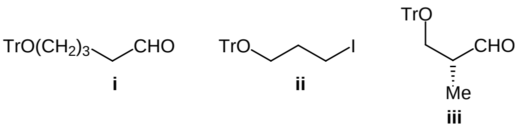


Figure 3

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(13) The β-ketoester corresponding to **1** was prepared from **i** (Figure 3) and methyl propionate [i)LDA, THF, -78 °C, 1 h, then **i**, -78 °C, 1 h. ii)PCC, CH_2Cl_2, r.t., 1 d]. The β-ketoesters corresponding to the ethylated products depicted in Figure 2 were prepared from **ii** (Figure3) + methyl acetoacetate (NaH, BuLi, THF, 0 °C, 0.5 h, then **ii**, 0 °C, 1 h), **iii** (Figure 3) + methyl propionate [i) LDA, THF, -78 °C, 1 h, then **iii**, -78 °C, 2 h. ii) PCC, CH_2Cl_2, r.t., 1 d], and **iii** + methyl acetate [i) LDA, THF, -78 °C, 1 h, then **iii**, -78 °C, 2 h. ii) PCC, CH_2Cl_2, r.t., 1 d]. The *(Z)*- and *(E)*-enol triflates were prepared under the Gibbs conditions[8b] from the β-ketoesters. All the enol triflates used in these experiments are stereochemically pure. The compound **ii** was prepared from 1,3-propanediol by tritylation (TrCl, Et_3N, CH_2Cl_2, r.t., 12 h) followed by iodination (I_2, Ph_3P, imidazole, CH_2Cl_2, r.t., 1.5 h). The compounds **i** and **iii** were prepared by the reported procedures, see: (a) Jones, G. B.; Hynd, G.; Wright, J. M.; Sharma, A. *J. Org. Chem.* **2000**, *65*, 263. (b) Ide, M.; Nakata, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2491.

(14) Satisfactory analytical data (NMR and IR spectra, elemental analyses and/or HRMS) were obtained for all new compounds. The double-bond geometry was confirmed by NMR nOe experiments.

(15) In contrast, when the coupling reaction and the preparation of the copper reagent were conducted at -78 °C in the absence of LiCl, the reduction product **3** was obtained as the major product.

(16) The effectiveness of the alkylhalide addition to the reaction mixture has already been described by Casey[4c] and Weiler.[6a] See also: Corey, E. J.; Katzenellenbogen, J. A.; Gilman, N. W.; Roman, S. A.; Erickson, B. W. *J. Am. Chem. Soc.* **1968**, *90*, 5618.

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(19) Unfortunately, the phenyl and vinyl groups could not effectively be incorporated under the optimized conditions.

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