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Advanced Synthesis & Catalysis

One-Pot Quinine-Catalyzed Synthesis of α-Chiral γ-Keto Esters: Enantioenriched Precursors of *cis*-α,γ-Substituted-γ-Butyrolactones

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Abstract: A highly enantioselective one-pot synthesis of important building blocks, α-chiral γ-keto esters, has been developed by combining a quinine-catalyzed Michael addition of malononitrile to *trans*-enones followed by magnesium monoperoxyphthalate (MMPP) oxidation. These synthons proved to be useful reagents for a simple access to challenging *cis*-α,γ-disubstituted γ-butyrolactones in good diastereoselectivity and high enantiocontrol.

Keywords: asymmetric synthesis; butyrolactones; Michael addition; organocatalysis; oxidation

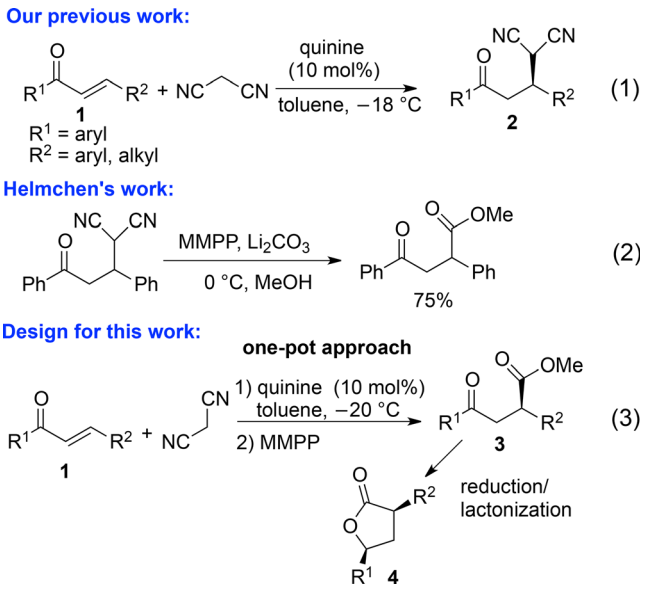
Modern synthetic approaches to produce organic molecules need to take into account the development of environmentally benign reaction conditions on one hand and the reduction of practical operations in order to cut the costs, minimize waste production and save time. Hence, with a view to set up green and convenient procedures, chemists have created useful concepts to follow such as step-economy,[1] atom-economy,[2] and pot-economy.[3]

In the area of asymmetric organocatalyzed reactions, an increasing number of processes follows these guidelines, especially one-pot sequential or multicomponent reactions focused on the preparation of pharmaceuticals and biologically active compounds.[4]

Over the last years we have been interested in the development of new asymmetric organocatalytic methods to prepare acyclic and heterocyclic compounds. According to the principles expressed above, we disclosed simple one-pot domino diastereo- and enantioselective reactions to access different class of compounds such as tetrahydrothiophenes,[5] tetrasubstituted 2-pyrrolines, 3-substituted piperazin-2-ones,[6] and γ-butyrolactones.[7]

Recently, we disclosed an efficient and highly enantioselective Michael addition of malononitrile to *trans*-enones **1** catalyzed by 10 mol% of quinine [Scheme 1, Eq. (1)].[8] Since all reagents and catalyst involved are low cost, commercially or easily available compounds, we were prompted to investigate further the potential of this transformation. Indeed, we envisioned adducts **2** could be useful intermediates for a facile synthesis of challenging acyclic targets such as α-chiral γ-keto esters.

Helmchen and co-workers demonstrated the feasibility of a clean oxidative degradation of racemic 2-(3-oxo-1,3-diphenylpropyl)malononitrile with magnesium monoperoxyphthalate (MMPP) to give methyl 4-oxo-2,4-diphenylbutanoate in good yield [Scheme 1, Eq. (2)].[9] Considering the synthetic importance of α-



Scheme 1. Asymmetric quinine-catalyzed approach to α-chiral γ-keto esters **3** and *cis*-α,γ-disubstituted γ-butyrolactones **4**.

chiral γ-keto esters and the paucity of asymmetric approaches reported to obtain these building blocks,[10] we thought that malononitrile could be used as an acyl anion equivalent to develop an asymmetric one-pot synthesis of α-chiral γ-keto esters **3** by combining a quinine-catalyzed Michael addition of malononitrile to *trans*-enones followed by oxidation with cheap and commercially available MMPP [Scheme 1, Eq. (3)].

Due to their interesting and manifold biological activities,[11] chiral substituted γ-butyrolactones are among the most relevant building blocks for the synthesis of natural products, such as flavours,[12] pheromones,[13] and alkaloids.[14]

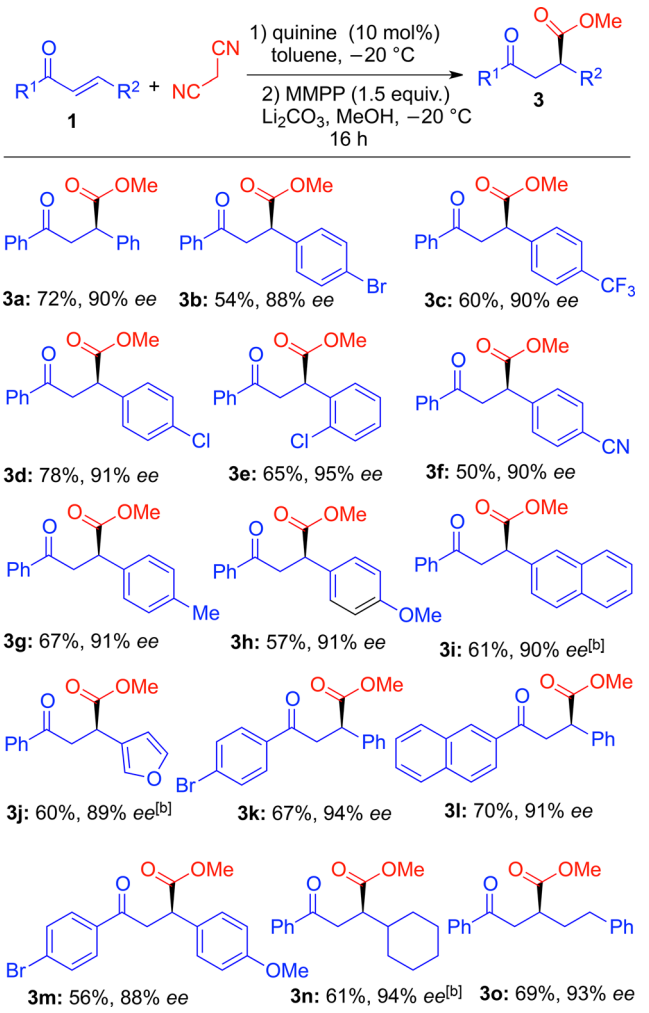
Although several investigations focused on their asymmetric synthesis, only few synthetic approaches have been reported to obtain enantioenriched *cis*-α,γ-tri- and disubstituted γ-butyrolactones, relying on a chiral auxiliary approach[15] or asymmetric metal-based[16] catalysis and organocatalysis.[17] To the best of our knowledge, no general methodology for the enantioselective synthesis of *cis*-α,γ-diaryl-substituted γ-butyrolactones has been reported. Hence, the development of a simple and convenient route to obtain this class of compounds is highly desirable. We anticipated that the $NaBH_4$-mediated reduction of enantiomerically enriched products **3** followed by acid-catalyzed lactonization would afford *cis*-α,γ-diaryl-substituted γ-butyrolactones **4** with good diastereoselectivity and high *ee* value [Scheme 1, Eq. (3)].

We commenced our investigation by reacting a variety of *trans*-enones **1** with 10 mol% of quinine under our previously reported conditions at −20 °C in toluene (Table 1).[8]

At the end of the reaction, toluene was evaporated from the reaction vessel and the crude product was reacted with MMPP under basic conditions in anhydrous MeOH.[9] The reaction was performed at −20 °C, to prevent eventual racemization and potential Baeyer–Villiger side reaction.[18] The feasibility of the one-pot protocol has been successfully demonstrated starting from chalcones substituted with electron-withdrawing or electron-donating groups at both aromatic rings. A heteroaromatic moiety is also tolerated as well as aliphatic groups at the β-position of the starting enone. In all the examples, α-chiral γ-keto esters **3** were isolated in fairly good overall yield and high enantioselectivity. No racemization occurred during the oxidation step as attested by the *ee* values measured for compounds **3**, found to be in line with those obtained for compounds **2**.

The synthetic utility of enantioenriched compounds **3** was further explored with the aim to access *cis*-α,γ-disubstituted butyrolactones *via* a reduction and lactonization sequence. Enantiomerically enriched *trans*-α,γ-disubstituted γ-butyrolactones can be synthesized by diastereoselective α-alkylation of enantioenriched γ-aryl-substituted butyrolactones.[19] As mentioned

Table 1. Scope of the one-pot organocatalytic enantioselective Michael addition/oxidation.[a]



[a] *Conditions*: **1** (0.4 mmol), malononitrile (0.48 mmol), quinine (0.04 mmol) in toluene (4 mL) at −20 °C. For the second step, after solvent evaporation, MeOH (3 mL), Li_2CO_3 (0.6 mmol) and MMPP (0.4 mmol) were added at −20 °C. The product was isolated after flash chromatography; the *ee* was determined *via* chiral HPLC analysis.
[b] Reaction carried out with 20 mol% of quinine.

before, only a few methodologies enable the asymmetric synthesis of *cis*-α,γ-dialkyl-substituted γ-butyrolactones[16] and *cis*-α-alkyl-γ-aryl-substituted γ-butyrolactones,[17] by derivatization of enantiomerically enriched intermediates.

Literature precedents, showed the reduction of compounds **3** or amide derivatives by (*R*)-MeCBS/BH_3[20,10b] or by $(t\text{-BuO})_3AlHLi$[21] to proceed with poor or good diastereoselectivity, respectively. Unexpectedly, Bahr et al. found that $NaBH_4$ in MeOH at room temperature simultaneously reduced both carbonyl groups of 4-aryl-4-oxo esters to yield 1-aryl-1,4-butanediols.[22] A preliminary investigation on the reaction of model racemic compound **3a** with different

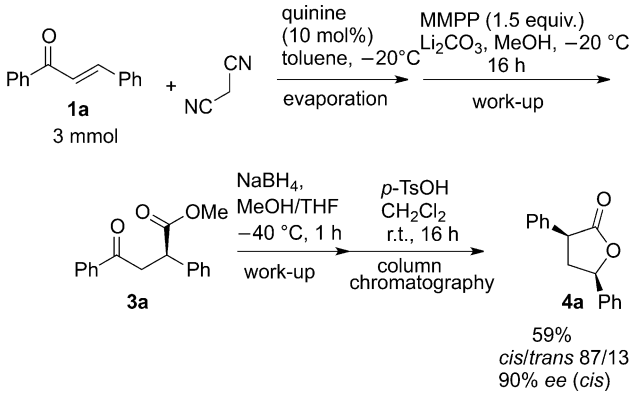
reducing agents followed, after aqueous work-up, by *p*-toluenesulfonic acid-catalyzed lactonization, was carried out.[23] Interestingly, $NaBH_4$ in THF/MeOH at −40 °C proved to be the most effective and convenient reducing system.

Under these conditions, the reduction of the ester group was disfavored and racemic product **4a** was isolated in 82% overall yield and *cis*/*trans* 85/15 ratio.

This protocol, applied on a range of enantioenriched compounds **3**, afforded *cis*-α,γ-diaryl-substituted and *cis*-α-alkyl-γ-aryl-substituted γ-butyrolactones in high yield, good diastereoselectivity and high *ee* (Table 2). The relative and absolute configurations of products **4** were confirmed by comparison with literature data.[17,21,24]

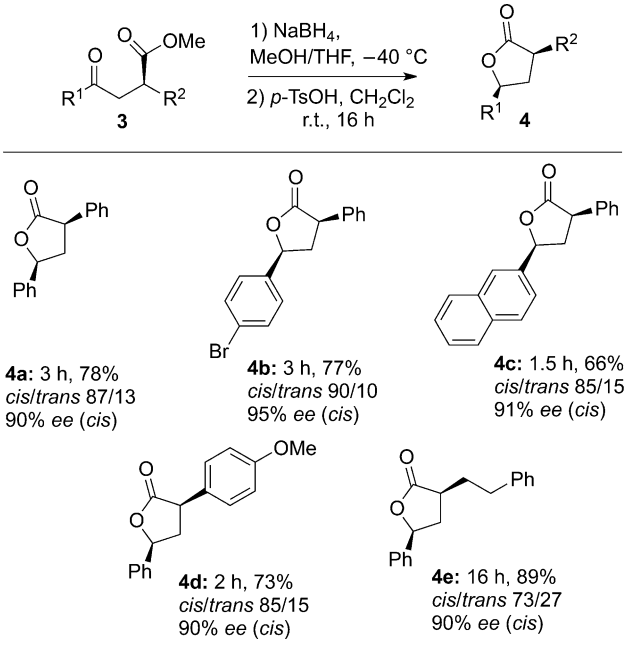
Finally, a scale-up asymmetric synthesis of *cis*-γ-butyrolactone **4a** has been carried out starting from 3 mmol of *trans*-chalcone **1a** (Scheme 2). The combined four-step sequence involving one-pot Michael addition/oxidation followed by reduction and acid-catalyzed lactonization required two aqueous work-up steps and one final column chromatography. The desired *cis*-γ-butyrolactone **4a** was isolated in 51% overall yield and 90% *ee*.

In summary, we developed a simple highly stereoselective one-pot approach to two classes of challenging compounds, that is, α-chiral γ-keto esters and *cis*-α,γ-disubstituted γ-butyrolactones by using readily accessible, inexpensive reagents and quinine as the organocatalyst. The four-step approach represents a first general and efficient asymmetric protocol to prepare *cis*-α,γ-diaryl-substituted γ-butyrolactones. The entire process, which includes only two aqueous work-up and one chromatographic purification step can be performed on a large scale starting from *trans*-enones.



Scheme 2. Scale-up asymmetric synthesis of *cis*-α,γ-diphenyl-substituted butyrolactone **4a**.

Table 2. Reduction/lactonization of enantioenriched **3** to *cis*-α,γ-disubstituted γ-butyrolactones.[a]



[a] *Conditions*: reduction step, **3** (0.2 mmol) $NaBH_4$ (1.2 mmol) in MeOH/THF 1/1 (2 mL), −40 °C. Lactonization step, crude mixture in CH_2Cl_2 (1.2 mL), *p*-TsOH (0.02 mmol), room temperature. The *dr* ratio was determined by ^1H NMR analysis of the crude reaction mixture. Isolated yield of *cis*/*trans*-diastereosiomers; the *ee* was determined *via* chiral HPLC analysis.

Experimental Section

General One-Pot Procedure for the Synthesis of α-Chiral γ-Keto Esters 3

Enone **1** (0.40 mmol) and quinine (13.0 mg, 0.040 mmol) were dissolved in dry toluene (4 mL). Malononitrile (32 mg, 0.48 mmol) was added, and the reaction stirred at −20 °C. After completion, toluene was removed, then anhydrous methanol (2.7 mL) and Li_2CO_3 (44.3 mg, 0.6 mmol) were added. The suspension was cooled to −20 °C and MMPP (80% technical grade 248 mg, 0.4 mmol) was added portionwise. The reaction mixture was stirred at −20 °C overnight. After completion, the reaction was quenched by the addition of water (15 mL) and diluted with ethyl acetate (15 mL). The aqueous layer was extracted with ethyl acetate (2×15 mL) and the combined organic layers were washed with water (2×15 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The reaction mixture was purified by flash chromatography (PE/ethyl acetate 98/2 to 95/5) to afford the products.

General Procedure for the Reduction/Lactonization of γ-Keto Esters 3 to *cis*-α,γ-Disubstituted γ-Butyrolactones 4

γ-Keto ester **3** (0.2 mmol) was dissolved in dry THF/MeOH 1/1 (2 mL) in a dried round-bottomed flask under a nitrogen atmosphere and the solution was cooled at −40 °C. After 10 min, $NaBH_4$ was added in 6 portions (1.2 mmol) waiting 10 min between two subsequent additions. The reaction mix-

ture was stirred at −40 °C until completion. Then, the reaction was quenched with brine (10 mL) and the mixture extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was dissolved in CH_2Cl_2 (1.2 mL) and *p*-TsOH·H_2O (3.8 mg, 0.02 mmol) was added. The reaction mixture was stirred overnight at room temperature. The diastereoisomeric ratio of γ-butyrolactones **4** was determined by ^{1}H NMR analysis of the crude reaction mixture. Purification by flash chromatography (eluting from PE/ethyl acetate 100:1 to 90:10) afforded the *cis*-lactone as major diastereomer (which in all cases was the second eluted compound).

Acknowledgements

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Adv. Synth. Catal. **2016**, *358*, 1 – 5

Sara Meninno, Chiara Volpe, Alessandra Lattanzi*

5