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Asymmetric Synthesis of α-Keto Esters via Cu(II)-Catalyzed Aerobic Deacylation of Acetoacetate Alkylation Products: An Unusually Simple Synthetic Equivalent to the Glyoxylate Anion Synthon

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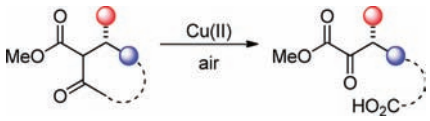
ABSTRACT



A simple and efficient method for the preparation of β-stereogenic α-keto esters is described using a copper(II)-catalyzed aerobic deacylation of substituted acetoacetate esters. The substrates for the title process arise from catalytic, enantioselective conjugate additions and alkylation reactions of acetoacetate esters. The mild conditions do not induce racemization of the incipient enolizable α-keto ester. The reaction is tolerant of esters, certain ketones, ketals, and nitro groups and utilizes inexpensive, readily available materials.

Formal nucleophilic glyoxylation of π-functional groups through the application of glyoxylate anion equivalents in principle defines a direct entry into α-keto esters, compounds of considerable importance in biochemistry[1] and organic synthesis.[2] This unique and versatile functional group provides access to useful building blocks such as α-hydroxy and α-amino esters.[3] Despite positive attributes, the existing reagents and strategies highlighted in Figure 1 are not amenable to widespread adoption of the "glyoxylate anion" tactic in organic synthesis due to case-dependent disadvantages and/or limitations.[4] A compelling case can be made that the full potential of α-keto esters has not been realized due to the absence of a general and convenient synthetic method for their preparation.

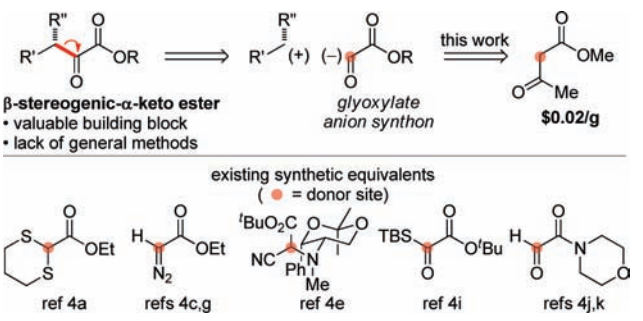


Figure 1. Synthetic equivalents for the glyoxylate anion synthon.

(1) Kiefel, M. J.; von Itzstein, M. *Chem. Rev.* **2002**, *102*, 471.
(2) (a) Cooper, A; Meister, G. A. *Chem. Rev.* **1983**, *83*, 321. (b) Kovacs, L. *Rec. Trav. Chim. Pays-Bas* **1993**, *112*, 471.
(3) (a) Yao, W.; Wang, J. *Org. Lett.* **2003**, *5*, 1527. (b) Kang, Q.; Zhao, Z. A.; You, S. L. *Adv. Synth. Catal.* **2007**, *349*, 1657.
(4) Select examples of α-keto ester synthesis: (a) Eliel, E.; Hartman, A. *J. Org. Chem.* **1972**, *37*, 505. (b) Takahashi, T.; Okano, T.; Harada, T.; Imamura, K.; Yamada, H. *Synlett* **1994**, *38*, 121. (c) Yao, W.; Wang, J. *Org. Lett.* **2003**, *5*, 1527. (d) Enders, D.; Bonten, M. H.; Raabe, G. *Synlett* **2007**, *51*, 885. (e) Enders, D; Bonten, M. H.; Raabe, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2314. (f) Radosevich, A. T.; Chan, V. S.; Shih, H.-W.; Toste, F. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 3755. (g) Trost, B. M.; Malhotra, S.; Fried, B. A. *J. Am. Chem. Soc.* **2009**, *131*, 1674. (h) Nakamura, A.; Lectard, S.; Hashizume, D.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2010**, *132*, 4036. (i) Steward, K. M.; Johnson, J. S. *Org. Lett.* **2010**, *12*, 2864. For catalytic, enantioselective synthesis of α-keto amides via umpolung catalysis with glyoxamides, see: (j) Liu, Q.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066. (k) Liu, Q.; Rovis, T. *Org. Lett.* **2009**, *11*, 2856.

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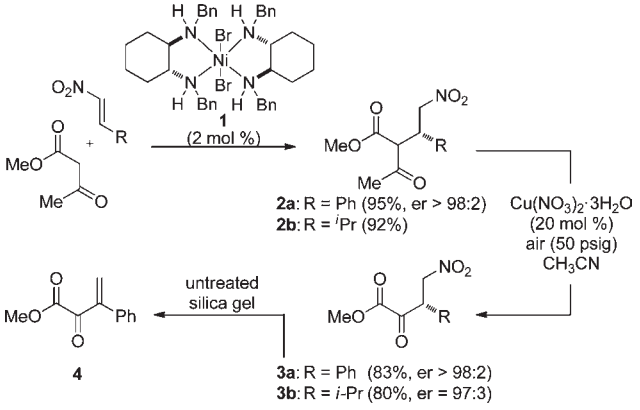
Introduced herein is an aerobic oxidation reaction for the preparation of β-stereogenic-α-keto esters that establishes synthetic equivalence between acetoacetate esters and the glyoxylate anion synthon in the context of asymmetric synthesis. The reaction sequences described give structurally diverse enantiomerically enriched products that are heretofore unknown even in racemic form. Practical attributes include the use of cheap starting materials, an unmodified commercial catalyst, and air as the oxidant for a powerful, yet underutilized aerobic cleavage reaction of β-keto esters.

To bring about the desired synthetic equivalence, a family of enantioselective reactions was needed that would deliver products to serve as the α-keto ester progenitor. The appeal of using β-dicarbonyl nucleophiles with π-electrophiles stems from the range of chiral catalysts that are available to mediate enantioselective enolate-based carbon−carbon bond constructions. These reactions offer significant practical advantages since the pronucleophiles are commercially available and inexpensive. Moreover, activation can be achieved under mild and convenient reaction conditions due to the low pK_a of the carbon acid. Enolates act as d^2-reagents and give normal polarity products with π-electrophiles. The corresponding umpolung products from d^1-reagents are more challenging to achieve[5,6] and the only two examples of direct asymmetric "glyoxylate anion" catalysis employ glyoxamides as the glyoxylate donor.[4j,k] The present work capitalizes on an operationally trivial aerobic cleavage reaction to establish acetoacetate esters as synthetic equivalents to the glyoxylate anion synthon. The tactic parlays the established advantages of enolate-based reactions into asymmetric syntheses of many families of chiral α-keto esters that have not been previously prepared and would not be accessible via a glyoxylate anion catalysis manifold.[4i−k]

In 2000, Clariant disclosed the conversion of substituted acetoacetates and malonates to the corresponding α-keto esters using O_2 and catalytic quantities of a Cu(II) or Fe(III) salt; a ring-cleavage variant had been previously disclosed by Cossy and co-workers.[7] While the products reported were achiral and unfunctionalized, the transformation is striking for its simplicity and use of cheap, unmodified catalysts. To the best of our knowledge, this reaction has not been employed in asymmetric synthesis. In light of the fact that the products are strong carbon acids,[8] it was an open question whether the reaction conditions would be sufficiently mild to avoid base- or acid-catalyzed racemization.

For our preliminary studies we purposely chose a challenging substrate (**2a**[9]) to assess the mildness and functional group compatibility of the reaction. The oxidative deacylation shown in Scheme 1 (**2a** → **3a**) was initially conducted under 1 atm of O_2, and after 48 h 60% conversion to the α-keto ester was observed. Further optimization[10] revealed that pressurized air (50 psig in a standard Fisher-Porter bottle) and 20 mol % of $Cu(NO_3)_2 \cdot 3H_2O$ provided the best results, affording **3a** in 83% yield. The fact that **3a** can readily eliminate HNO_2 to give the β,γ-unsaturated-α-keto ester **4** on untreated silica gel underscores the mildness of these oxidation conditions.[11] Indeed, despite the C−H acidity of the product **3a** and accompanying possibility of racemization, no loss in enantiopurity is observed during the course of the reaction. Conjugate adduct **2b** (R = ^{i}Pr) was not previously described using catalyst **1**, but efficient enantioselective catalysis was observed and aerobic deacylation of the tautomeric and stereoisomeric mixture provided α-keto ester **3b** in good yield without measurable racemization.

Scheme 1. Formal Nucleophilic Glyoxylation of Nitroalkenes



With the goal of diversifying available product classes, attention was directed to finding other cases that might be applicable to aerobic deacylation. Scheme 2 illustrates formal conjugate glyoxylation of α,β-unsaturated ketones. Asymmetric addition of methyl acetoacetate to both 2-cyclopenten-1-one[12] and 2-cyclohexen-1-one[13] using known chiral catalysts (**4** and **5**) followed by site-selective ketalization[14] provided **6a** and **6b**, respectively, with excellent enantiocontrol. Cu(II)-catalyzed aerobic deacylation of β-keto ester **6a** occurred with concomitant ketal

(5) (a) Seebach, D. *Angew. Chem., Int. Ed.* **1979**, *18*, 239. (b) Johnson, J. S. *Curr. Opin. Drug Disc. Dev.* **2007**, *10*, 691.

(6) By the Seebach definition, an a^n- or d^n-synthon is, "respectively, a synthon with an O- or N-heteroatom at C^1 and an acceptor or donor center at C^n." For donor synthons, normal reactivity corresponds to $d^{2,4,6,\cdots}$ (an enolate would correspond to a d^2 synthon), while umpolung reactivity corresponds to $d^{1,3,5,\cdots}$ (an acyl anion is a d^1 synthon).

(7) (a) Cossy, J.; Belotti, V.; Bellosta, V.; Brocca, D. *Tetrahedron Lett.* **1994**, *35*, 6089. (b) Vallejos, J.-C.; Capelle, N.; Arzoumanian, H. U. S. Patent 6,057,474, 2000.

(8) The pK_a (H_2O) of ethyl pyruvate has been estimated to be 16.6: Bell, R. P.; Ridgewell, H. F. F. *Proc. Royal Soc. London. Ser. A, Math Phys. Sci.* **1967**, *298*, 178–183.

(9) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958.

(10) See the Supporting Information for details.

(11) β-Aryl-γ-nitro-α-keto esters like **3a** could not be prepared using an auxiliary-based glyoxylate anion synthetic equivalent because of this elimination. See ref 4e.

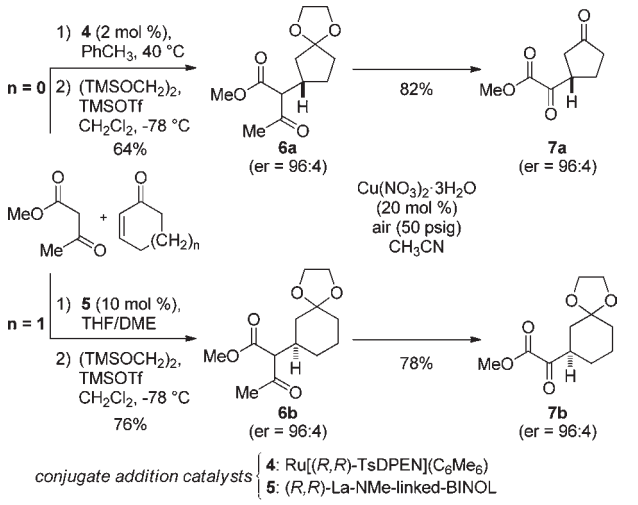
(12) Watanabe, M.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* **2003**, *125*, 7508.

(13) Majima, K.; Takita, R.; Okada, A.; Oshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 15837.

(14) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357. Subjecting these Michael adducts directly to the aerobic deacylation conditions afforded a complex mixture of products.

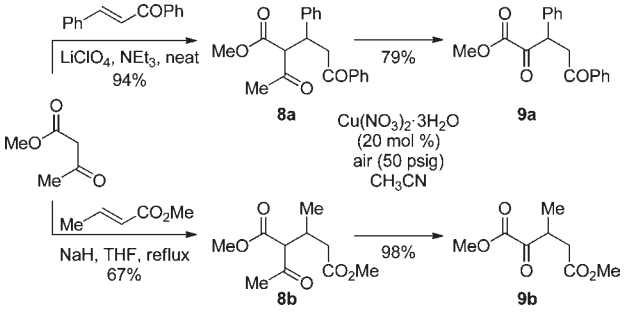
deprotection to provide dione **7a** (82%, er 96:4). Conversely, the ketal remained intact for the cyclohexanone ketal **6b**, yielding **7b** (78%, er 96:4) with all three oxygenated functional groups differentiated.

Scheme 2. Formal Conjugate Glyoxylation of Cyclic Enones



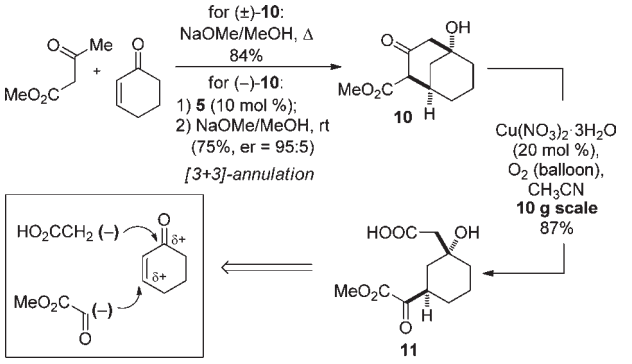
Because α-keto esters are potential substrates for dynamic kinetic resolution,[4i] it is not a prerequisite that the acetoacetate-based bond construction have an associated asymmetric variant. Enantioselective acetoacetate additions to acyclic α,β-unsaturated carbonyls await discovery, but the easily accessible adducts (±)-**8a**[15] and (±)-**8b**[16] provide their derived α-keto esters (±)-**9a** and (±)-**9b** in the presence of Cu(II)/air (Scheme 3). The utility of these racemic products in subsequent stereodynamic processes is under investigation. Conjugate addition of dimethyl malonate to chalcone using a chiral strontium catalyst has been reported,[17] but the use of this catalyst with methyl acetoacetate provided racemic product. The Clariant patent described the aerobic cleavage of simple linear malonates; however, in our hands the oxidative cleavage of the branched and more highly functionalized malonate derivatives to the α-ketoesters has to date been unsuccessful.

Scheme 3. Formal Conjugate Glyoxylation of Acyclic Michael Acceptors



Even more value-added products can be obtained by utilizing the second nucleophilic site on methyl acetoacetate. With an ambident electrophile such as 2-cyclohexen-1-one, methyl acetoacetate undergoes (3 + 3)-annulation[18] providing bicyclo[3.3.1]nonanone **10** (Scheme 4). Oxidative deacylation of (±)-**10** led to a ring-cleavage reaction[7a] that yielded cyclohexanol **11** as a single isomer (87% yield) with all four oxygenated functional groups differentiated. Notably, the product is the synthetic equivalent of two challenging reactions: enone conjugate glyoxylation and diastereoselective ketone acetate aldolization. The reaction was operationally trivial on a 10 g scale, and the product was isolated in pure form without the need for chromatography by precipitation from Et_2O using hexanes as the antisolvent. The acetoacetate/cyclohexenone (3 + 3)-annulation has only been reported in racemic form, but aldolization of the enantioenriched 1,4-adduct[13] under modified conditions (NaOMe, MeOH, rt) led to (−)-**10** in good yield. Aerobic deacylation provided (−)-**11** with no loss of enantiopurity (er 95:5).

Scheme 4. Formal Conjugate Glyoxylation/Ketone Acetate Aldolization Sequence



Dual functionalization was also achieved with the unsaturated β-keto ester derived from the asymmetric allylic alkylation of benzyl acetoacetate with cyclohexen-3-yl acetate (**12**, Scheme 5).[19] Under the standard conditions, both aerobic deacylation and epoxidation occurred, providing **13** with >95:5 diastereoselection. The *syn*-stereochemical relationship strongly implicates participation of the α-keto ester or a precursor thereto in the epoxidation.[20,21] The conversion of **12** to **13** also establishes the feasibility of employing other acetoacetate starting materials (i.e., benzyl ester).

(15) Saidi, M. R.; Azizi, N.; Akbari, E.; Ebrahimi, F. *J. Mol. Catal. Chem-A.* **2008**, *292*, 44.

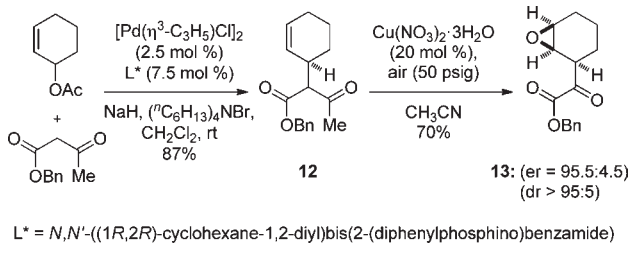
(16) Xian, M.; Alaux, S.; Sagot, E.; Gefflaut, T. *J. Org. Chem.* **2007**, *72*, 7560.

(17) Agostinho, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 2430.

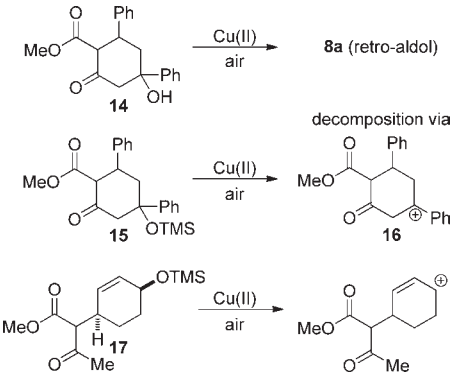
(18) Momose, T; Muraoka, O. *Chem. Pharm. Bull.* **1978**, *26*, 288.

(19) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089. It is interesting to note that the reaction of malonate esters with cyclohexen-3-yl acetate is a standard test for new allylic alkylation catalysts, but the analogous asymmetric reaction with acetoacetate esters was to the best of our knowledge unknown.

Scheme 5. Merged Aerobic Deacylation/Epoxidation



Scheme 6. Current Substrate Limitations



Scheme 6 summarizes initial observations that help define the method's limitations at the current level of development. While investigating the aerobic ring cleavage of substrate **14**, a retro-aldol reaction was found to be operative under the reaction conditions, providing Michael adduct **8a**. The related trimethylsilyl ether **15** decomposed in the presence of Cu(II)/air, perhaps due to the formation of the benzylic carbocation **16**. Decomposition of allylic silyl ether **17** was also observed, presumably through a similar pathway. Addressing these limitations and extending the scope of the aerobic deacylation are current areas of interest.

In summary, a simple protocol for the preparation of β-stereogenic α-keto esters has been established through the aerobic deacylation of substituted acetoacetate derivatives. A heretofore underdeveloped relationship between chiral β-keto esters and α-keto esters has been realized that dramatically simplifies the glyoxylate anion problem. The strategy described herein captures many characteristics that are often described in "ideal" synthetic methods: aerobic deacylation is operationally simple and scalable, employs starting materials that are commercially available and cheap, generates an innocuous byproduct, provides product diversity, and is compatible with a number of useful functional groups.

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Supporting Information Available. Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) (a) Komiya, N.; Naota, T.; Oda, Y.; Murahashi, S. *J. Mol. Catal. Chem-A.* **1997**, *117*, 21. (b) Schröder, K; Join, B.; Amali, A. J; Junge, K; Ribas, X.; Costas, M.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 1425.

(21) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.