Asymmetric Catalysis

DOI: 10.1002/ange.201107324

Enantioselective Copper-Catalyzed Conjugate Addition of Trimethylaluminium to β,γ-Unsaturated α-Ketoesters**

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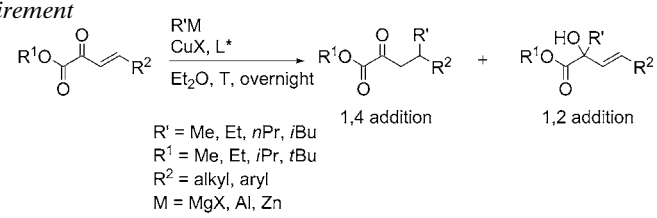
Dedicated to Professor Alfredo Ricci on the occasion of his retirement



Scheme 1. Copper-catalyzed ACA of β,γ-unsaturated α-ketoesters.

Since the end of the last century, transition metal catalyzed asymmetric conjugate addition (ACA) of organometallic reagents to Michael acceptors has been one of the most powerful methods for obtaining enantioenriched β-substituted natural or unnatural building blocks as intermediates through C–C bond formation.[1] The advantages of the ACA in the presence of copper as the transition-metal catalyst are the low cost of the copper salts, the high regio- and enantioselectivity, and the compatibility with many functional groups.[2] In this field, a large variety of α,β-unsaturated compounds such as carbonyl derivatives, sulfones, and nitroalkenes have been used successfully. All of the corresponding products obtained during this transformation were used as chiral building blocks, but methyl-substituted derivatives are the most important if we consider natural compounds described in the literature. To access new families of chiral and complex synthons at the same time, we aimed at developing an efficient methodology that would allow access to natural and unnatural products using the same starting material. To achieve this purpose, we investigated a new copper-catalyzed asymmetric conjugate addition of various organometallic reagents to functionalized β,γ-unsaturated α-ketoesters (Scheme 1).

So far, these compounds have never been used for the asymmetric conjugate addition of organometallic reagents in the presence of a transition-metal catalyst. However, during the last decade a wide range of asymmetric organocatalytic conjugate additions to various β,γ-unsaturated α-ketoesters were described in the literature.[3–9] One of the most studied reactions with β,γ-unsaturated α-ketoesters was the Michael addition of hydroxycoumarines catalyzed by chiral squaramides,[10] thioureas,[11] or bisoxazoline-copper complexes[12] to obtain coumarine derivatives, which are reported to have anti-HIV and antimalaria activities. More recently, the groups of Calter[13] and Feng[14] were able to obtain new derivatives by an asymmetric conjugate addition of cyclic diketones to β,γ-unsaturated α-ketoesters with the same kinds of chiral organocatalysts. During our investigations, Gravel and coworkers developed an interesting enantioselective intermolecular Stetter reaction on β,γ-unsaturated α-ketoesters in the presence of triazolium catalysts to obtain useful synthetic building blocks with promising selectivities. After a small derivatization, they obtained disubstituted lactones, trisubstituted tetrahydrofuranes, or α-amino esters.[15] β,γ-unsaturated α-ketoesters are therefore considered versatile synthons because of their dense functionalization. Four pathways give access to a wide range of aryl and alkyl derivatives in good yield: 1) nucleophilic substitution,[16] 2) aldol condensation,[17] 3) Mukaiyama aldol addition,[18] or 4) Horner–Wadsworth–Emmons[3].

During our previous work with α,β-unsaturated aldehydes, we were faced with much more challenging substrates than the corresponding ketones, due to the high reactivity of the carbonyl group, which easily leads to the formation of an undesired mixture of 1,4-, 1,2-addition products as well as aldol by-product.[19] β,γ-Unsaturated α-ketoesters pose the same problems, the keto functionality being as reactive as an aldehyde. From a synthetic point of view, the resulting chiral γ-substituted building blocks can be easily transformed into the corresponding β-substituted aldehydes, coumarines, quinolinones, tolterodines, chiral β-turn or α-amino acid precursors.

We initially investigated the ACA with the simplest derivative, **1**, containing an ethyl ester and a phenyl group appended to the alkene. This first attempt was done using the reaction conditions developed for the asymmetric conjugate addition to α,β-unsaturated aldehydes: 1.2 equivalents of an organometallic reagent, 5 mol% of copper(I) thiophene-2-carboxylate (CuTC), 5.25 mol% of (*R*)-binap in diethyl ether (Et_2O) at −78 °C (Table 1).

With the Grignard reagent, the substrate was totally consumed after 13 hours, but unfortunately we obtained exclusively the 1,2-addition product (Table 1, entry 1). By adding TMSCl as an additive[20] the regioselectivity was not improved (Table 1, entry 2). Use of Me_2Zn under the same

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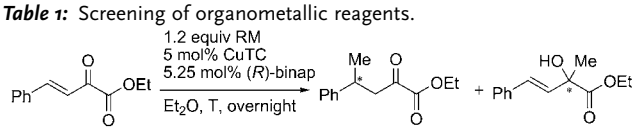
[**] The authors thank the Swiss National Research Foundation (grant No. 200020-126663) and COST action D40 (SER contract No. C07.0097) for financial support, as well as Stéphane Grass (Lacour's group, University of Geneva) for some chiral separation on HPLC. BINAP was generously provided by Takasago company, Japan.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201107324.

Table 1: Screening of organometallic reagents.



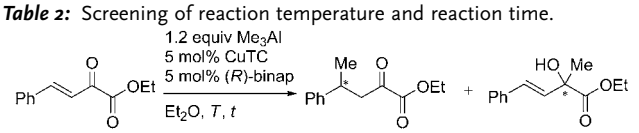
Entry	RM	*T* [°C]	Conv. [%][a]	1,4/1,2[a]	*ee* [%][b,c]
1[d]	MeMgBr	−78	>99	1:99	n.d.
2	MeMgBr	−78	>99	1:99	n.d.
3	Me_2Zn	0	0	n.d.	n.d.
4[e]	Me_2Zn	0	>99(14)[f]	99:1	93
5	Me_3Al	−20	>99(40)[f]	43:57	55

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by GC analysis using a chiral stationary phase[c] Enantiomeric excess for 1,4-addition product. [d] Reaction performed with 1.3 equiv TMSCl. [e] Reaction performed with 2 equiv Me_2Zn, 5 mol% CuTC, and (*R*)-binap in THF. [f] Yield of isolated product. binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, TMS = trimethylsilyl.

reaction conditions, with the exception of temperature, resulted in no conversion. However, with the best reaction conditions developed, 14% of 1,4-addition product could be isolated with 93% *ee* (Table 1, entry 3). The use of trimethylaluminium was envisaged to introduce the methyl group because it is a mild organometallic reagent. At −20°C we obtained full conversion with approximately a 1:1 ratio for the 1,4-adduct to 1,2-adduct selectivity, thus reaching a promising 55% *ee* for the 1,4-adduct (Table 1, entry 4).

By changing the reaction temperature from −20°C to −78°C, and increasing the reaction time from 3 hours to 17 hours, the 1,4-addition adduct was obtained as the major product (Table 2, entries 1–5). Upon changing the order of addition no improvement was observed for the regio- and enantioselectivity (Table 2, entry 6). It was reasoned that in presence of a more hindered ester moiety the undesired conformational flexibility of the molecule could be avoided and thus lead exclusively to the 1,4 addition product. However, by substituting the ethyl ester by an isopropyl ester, no improvement in the selectivity was obtained (Table 2, entry 7).

Table 2: Screening of reaction temperature and reaction time.

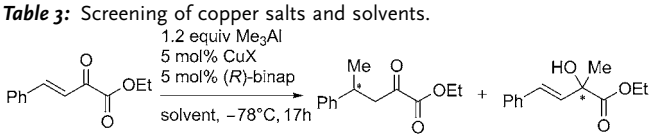


Entry	*t* [h]	*T* [°C]	Conv. [%][a]	1,4/1,2[a]	*ee* [%][b]
1	13	−20	>99	43:57	55
2	3	−40	>99	60:40	60
3	3	−60	>99	63:37	94
4	3	−78	52	72:28	95
5	17	−78	>99	70:30	94
6[c]	17	−78	85	67:33	96
7[d]	17	−78	>99	64:36	n.d.

[a] Determined by ^{1}H NMR spectroscopy. [b] Reported values are for the 1,4-adduct. Determined by GC analysis using a chiral stationary phase. [c] Addition of substrate before the organometallic reagents. [d] Reaction performed with **5** where O*i*Pr is used in place of OEt.

Although various copper salts were tested in Et_2O (Table 3, entries 1 and 2), CuTC was found to be the most efficient in terms of conversion, as well as regio- and enantioselectivity. Keeping CuTC as copper source, different solvents were screened, and tetrahydrofuran (THF) was identified as the solvent of choice (Table 3, entry 3–5).[21] The formation of the product **2** was observed with full regioselectivity and very high enantiomeric excess. Various other solvents and copper salts were screened but did not manage to improve this result (Table 3, entry 6–7).[22] When using excess trimethylaluminium (2 equiv), full conversion and complete regioselectivity in favor of the 1,4-adduct were reached with a very high *ee* value (Table 3, entry 8). If the catalyst loading was decreased from 5 mol% to 1 mol% the reactivity and selectivity fell (Table 3, entry 9). Finally, it should be mentioned that other chiral ligands were tested but were less efficient than the simple commercially available binap.

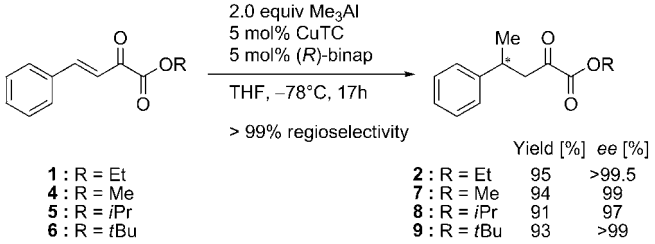
Table 3: Screening of copper salts and solvents.



Entry	CuX	Sol.	Conv. [%][a]	1,4/1,2[a]	*ee* [%][b]
1	$Cu(OAc)_2$	Et_2O	>99	50:50	95
2	$Cu(OTf)_2$	Et_2O	>99	20:80	27
3	CuTC	MTBE	>99	8:92	n.d.
4	CuTC	EtOAc	>99	77:23	48
5	CuTC	THF	70	>99:1	98
6	$Cu(OAc)_2$	THF	87	97:3	42
7	$Cu(OTf)_2$	THF	>99	85:15	0
8[c]	CuTC	THF	>99	>99:1	>99.5
9[d]	CuTC	THF	31	80:20	65

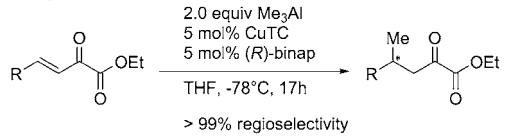
[a] Determined by ^{1}H NMR spectroscopy. [b] Reported values are for the 1,4-adduct. Determined by GC analysis using a chiral stationary phase. [c] Used 2 equiv of organometallic reagents. [d] Reaction performed with 1 mol% CuTC, and (*R*)-binap. MTBE = methyl *tert*-butyl ether, Tf = trifluoromethanesulfonyl.

As mentioned previously, the ester can play a very important role for some organocatalyzed ACAs. However, in our case, the use of more hindered ester moieties did not affect the reactivity or selectivity, even when using the *tert*-butyl ester (Scheme 2).



Scheme 2. Scope of ester reagents.

Table 4: Scope of substrate.



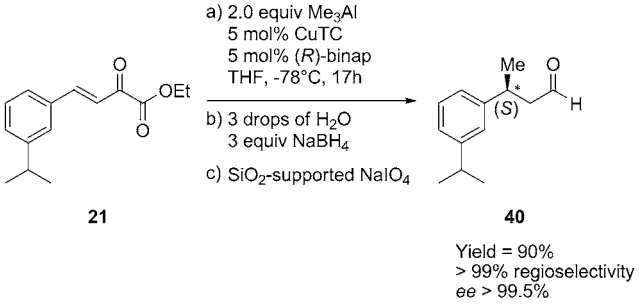
Entry	Sub.	R	Prod.	Yield [%]	*ee* [%][a]
1	**10**	*p*-FC_6H_4	**25**	68	97
2	**11**	*p*-ClC_6H_4	**26**	87	97
3	**12**	*p*-BrC_6H_4	**27**	91	98
4	**13**	*m*-BrC_6H_4	**28**	85	>99.5
5	**14**	*o*-BrC_6H_4	**29**	89	99
6	**15**	*p*-$MeOC_6H_4$	**30**	55	97
7	**16**	*m*-$MeOC_6H_4$	**31**	35	94
8	**17**	*o*-$MeOC_6H_4$	**32**	29	27
9	**18**	*p*-$NO_2C_6H_4$	**33**	88	96
10	**19**	*m*-$NO_2C_6H_4$	**34**	91	88
11	**20**	*o*-$NO_2C_6H_4$	**35**	90	92
12	**21**	*m*-*i*PrC_6H_4	**36**	93	98
13	**22**	C_7H_{15}	**37**	93	91
14	**23**	cyclohexyl	**38**	90	82
15[b]	**24**	$C_6H_4CH{=}CH$	**39**	92	98

[a] Determined by either GC, SFC, or HPLC using a chiral stationary phase. [b] No 1,6-addition product was observed.

Finally, the substrate scope was investigated. Table 4 shows that a wide range of substituted aromatic β,γ-unsaturated α-ketoesters with electron-donating and electron-withdrawing groups are compatible under the reaction conditions. As can be seen in Table 4, halogenated, nitro, or methoxy aryl derivatives tolerate the reaction conditions. Linear and cyclic β,γ-unsaturated α-ketoesters also gave very good selectivities considering the conformational flexibility of the alkyl chain and comparing theses results with previous ACA to enones or enals. Only strongly donating groups (*o*,*m*,*p*-OMePh) afforded lower conversions and yields, although no by-products were observed. For R = *o*-OMePh we also observe a dramatic drop of enantioselectivity to 27%. It is interesting to notice that dienic substrate **24** (Table 4, entry 15) provides exclusively the 1,4-adduct, without trace of the 1,6-regioisomer.

The generality of the reaction was finally explored using other organoaluminium and organozinc reagents, but unfortunately a mixture of the 1,4- and 1,2-addition products or low enantioselectivities were obtained under our reaction conditions. Such divergent results with higher aluminium homologues are not unprecedented, although no clear explanation could be given.[23]

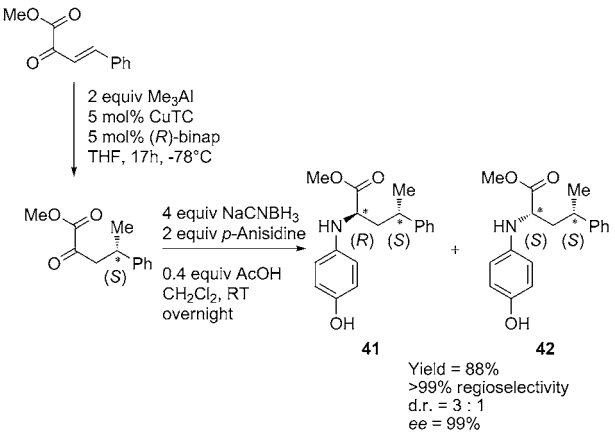
As mentioned in the introduction, the functionalities on β,γ-unsaturated α-ketoesters give access to a wide range of chiral building blocks for further derivatization. To complement our previous work with α,β-unsaturated aldehydes,[19] we decided to apply a simple derivatization procedure to obtain the corresponding chiral β-substituted aldehyde. The groups of Feringa,[24] Hoveyda,[25] Palomo,[26] and Mazet[27] have already developed alternative methodologies to obtain this type of product but the yield, regio- and/or enantioselectivity left room for improvement. A two-step, reduction/oxidation[28] procedure was applied to the synthesis of (*S*)-florhydral.[29] The synthesis of this compound was already described in the literature but with poor yield or enantioselectivity.[30] With our strategy, we were able to obtain the (*S*)-florhydral (**40**) with very good yield, and high regio- and enantioselectivity (Scheme 3).



Scheme 3. Synthesis of (*S*)-florhydral (**40**).

The β-substituted aldehyde was obtained with complete retention of the chiral information. By a simple one-pot procedure, the same result was obtained. This application also allowed us to determined the absolute configuration by comparison of the results with our previous work.[19]

We can also easily prepare chiral α-amino acid precursors from the corresponding γ-substituted-α-ketoesters by a one-step procedure. By simple reductive amination on chiral γ-substituted-α-ketoesters we obtained, under nonoptimized reaction conditions, the corresponding unnatural chiral α-amino acid precursors with complete retention of the chiral information and with a promising diastereoselectivity of up to 3:1 (Scheme 4).



Scheme 4. Synthesis of unnatural α-amino acid precursors.

In conclusion, β,γ-unsaturated α-ketoesters are shown to be very efficient substrates for the copper-catalyzed asymmetric conjugate addition.[31] Whilst a lower reaction temperature and THF are required for the case where trimethylaluminium is used as the organometallic reagent, just 5 mol% of CuTC and (*R*)-binap afforded the desired reaction product. The simple commercially available binap ligand can catalyze the reaction with very high efficiency. A wide range of

electron-donating and electron-withdrawing aryl derivatives were tolerated under our reaction conditions to give full conversion and regioselectivities up to 99.5% *ee*. However, a strong electronic, steric, and chelating effect with aryl methoxy derivatives was observed, and resulted in a decrease of reactivity and enantioselectivity. Some alkyl derivatives were also screened and are compatible under our reaction conditions even if a small drop in the enantioselectivity was observed. Progressively increasing the steric bulk of the ester moiety from methyl to *tert*-butyl did not affect the enantioselectivity of the reaction. Furthermore, γ-substituted-α-ketoesters were used as chiral building blocks for further derivatization. We obtained the corresponding β-substituted aldehydes by a simple one-pot methodology with complete retention of the chiral information. Finally, a convenient reductive amination was used to access unnatural chiral α-amino acid precursors also with complete retention of the chiral information and with promising diastereoselectivity.

Received: October 17, 2011
Published online: December 1, 2011

Keywords: amino acids · asymmetric catalysis · copper · enantioselectivity · synthetic methods

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