Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 48 (2007) 7408–7412
Tetrahedron Letters

Tandem asymmetric conjugate addition-enolacetates formation of enantiomerically enriched zinc and aluminium enolates

Magali Vuagnoux-d'Augustin and Alexandre Alexakis*

Department of Organic Chemistry, University of Geneva, 30, Quai Ernest Ansermet, 1211 Geneva 4, Switzerland

Received 18 May 2007; revised 28 July 2007; accepted 31 July 2007
Available online 6 August 2007

Abstract—The metal enolates, resulting from the copper-catalyzed enantioselective conjugate addition of organometallic reagents (Et_2Zn or R_3Al) to cyclic and acyclic enones are quantitatively trapped as enolacetates with acetic anhydride.

The asymmetric conjugate addition reaction has received an impressive interest over the past decade.[1,2] Enantioselectivities reaching more than 99% can be obtained on cyclic and acyclic substrates when diethylzinc species[2–5] is used, whereas the use of trialkylalanes[6,7] can be envisaged with high levels of asymmetric induction. The common feature of this kind of reaction is the generation of enantiomerically enriched metal enolates.

Tandem conjugate addition and trapping of the zinc enolates with an electrophile can be an excellent way to quickly build molecules that are more complex.[8] We have already shown that silylenolethers can be obtained from enantiomerically enriched zinc enolates in good to high yield.[9] This methodology enhanced the scope of the asymmetric conjugate addition. However, the high level of reactivity of such silylenolethers implies to work with a small excess of the organometallic species in order to avoid the cleavage of the silyl moiety due to the exothermicity and the slightly acidic work-up. Previously, Rivière reported the use of acetic anhydride as an acylating agent of magnesium enolates, generated via a copper-catalyzed conjugate addition (C.A.), in a racemic version.[10] Few months later, Mole and co-workers reported the use of acetic anhydride as an acylating agent of aluminium enolates generated by nickel-catalyzed C.A.[11] These articles enlightened us about potential alternatives to silylation trapping, by formation of enolacetates derived from enantiomerically enriched zinc or aluminium enolates. Moreover, it was demonstrated that O-acylation can usually be achieved using acetic anhydride as the acylating agent and diethylether as solvent of choice,[12] which corresponds appreciably to our experimental conditions.[7] Presumably, other anhydrides would give similar results but this has not been investigated. We detail here the use of acetic anhydride as an alternative pathway to generate the more stable enantio-enriched enolacetates.

This methodology was applied to several cyclic or acyclic α,β-unsaturated ketones (Fig. 1) in order to obtain their corresponding enantio-enriched enolacetates.

To obtain the best results in terms of enantioselectivity and conversion of the copper-catalyzed asymmetric conjugate addition, previously described phosphoramidite type ligands (**L1** and **L2**) were used for all substrates except cylopent-2-enone (**1**) where diphosphite **L3** gives better enantioselectivity[6g] than phosphoramidites (Fig. 2).

Preliminary investigations focused on cyclic Michael acceptors (**1**, **2** and **3**; Fig. 1, Table 1). Surprisingly, in contrast to Pfaltz's results on cyclopent-2-enone (**1**),

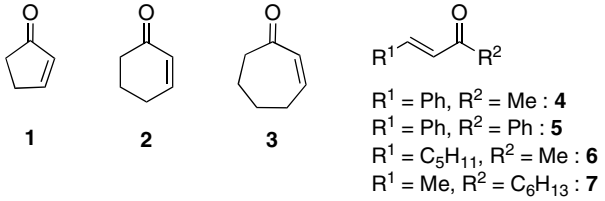


Figure 1. α,β-Unsaturated ketones used in this study.

Keywords: Michael addition; Copper; Enolacetate.
* Corresponding author. Tel.: +41 22 379 65 22; fax: +41 22 379 32 15; e-mail: alexandre.alexakis@chiorg.unige.ch

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.07.220

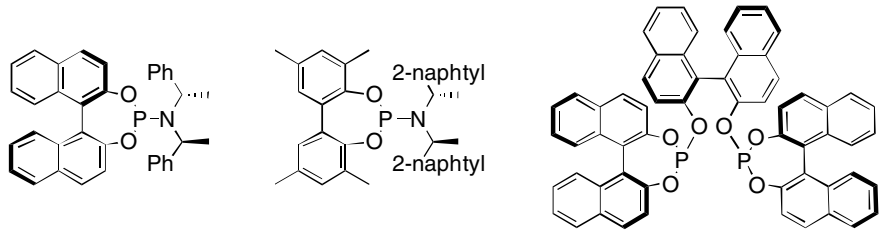


Figure 2. Ligands used in this study.

Table 1. O-Acyclation of cyclic metal enolates

Entry	Substrate	R_xM (equiv)	CuX (mol %)	Ligand (mol %)	Conv.[a] (%)	ee[b] (%)
1[c]	1	Et_2Zn (1.5)	$Cu(OTf)_2$ (1.0)	**L3** (2.0)	>98	77 (*S*)
2[d]	2	Et_2Zn (1.2)	$Cu(OAc)_2,H_2O$ (2.0)	**L1** (4.0)	>98 (73)[e]	96 (*R*)
3	2	Et_3Al (1.5)	CuTC (2.0)	**L1** (4.0)	>98	86 (*R*)
4	2	Me_3Al (1.5)	CuTC (2.0)	**L2** (4.0)	>98	97 (*R*)
5	3	Et_2Zn (1.2)	$Cu(OAc)_2,H_2O$ (2.0)	**L1** (4.0)	>98 (50)[e]	96 (*R*)
6	3	Et_3Al (1.5)	CuTC (2.0)	**L1** (4.0)	>98	84 (*R*)
7	3	Me_3Al (1.5)	CuTC (1.0)	**L1** (4.0)	>98	76 (*R*)

[a] Conversion determined by GC–MS and ^1H NMR spectroscopy.
[b] Ee determined on deprotected ketone by GC with chiral stationary phase.
[c] According to the conditions described by Chan. See Ref. 6h.
[d] Scale-up on 20 mmol.
[e] Isolated yield.

no trace of the C-acylation product was observed.[13] For each enone the corresponding enantio-enriched enolacetate was formed with complete conversion, even on large scale (Table 2, entry 2), with a high level of enantioselectivity. The use of freshly distilled Ac_2O was not necessary since it seemed that the reactivity of the enolate was higher towards the acetic anhydride than the residual acetic acid. This was confirmed by the fact that we never observed the free 1,4-adduct in the unpurified mixture. Nevertheless, it was not possible to reduce the reaction time by adding Ac_2O at the beginning of the reaction when organoaluminium reagents were used. The Ac_2O was cleaved by the organometallic species and the reaction was stopped by a lack of reagent. In contrast, when zinc species were used, Ac_2O could be added to the mixture at the beginning of the reaction with good results.[14]

We then applied our methodology to acyclic substrates, in order to generate acyclic enolacetates, following the general protocol described in Scheme 1. With an aim of comparing the influences of the substituents on the enone, two types of substrates were used, the aromatic ones (Table 3), and the aliphatic ones (Table 4).

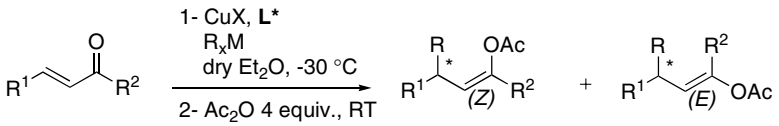
Just as for the silylenolethers, two types of isomers (*E* and *Z*) can be obtained after the reaction with acetic anhydride. In order to assign the geometry of enolacetates we based our experiment on earlier work of House[15] and Rivière.[10] Moreover, our results were correlated with those previously published by our group about the substrate conformation (*s-cis* and *s-trans*) and the double bond geometry of zinc enolates during the copper-catalyzed asymmetric conjugate addition reaction in presence of phosphoramidite type ligands.[9]

As shown in Table 2, the reaction of acyclic aromatic enolates with anhydride worked well in terms of conversions and enantioselectivities. The most interesting point is the inversion of the *E*–*Z* ratio by changing the

Table 2. Acylation of aromatic acyclic metal enolates

Entry	Substrate	R_xM (equiv)	CuX (2.0 mol %)	Ligand (4.0 mol %)	Conv.[a] (%) (yield %)[b]	ee[c] (%)	*E*–*Z* ratio[d]
1	4	Et_2Zn (1.2)	$Cu(OTf)_2$	**L1**	>98 (48)	80 (*S*)	75–25
2	4	Et_3Al (1.5)	CuTC	**L1**	>98 (45)	92 (*S*)	52–48
3	4	Me_3Al (1.5)	CuTC	**L1**	>98 (45)	94 (*S*)	39–61
4	5	Et_2Zn (1.2)	$Cu(OTf)_2$	**L1**	>98 (58)	60 (*S*)	0–100
5	5	Et_3Al (1.5)	CuTC	**L1**	>98 (16)	93 (*S*)	0–100 (2-1)[e]
6	5	Me_3Al (1.5)	CuTC	**L1**	>98 (22)	98 (*S*)	0–100 (2-1)[e]

[a] Conversion determined by GC–MS and ^1H NMR spectroscopy.
[b] Isolated yield.
[c] Ee determined on deprotected ketone by GC with chiral stationary phase or SFC.
[d] Ratio determined on the unpurified mixture by ^1H NMR spectroscopy.
[e] C–O-Acylation ratio determined by ^1H NMR spectroscopy of the unpurified mixture.



Scheme 1. General procedure for tandem A.C.A.–acylation reaction.

Table 3. Acylation of aliphatic acyclic metal enolates

Entry	Substrate	R_xM (equiv)	CuX (2.0 mol %)	Ligand (4.0 mol %)	Conv.[a] (%) (yield %)[b]	ee[c] (%)	*E*–*Z* ratio[d]
1	6	Et_2Zn (1.2)	$Cu(OTf)_2$	**L1**	>98 (73)	62 (*S*)	85–15
2	6	Et_3Al (1.5)	CuTC	**L1**	>98 (40)	68 (*R*)	52–48
3	6	Me_3Al (1.5)	CuTC	**L1**	>98 (45)	68 (*R*)	22–78
4	7	Et_2Zn (1.2)	$Cu(OTf)_2$	**L1**	>98 (57)	69 (*S*)	86–14
5	7	Et_3Al (1.5)	CuTC	**L1**	>98	nd[e]	nd[e]

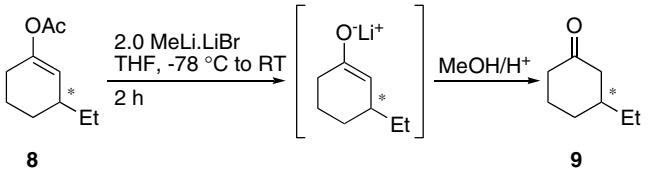
[a] Conversion determined by GC–MS and ^1H NMR spectroscopy.
[b] Isolated yield.
[c] Ee determined on deprotected ketone by GC with chiral stationary phase.
[d] Determined on the unpurified mixture by ^1H NMR spectroscopy.
[e] Aldol contaminents did not allow this measurement.

organometallic species (Al or Zn). This could be explained by the Lewis acid character of diethylzinc and trialkylalanes. Indeed, it seemed that the *s-cis*/*s-trans* conformation of the starting material was influenced by the Lewis acidity of the organometallic species. In theory, by using aluminium species instead of zinc reagents, the Lewis acidity of the organometallic species increases, and a stronger interaction must be observed between the oxygen atom of the carbonyl moiety and the metal. That could favour the *s-trans* conformation of the enone. Surprisingly, the reverse observation was made since the *Z*-enolacetate is mainly observed by changing the organometallic species. However, Mole studied the geometry of aluminium enolates generated by Ni-catalyzed C.A. of organoaluminium reagents to mesityloxide.[11] He isolated the aluminium enolate and confirmed the *Z*-geometry by several analyses. The existence of a dimeric form of the *Z*-aluminium enolate and a mixture of dimeric and trimeric structures of the *E*-aluminium enolate was proven. Unfortunately, the authors did not say anything about the influence on the Lewis acidity of the trimethylaluminium on the conformation of the Michael acceptor and about its influence on the aluminium enolate structure. However, it is interesting to notice that similar observations about the preferred *Z*-aluminium enolate geometry and *Z*-enolacetates were made when R_3Al species were used. To determine the enolacetate stability in our experimental conditions, two kind of reactions with substrate **4** were performed. Firstly, the experiment was quenched at 90% conversion and an *E*–*Z* ratio of 43–57 was measured. Secondly, the reaction was left at room temperature overnight to reach a thermodynamic equilibrium. An *E*–*Z* ratio of 52–48 was measured. This difference between the two ratios confirmed that the equilibration was very slow, and that the *Z*-enolacetate was the kinetic product. Surprisingly, chalcone (**5**) led, in the presence of trialkylalane, to a non-negligible part of C-acylation product as a single diastereoisomer (67%; Table 2, entries 5 and 6 vs 4) while zinc species provided only the O-acylation product (Table 2, entry 4). That explained the very low isolated yields in these two cases. Only *Z*-enolacetates were obtained whatever the organometallic species (Table 2, entries 4–6). The *Z*-selectivity was probably due to the *s-cis* preferential conformation of chalcone (**5**).[16]

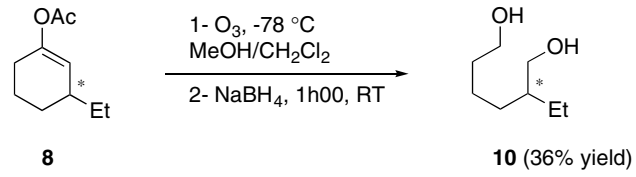
Only O-acylation was observed when aliphatic acyclic α,β-unsaturated ketones were used (Table 3) with complete conversion. The inversion of the *E*–*Z* ratio, due to a change of the organometallic species, was also observed here (Table 3, entries 1 vs 2 vs 3). A small increase of the enantioselectivity was noticed when Et_3Al was used instead of Et_2Zn (Table 3, entries 1 vs 2). Finally, enone **7** bearing a small methyl group in β-position seemed to be much more reactive than the other substrates and the Lewis acidic activation due to the triethylaluminium led to a polymerization process rather that an A.C.A. reaction.

To conclude, we found an interesting alternative to the formation of enantio-enriched silylenolethers by trapping the enantio-enriched metal enolates with acetic anhydride.[17] Moreover, this methodology is tolerant to large-scale reactions with no loss of enantioselectivity in good yield.

Enolacetates have a number of synthetic uses. In certain acid-sensitive systems, C.A.-O-acylation-basic hydrolysis gives higher yields of the β-substituted ketone than direct C.A.-hydrolysis.[8a,18] Their major use, however, is as regiospecific enolate equivalent. The lithium enolate could be quantitatively regenerated with no loss of enantioselectivity following procedures described by House[19] and Posner[20] (Scheme 2). The main disadvantage of this method is the in situ generation of the lithium *tert*-butoxide, which could act as base in the media. This problem could eventually be overcome by using just one equivalent of potassium *tert*-butoxide as described by Duhamel.[21]



Scheme 2. Lithium enolate formation.



Scheme 3. Reductive ozonolysis reaction.

Enolacetate **8** could also be a precursor of an asymmetric diol, which was obtained via reductive ozonolysis (Scheme 3).[22]

Acknowledgements

The authors thank the Swiss National Science Foundation (No. 200020-113332) for financial support. They also thank C. Sénat for help.

References and notes

1. (a) Alexakis, A. In *Transition Metal Catalysed Reactions*; Murahashi, S. I., Davies, S. G., Eds.; IUPAC Blackwell Science: Oxford, 1999; p 303; (b) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 2000; p 1105; (c) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061; (d) Ibuka, T. *Organocopper Reagents in Organic Synthesis*; Rose Press: Osaka, 2000; (e) Krause, N. *Modern Organocopper Chemistry*; VCH: Weinheim, 2002.
2. Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221–3236.
3. (a) Alexakis, A.; Mutti, S.; Normant, J. F. *J. Am. Chem. Soc.* **1991**, *113*, 6332–6334; (b) Alexakis, A.; Frutos, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2427–2430; (c) Feringa, B. L.; Pineshi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Ang. Chem., Int. Ed.* **1997**, *36*, 2620–2623; (d) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353; (e) Alexakis, A.; Benhaim, C.; Rosset, S.; Human, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262–5263; (f) Benhaim, C. PhD Dissertation No. 3368, University of Geneva, 2002; (g) Alexakis, A.; Polet, D.; Benhaim, C.; Rosset, S. *Tetrahedron: Asymmetry* **2004**, *15*, 2199–2203; (h) Alexakis, A.; Polet, D.; Benhaim, C.; Rosset, S.; March, S. *J. Org. Chem.* **2004**, *69*, 5660–5667; (i) Polet, D. PhD Dissertation No. 3668, University of Geneva, 2005; (j) Watanabe, T.; Knopfel, T. F.; Carreira, E. M. *Org. Lett.* **2003**, *5*, 4557–4558; (k) Schuppan, J.; Minnaard, A.; Feringa, B. L. *Chem. Commun.* **2004**, 792–793; (l) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. *Chem. Commun.* **2004**, 1779–1785, and references therein.
4. (a) Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584–4585; (b) Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988–14989; (c) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774–2775.
5. Fillion, E.; Wilsily, A.; Liao, E.-T. *Tetrahedron: Asymmetry* **2006**, *17*, 2957.
6. (a) Takemoto, Y.; Kuraoka, S.; Hamaue, N.; Aoe, K.; Hiramatsu, H.; Iwata, C. *Tetrahedron* **1996**, *52*, 14177–14188; (b) Takemoto, Y.; Baba, Y.; Noguchi, I.; Iwata, C. *Tetrahedron Lett.* **1996**, *37*, 3345–3346; (c) Woodward, S.; Fraser, P. K. *Chem. Eur. J.* **2003**, *9*, 776–783; (d) Benett, S. M. W.; Brown, S. M.; Muxworthy, J. P.; Woodward, S. *Tetrahedron Lett.* **1999**, *40*, 1767–1770; (e) Benett, S. M. W.; Brown, S. M.; Conole, G.; Dennis, M. R.; Fraser, P. K.; Radojevic, S.; McPartlin, M.; Topping, C. M.; Woodward, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3127–3132; (f) Liang, L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2002**, *13*, 1393–1396; (g) Liang, L.; Yan, M.; Li, Y.-M.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 1865–1869; (h) Yan, M.; Chan, A. S. C. *Tetrahedron Lett.* **1999**, *40*, 6645–6648.
7. Alexakis, A.; Albrow, V.; Biswas, K.; d'Augustin, M.; Prieto, O.; Woodward, S. *Chem. Commun.* **2005**, *22*, 2843–2845.
8. (a) Taylor, R. J. K. *Synthesis* **1985**, 364–392; (b) Chapdelaine, M. J.; Hulce, M. *Org. React.* **1990**, *38*, 225–653; (c) Li, K.; Alexakis, A. *Tetrahedron Lett.* **2005**, *46*, 8019–8022; (d) Li, K.; Alexakis, A. *Tetrahedron Lett.* **2005**, *46*, 5823–5826; (e) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354–366.
9. Knopff, O.; Alexakis, A. *Org. Lett.* **2002**, *4*, 3835–3837.
10. (a) Rivière, H.; Tang, P.-W. *Bull. Soc. Chim.* **1973**, 2455–2460; (b) Marets, J.-P.; Rivière, H. *Bull. Soc. Chim.* **1979**, 4320–4326.
11. (a) Jeffery, E. A.; Meisters, A.; Mole, T. *J. Organometal. Chem.* **1974**, *74*, 365–371; (b) Jeffery, E. A.; Meisters, A.; Mole, T. *J. Organometal. Chem.* **1974**, *74*, 373–384; (c) Bagnell, L.; Jeffery, E. A.; Meisters, A.; Mole, T. *Aust. J. Chem.* **1975**, *28*, 801–815.
12. Kowalsky, C. J.; Weber, A. E.; Fields, K. W. *J. Org. Chem.* **1982**, *47*, 5088–5093.
13. Esher, I. PhD Dissertation, University of Basel, 2000.
14. Fuchs, N. PhD Dissertation No. 3791, University of Geneva, 2006.
15. House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324–2336.
16. Montaudo, G.; Librando, S.; Caccamese, S.; Maravigna, P. *J. Am. Chem. Soc.* **1973**, *95*, 6365–6370.
17. Typical procedure (Table 1, entry 3). The ligand (0.04 mmol) was added to a solution of copper thiophene carboxylate (CuTC, 0.02 mmol) in dry Et_2O (2.5 mL) at room temperature under argon. The solution was stirred at room temperature for 30 min and enone (1.0 mmol) in 0.5 mL of dry Et_2O was then added dropwise. The mixture was then cooled to −30 °C and the trialkylalane was added dropwise so that the temperature did not rise over −30 °C. The reaction mixture was stirred at −30 °C until complete consumption of the starting material. Ac_2O (0.4 mL, 4.2 mmol) was added dropwise at −30 °C and the reaction mixture was allowed to warm up to room temperature until complete conversion. The mixture was quenched by adding NH_4Cl_{satd}/HCl and Et_2O. The aqueous layer was extracted 3 times with Et_2O, and the organic layers were washed with a saturated solution of $NaHCO_3$ and water before drying over $MgSO_4$ and filtered off. The solvents were removed in vacuo to offer the unpurified mixture, which was purified by flash

chromatography (pentane/Et_2O as eluent). Enantiomeric excess was determined on an aliquot before the addition of the acetic anhydride by GC with chiral stationary phase. The E/Z ratio was determined on the unpurified mixture by ^1H NMR spectroscopy.

18. Pitts, E.; de Wall, B.; Britton, R. W. *J. Am. Chem. Soc.* **1971**, *93*, 5113–5120.
19. (a) House, H. O.; Kramar, V. *J. Org. Chem.* **1963**, *28*, 3362–3379; (b) House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 1341–1348; (c) House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 2502–2512.
20. Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934–946.
21. (a) Duhamel, P.; Cahard, D.; Poirier, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2509–2511; (b) Cahard, D.; Duhamel, P. *Eur. J. Org. Chem.* **2001**, 1023–1031.
22. Endo, A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 8298–8299.