Asymmetric Catalysis

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Enantioselective Copper-Catalyzed Conjugate Addition of Trimethylaluminum to β,γ-Unsaturated α-Ketoamides: Efficient Access to γ-Methyl-Substituted Carbonyl Compounds**

*Sylvie Goncalves-Contal, Ludovic Gremaud, and Alexandre Alexakis**

Chiral α-, β-, or γ-methyl-substituted carbonyl groups are important scaffolds in organic synthesis and are present in numerous natural products. α-Methyl-substituted carbonyls can be easily obtained by asymmetric α-alkylation of carbonyls (Figure 1). One simple strategy to access β-methyl-substituted carbonyls is a copper-catalyzed asymmetric conjugate addition (ACA) to α,β-unsaturated carbonyls, a reaction widely reported in the literature.[1] But the preparation of chiral γ-methyl-substituted carbonyls is not so trivial compared to its parent α- and β-substituted carbonyls. The main methodology relies on ring-opening, by copper, of chiral cyclopropanes with subsequent decarboxylation and amide reduction (Figure 1, route a).[2] By using this approach, Charette et al. reported one example of the preparation of γ-methyl-substituted aldehydes with complete retention of enantioselectivity. The starting chiral cyclopropanes were elegantly synthesized by rhodium(II)-catalyzed cyclopropanation of α-amido diazoacetate derivatives. However, this was limited to the preparation of aryl-substituted cyclopropanes.

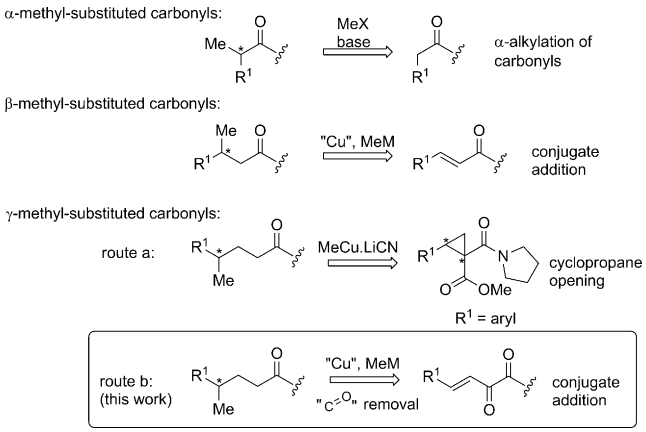

Figure 1. Strategies to α-, β-, or γ-methyl-substituted carbonyls.

Consequently, new methodologies to access chiral γ-methyl-substituted carbonyls are needed and are of interest if we consider the importance of this scaffold in nature. With the aim of providing an efficient strategy, we felt that ACA to β,γ-unsaturated α-ketocarbonyls would permit their synthesis (Figure 1, route b).

Even if they were widely studied, β,γ-unsaturated α-ketocarbonyls remain unexplored as Michael acceptors, the sole example being α-ketoesters.[3] Indeed, we reported in 2012 the conjugate addition of trimethylaluminum to β,γ-unsaturated α-ketoesters. However, derivatization of 1,4-adducts containing the α-ketoester moiety could afford only β-methyl-substituted aldehydes. As a result of the similar reactivity between the ketone and ester, selective reduction was not possible. Thus, we thought that replacing the ketoester by a ketoamide would allow selective transformations and efficiently provide γ-methyl-substituted carbonyls, which are key building blocks in natural product synthesis. For example, 1,4-adducts obtained by ACA to β,γ-unsaturated α-ketoamides could be transformed into 4-aryl-4-methylbutanoic acid, an important scaffold for the preparation of numerous acyclic and cyclic natural products (Figure 2).[4] Indeed, our methodology would provide a new route to this chiral building block as only four asymmetric methods have been reported for its synthesis (hydrogenation of unsaturated carboxylic acid,[4] hydrovinylation of alkene,[5] isomerization of allylic alcohol[6] and enzymatic procedures[7]).

Thus, α-ketoamides appeared interesting in terms of synthetic utility, but also in terms of reactivity. In fact, they were less studied than the corresponding ester and phospho-

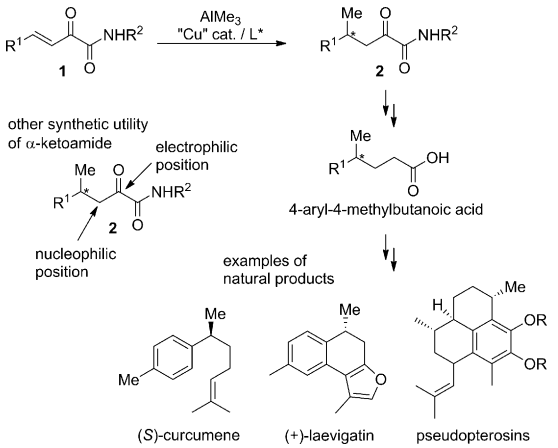

Figure 2. ACA to β,γ-unsaturated α-ketoamide and derivatizations.

[*] Dr. S. Goncalves-Contal, Dr. L. Gremaud, Prof. A. Alexakis
Department of organic chemistry, University of Geneva
Sciences II, Quai Ernest-Ansermet, 1211 Geneve 4 (Switzerland)
E-mail: alexandre.alexakis@unige.ch

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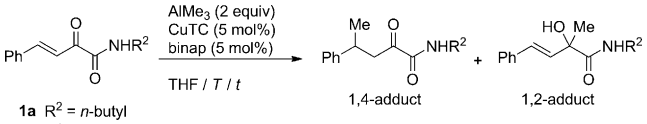
nate. Indeed, they were never envisioned for ACAs of organometallic reagents and few reactions employing them are described in literature. A report in 1998 described only two examples of hetero-Diels–Alder reactions between α-ketoamides and ethylvinylethers under bis(oxazoline)/copper(II) catalysis.[8] Later, Rodriguez et al. described their use in the synthesis of highly functionalized pyridines by a multicomponent reaction in the presence of ammonium acetate and malonate derivatives.[9] Examples of quinoline[10] and pyrazolinecarboxamide[11] syntheses were finally reported using an α-ketoamide and *m*-*N*,*N*-dimethylamino aniline and *N*-pentylhydrazine, respectively.

In the course of our studies on the ACA of organometallic reagents, and with the aim of providing efficient access to γ-methyl-substituted carbonyls, we report herein the ACA of $AlMe_3$ to β,γ-unsaturated α-ketoamides with excellent regio- and enantioselectivities. If we consider the synthetic potentiality of γ-methyl-substituted α-ketoamides, we feel that this method represents a new and powerful tool in organic chemistry. To highlight it, we also describe the transformation of the 1,4-adducts into chiral γ-methyl-substituted building blocks of interest.

Because of a structural similarity between ketoesters and ketoamides, the same reaction conditions were first envisioned: $AlMe_3$ (2.0 equiv), copper thiophene carboxylate (CuTC, 5 mol%), *rac*-binap (5 mol%) in THF. The optimization of the secondary amide moiety was first realized by testing primary, secondary, and tertiary alkyl substituents as well as *p*-methoxyphenyl and benzyl groups (Table 1). The

Table 1: Optimization of the β,γ-unsaturated α-ketoamide structure.



1a R^2 = *n*-butyl
1b R^2 = cyclohexyl
1c R^2 = *tert*-butyl
1d R^2 = *p*-methoxyphenyl
1e R^2 = benzyl

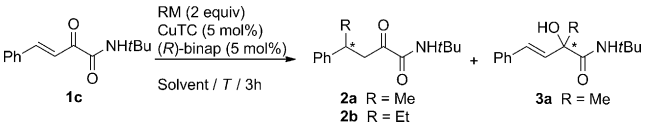
Entry[a]	α-Ketoamide	*T* [°C]	*t*	1,4-adduct [%][b]	1,2-adduct [%][b]
1	**1a**	−78	30 min	46	32
2	**1b**	−78	3 h	68	16
3	**1c**	−78	3 h	89	–
4	**1d**	25	30 min	63	–
5	**1e**	25	1 h	45	26

[a] Reaction done with α-ketoamide (0.416 mmol) and THF (1.5 mL). [b] Yield of isolated product. binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

β,γ-unsaturated α-ketoamides were easily synthesized by a two-step procedure: a Passerini-like reaction gives a α-hydroxyamide[12] followed by Dess–Martin periodinane oxidation (see the Supporting Information). In the first attempt, the *n*-butyl-substituted amide **1a** gave a mixture of 1,4- and 1,2-adducts with a ratio of 46:32 (entry 1). By increasing steric hindrance on the amide, exclusive formation of the conjugated adduct was possible. Indeed, the *tert*-butyl-substituted amide **1c** gave rise to the desired compound in 89% yield with perfect 1,4-regioselectivity (entry 3). Concerning the α-ketoamides **1d** and **1e**, bearing phenyl and benzyl substituents, respectively, on the nitrogen atom, the reactions had to be run at room temperature for solubility reasons (entries 4 and 5). Only **1d** exclusively afforded the 1,4-adduct but with a lower yield compared to that of **1c**, and **1e** gave a 1,4-adduct:1,2-adduct ratio of 45:26. Finally, it appeared that the *tert*-butyl group on the nitrogen atom was the substituent of choice for a highly regioselective conjugate addition.

Having identified the best β,γ-unsaturated α-ketoamide structure, we next considered the use of various organometallic reagents (Table 2). An asymmetric version was performed using (*R*)-binap as a ligand. $AlMe_3$ provided the desired 1,4-adduct **2a** exclusively in excellent yield (89%) and 99% *ee* (entry 1). Methylmagnesium bromide failed to

Table 2: Screening of organometallic reagents.



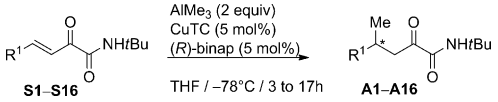
Entry[a]	RM	Solvent	*T* [°C]	**2**/**3**	Yield [%][b]	*ee* [%][c]
1	$AlMe_3$	THF	−78	99:1	89	99
2	MeMgBr	Et_2O	−78	1:99	85	rac.
3[d]	MeMgBr	Et_2O	−78	1:99	88	rac.
4	MeMgBr	THF	−78	1:99	92	rac.
5	Me_2Zn	Et_2O	0	–[e]	–	–
6	Et_2Zn	Et_2O	−20	–[f]	–	–
7	$AlEt_3$	THF	−65	99:1	69	24
8	$AlEt_3$	Et_2O	−65	40:60	100[g]	rac.

[a] Reaction done with α-ketoamide (0.416 mmol) and THF (1.5 mL. [b] Yield of the isolated 1,4- or 1,2-adduct. [c] Determined by SFC using a chiral stationary phase. [d] TMSCl (1.3 equiv) was used as additive. [e] No reaction. [f] Complex reaction mixture. [g] Conversion.

provide **2a**, but the racemic 1,2-adduct **3a** was obtained (entry 2). TMSCl was also tested as an additive as it is known to promote conjugate addition on enals.[13] However, in the case of ACAs to an β,γ-unsaturated α-ketoamide, no traces of **2a** were observed (entry 3). Dimethylzinc and diethylzinc were not suitable for the reaction. With Me_2Zn, no reaction occurred and Et_2Zn led to a complex reaction mixture (entries 5 and 6). In the end, a triorganoaluminum reagent proved to be the most efficient and so, we decided to introduce an ethyl substituent by using Et_3Al. The reaction proceeded with perfect 1,4-regioselectivity, thus giving **2b** in 69% yield (entry 7). Unfortunately, the *ee* value decreased significantly to 24%.

These best reaction conditions were then applied to a wide range of β,γ-unsaturated α-ketoamides to evaluate the limits of the methodology (Table 3). In all cases, reactions proceeded with perfect 1,4-regioselectivity as only 1,4-adducts were recovered. First, if we considered *para* substituents (alkyl, halide, or methoxy groups) on the aryl moiety had no influence on regio- or enantioselectivity (entries 1–5). For each α-ketoamide (**S1**–**S5**), the corresponding 1,4-adducts **A1**–**A5** were isolated in good to excellent yields (70–97%) with excellent *ee* values (96–98.5%). Moreover, excellent

Table 3: ACA on various β,γ-unsaturated α-ketoamides.

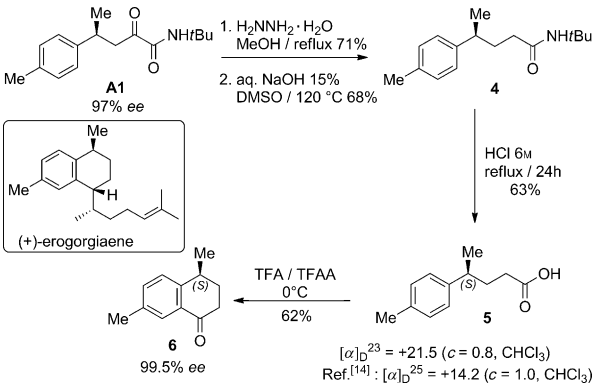


Entry[a]	α-Ketoamide	R^1	1,4-adduct	Yield [%][b]	*ee* [%][c]
1	**S1**	*p*-MeC_6H_4	**A1**	89	97
2	**S2**	*p*-BrC_6H_4	**A2**	93	98
3	**S3**	*p*-ClC_6H_4	**A3**	97	98.5
4	**S4**	*p*-FC_6H_4	**A4**	87	97
5	**S5**	*p*-$MeOC_6H_4$	**A5**	70	96
6	**S6**	*m*-$MeOC_6H_4$	**A6**	85	98
7	**S7**	*m*-BrC_6H_4	**A7**	89	98
8	**S8**	*m*-$NO_2C_6H_4$	**A8**	83	96
9	**S9**	*o*-$MeOC_6H_4$	**A9**	23	60
10	**S10**	*o*-BrC_6H_4	**A10**	88	99.9
11	**S11**	*o*-$NO_2C_6H_4$	**A11**	80	96
12	**S12**	piperonyl	**A12**	86	99
13	**S13**	thienyl	**A13**	89	98
14	**S14**	$PhCH_2CH_2$	**A14**	78	99
15	**S15**	cyclohexyl	**A15**	54	79
16	**S16**	Ph-CH=CH	**A16**	94	99.9

[a] Reaction done with α-ketoamide (0.416 mmol) and THF (1.5 mL). [b] Yield of isolated product. [c] Determined by SFC using a chiral stationary phase.

results were always obtained by changing the substitution pattern from *para* to either *meta* or *ortho*, except for the methoxy group (entries 6–11). In the latter case, reactions were done successfully with the methoxy group in the *para* or *meta* positions (entries 5 and 6). With the methoxy group in the *ortho* position, the desired 1,4-adduct **A9** was isolated with a low yield (23%) because of low conversion, and a decreased *ee* value of 60% (entry 9). The nitro functional group was also compatible with our reaction conditions, as compounds **A8** and **A11** were obtained with good yields and excellent *ee* values (entries 8 and 11). More-substituted aromatic and heteroaromatic counterparts were also considered with the α-ketoamides **S12** and **S13** bearing piperonyl and thienyl moieties, respectively. The adducts **A12** and **A13** were recovered with very good yields (86 and 89%) and good *ee* values (entries 12 and 13). Primary alkyl substituents allowed an efficient reaction whereas secondary alkyl ones led to a decreased yield and *ee* value (entries 14 and 15). Indeed, the cyclohexyl α-ketoamide **A15** was isolated with moderate yield (54%) and a satisfactory *ee* value (79%). Concerning the case of an alkyl substituent, it also has to be noted that an *n*-butyl ketoamide was tested, but unfortunately gave a poor result in terms of conversion. In this case, the reaction was not complete, and finally, only 1,4-addition took place efficiently in the case of **S16** with no traces of the 1,6-addition product; the adduct **A16** was recovered in 94% yield with 99.9% *ee* (entry 16).

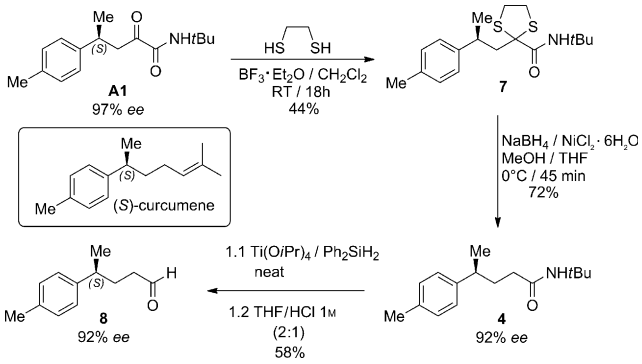
To demonstrate the potential synthetic utility of the ACAs to β,γ-unsaturated α-ketoamide, we focused on the synthesis of several chiral small building blocks, precursors of many natural products. To reach this goal, we first studied the derivatization of **A1** to tetralone **6** (Scheme 1). Selective reduction of the ketone function to the alkane was realized by Wolff–Kishner reduction in two steps. The amide **4** was thus



Scheme 1. Derivatization of **A1** to tetralone **6**. DMSO = dimethylsulfoxide, TFA = trifluoroacetic acid, TFAA = trifluoroacetic anhydride.

isolated and then hydrolyzed to afford the 4-*p*-tolylpentanoic acid **5** in 63% yield. With **5** in hand, and by comparison of optical rotations, we were able to determine the *S* stereochemistry of the stereogenic center created. Finally, Friedel–Crafts acylation gave the desired tetralone **6** with 99.5% *ee*. This tetralone is, for example, an intermediate in the total synthesis of (−)-laevigatin,[14] (*S*)-*ar*-himachalene,[15] and (+)-erogorgiaene.[16]

Starting from **A1**, we also considered the possibility of accessing acyclic natural compounds. We decided to synthesize the 4-*p*-tolylpentanal **8**, a precursor to (*S*)-curcumene for example (Scheme 2).[2] This time, **4** was obtained successfully

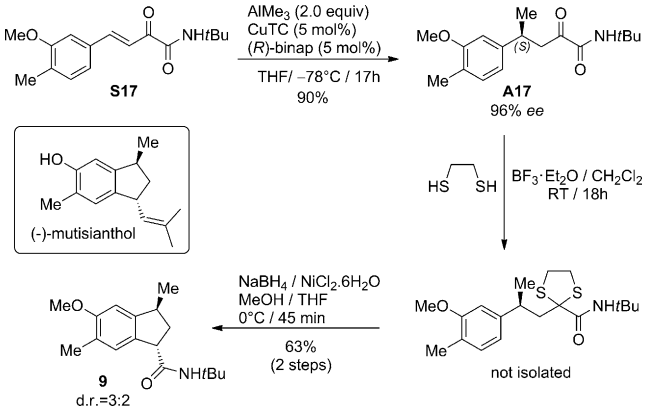


Scheme 2. Derivatization of **A1** to aldehyde **8**.

in two steps: first transformation of the ketone function into the 1,3-dithiolane **7** and then reduction in the presence of sodium borohydride and nickel(II) chloride hexahydrate.[17] However, this procedure led to a slight decrease of the *ee* value to 92%, maybe as a result of isomerization at the benzylic position during the reduction. Finally, titanium(IV) isopropoxide in the presence of diphenylsilane[18] and subsequent acidic treatment afforded the desired aldehyde **8**, a precursor of (*S*)-curcumene, with 92% *ee*.

In the end, we envisioned derivatization of **A17** as we identified a *m*-methoxy-*p*-methylphenyl moiety in several natural products like (−)-mutisianthol,[19] (−)-7-hydroxycalamanene,[6b] (*S*)-xanthorrizol,[4] (*S*)-aristelegon A,[4] and (+)-heritol,[20] for example. These natural products could be obtained from **A17** by using the synthetic route described in

Scheme 1. However, we decided to apply the second reduction strategy to **A17**, which was obtained by conjugate addition of $AlMe_3$ to the corresponding β,γ-unsaturated α-ketoamide **S17** with in 90% yield and 96% *ee* (Scheme 3).



Scheme 3. Derivatization of **A17** to bicycle **9**.

Here, reduction of the 1,3-dithiolane under the previous reaction conditions gave rise to the bicyclic compound **9**, with a low diastereoselectivity of 3:2 in favor of the *trans* diastereoisomer. However, **9** represents an interesting potential intermediate to (−)-mutisianthol.

To conclude, we developed the first asymmetric conjugate addition of $AlMe_3$ to β,γ-unsaturated α-ketoamides with perfect 1,4-regioselectivity and good to excellent *ee* values (79–99.9%). We thus showed that β,γ-unsaturated α-ketoamides represent a new class of Michael acceptors. The experimental conditions are mild, as several functional groups are tolerated. Heteroaromatic as well as alkyl substituents at the γ position were also tolerated in the ACAs. The potential synthetic utility was demonstrated with the preparation of key chiral building blocks for many acyclic and cyclic natural products, which were obtained successfully with good *ee* values. This methodology thus allowed efficient synthesis of γ-methyl-substituted carbonyls. It has to be mentioned that these important scaffolds in natural product synthesis could not be previously obtained from α-ketoesters. Efforts to develop other 1,2-dicarbonyl systems for asymmetric conjugate addition are in progress in our laboratory and will be reported in due course.

Experimental Section

General procedure for the ACA: A mixture of CuTC (0.021 mmol, 0.05 equiv), and (*R*)-binap (0.021 mmol, 0.05 equiv) in dry THF (1 mL) was stirred for 20 min at room temperature and then for 20 min at −78 °C. $AlMe_3$ 2.0 M in heptane (0.832 mmol, 3.0 equiv) was added over a period of 20 min and the reaction was stirred for 30 min at −78 °C. A solution of β,γ-unsaturated α-ketoamide (**S1**–**S17**; 0.416 mmol, 1.0 equiv) in THF (0.5 mL) was slowly added over 1 h and the reaction was finally stirred 16 h at −78 °C. After addition of NH_4Cl (sat.) and extraction with CH_2Cl_2, the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel (eluent: ethyl acetate/cyclohexane) to give the pure 1,4-adduct (**A1**–**A17**).

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