A New Catalytic Enantioselective Approach to Optically Active Lactones by Addition Reactions to α-Dicarbonyl Compounds

Hélène Audrain and Karl Anker Jørgensen*

Center for Metal Catalyzed Reactions
Department of Chemistry, Aarhus University
DK-8000 Aarhus C, Denmark

Received August 21, 2000

Optically active lactones are important molecules in chemistry, biology, and medicine.[1] Since these motifs are widely found in compounds of biological interest, a variety of methods including mainly diastereoselective reactions have been developed for the synthesis of optically active δ-lactones,[2] and these often include multistep reactions and have been performed using more or less complicated strategies. The enantioselective synthesis of such compounds have also been achieved;[3] however, according to our knowledge, no catalytic enantioselective synthetic procedure for the formation of optically active functionalized δ-lactones from simple reagents is available.

This report presents a catalytic enantioselective reaction of α-dicarbonyl compounds **1** with ketene diethylacetal **2** leading to δ-lactone derivatives **3** in good yield and high enantiomeric excess (ee) (eq 1).[4,5] Hydrolysis of **3** produces the functionalized optically active δ-lactones **4** (eq 1). During the course of the reaction, a chiral quaternary carbon center is formed, which is a quite demanding task in organic synthesis.[6]

Reaction of ethyl benzoylformate **1a** with ketene diethylacetal **2** in the presence of chiral Lewis acids afforded a sequential-aldol type of addition of **2** to the keto group of **1a** giving **3a** as the major product and a small amount of the mono-addition product **6a**. Different chiral Lewis acid complexes have been screened for this reaction, and the most promising results were found for the chiral bisoxazoline−copper(II) complexes[7,8] (*S*)-**5a**-CuX_2 and (*R*)-**5b**-CuX_2. Some results for the screening of the reaction are presented in Table 1.

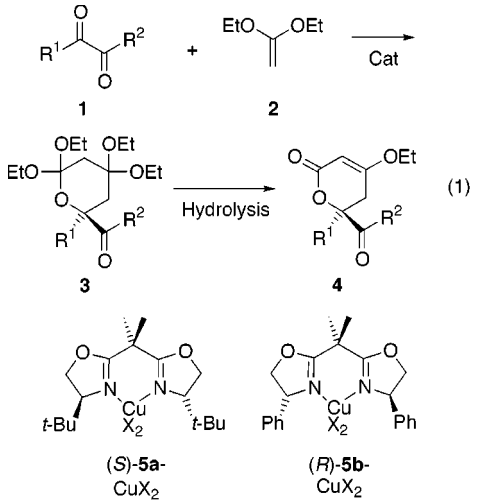
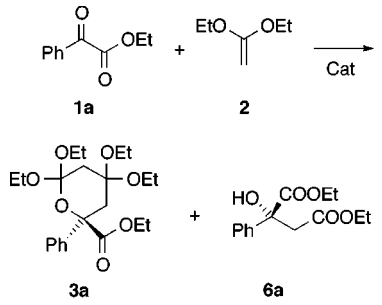


Table 1. Results from the Screening of the Reaction of Ethyl Benzoylformate **1a** with Ketene Diethylacetal **2**



entry	catalyst	loading mol %	solvent	yield **3a**/**6a**[a] %	ee **3a**/**6a**[b] %
1	(*S*)-**5a** X = OTf	20	CH_2Cl_2	<20	n.d.
2	(*S*)-**5a** X = OTf	20	THF	61/30	77/85
3	(*S*)-**5a** X = OTf	20	Et_2O	80/10	90/85
4	(*S*)-**5a** X = OTf	15	Et_2O	80/14	90/99
5	(*S*)-**5a** X = OTf	10	Et_2O	70/20	87/96
6	(*S*)-**5a** X = SbF_6	20	CH_2Cl_2	<20	n.d.
7	(*R*)-**5b** X = OTf	20	Et_2O	79/6	12/-

[a] Isolated yield. [b] ee measured by HPLC using an OD column.

The results in Table 1 shows that **3a** is formed in up to 80% isolated yield and 90% ee by the application of *tert*-butyl-bisoxazoline catalyst (*S*)-**5a**-$Cu(OTf)_2$ (15 mol %) in Et_2O as the solvent, together with 14% of the mono-addition product **6a** with 99% ee (entry 4). The reaction is solvent- and counterion-dependent as in, for example, CH_2Cl_2 as the solvent and SbF_6 as the counterion, very low yield of **3a** is formed (entries 1 and 6). The use of the phenyl-bisoxazoline catalyst (*R*)-**5b**-$Cu(OTf)_2$ gives **3a** in good yield, however, with low ee (entry 7).

The reaction was found to be quite general, and Table 2 shows the results of different α-dicarbonyl compounds **1a**−**i** reacting with **2** in the presence of (*S*)-**5a**-$Cu(OTf)_2$ as the catalyst.

It appears from the results in Table 2 that the α-dicarbonyl compounds derivatives **1a**−**f**, which have an ester functionality, all react with **2** giving the δ-lactone derivatives **3a**−**d**,**f** in good

(1) See e.g.: (a) Dunkel, R.; Mentzel, M.; Hoffmann, H. M. R. *Tetrahedron* **1997**, *53*, 14929 and references therein. (b) Yasui, K.; Tamura, Y.; Nakatani, T.; Kawada, K.; Ohtani, M. *J. Org. Chem.* **1995**, *60*, 7567 and references therein. (c) Fang, X.-P.; Anderson, J. E.; Chang, C.-J.; McLaughlin, J. L.; Fanwick, P. E. *J. Nat. Prod.* **1991**, *54*, 1034.

(2) (a) Schlessinger, R. H.; Gillman, K. W. *Tetrahedron Lett.* **1999**, *40*, 1257. (b) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377. (c) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1869. (d) Dujardin, G.; Rossignol, S.; Brown, E. *Synthesis* **1998**, 763. (e) Honda, T.; Sano, N.; Kanai, K. *Heterocycles* **1995**, *41*, 425.

(3) Examples of enantioselective syntheses. From kinetic resolutions: (a) Harris, J. M.; O'Doherty, G. A. *Tetrahedron Lett.* **2000**, *41*, 183. (b) Maddrell, S. J.; Turner, N. J.; Kerridge, A.; Willets, A. J.; Crosby, J. *Tetrahedron Lett.* **1996**, *37*, 6001. Other enantioselective syntheses: (c) Murakami, N.; Wand, W.; Aoki, M.; Tsutsui, Y.; Sugimoto, M.; Kobayashi, M. *Tetrahedron Lett.* **1998**, *39*, 2349. (d) Corey, E. J.; Guzman-Perez, A.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1997**, *119*, 11769. (e) Kiyooka, S.-I.; Yamaguchi, T.; Maeda, H.; Kira, H.; Hena, M. A.; Horiike, M. *Tetrahedron Lett.* **1997**, *38*, 3553.

(4) The present reaction was found during our development of inverse electron-demand hetero-Diels−Alder reactions: (a) Thorhauge, J.; Johannsen, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2404. (b) Audrain, H.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2000**, *65*, 4487. See also: (c) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4895. (d) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3372. (e) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635.

(5) Use of ketene acetals in the formation of β-lactones: (a) through the use of a tandem Mukaiyama aldol-lactonization: Yang, H. W.; Romo, D. *J. Org. Chem.* **1998**, *63*, 1344. (b) Through the use of [2 + 2] addition: Mattay, J.; Buchkremer, K. *Heterocycles* **1988**, *27*, 2153. (c) Mattay, J.; Gersdof, J.; Buchkremer, K. *Chem. Ber.* **1987**, *120*, 307. (d) Araki, Y.; Nagasawa, J.-I., Ishido, Y. *J. Chem. Soc., Perkin Trans. 1* **1981**, 12.

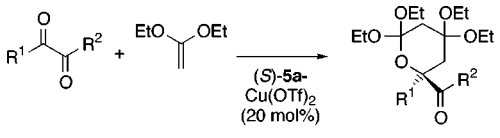
(6) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 389.

(7) For recent reviews dealing with the use of chiral bisoxazoline-Lewis acids as catalysts, see: (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (b) Jørgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605. (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

(8) For the use of C_2-symmetric BOX complexes to Mukaiyama-aldol reactions, see e.g.: Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669 and references therein; Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686 and references therein.

10.1021/ja003097y CCC: $19.00
Published on Web 11/03/2000

Table 2. Reaction of the α-dicarbonyl Compounds **1a**−**i** with Ketene Diethylacetal **2** Catalyzed by (*S*)-**5a**-Cu(OTf)$_2$ with the Formation of the *δ*-Lactone Derivatives **3a**−**i**



1: **a**: R^1 = Ph, R^2 = OEt; **b**: R^1 = Me, R^2 = OMe; **c**: R^1 = Et, R^2 = OMe; **d**: R^1 = *i*-Pr, R^2 = OEt; **e**: R^1 = $BrCH_2$, R^2 = OEt; **f**: R^1 = *trans*-PhCH=CH, R^2 = OMe; **g**: R^1 = Me, R^2 = Me; **h**: R^1 = Me, R^2 = Et; **i**: R^1 = Me, R^2 = Ph

2

3: **a**: R^1 = Ph, R^2 = OEt; **b**: R^1 = Me, R^2 = OMe; **c**: R^1 = Et, R^2 = OMe; **d**: R^1 = *i*-Pr, R^2 = OEt; **e**: R^1 = $BrCH_2$, R^2 = OEt; **f**: R^1 = *trans*-PhCH=CH, R^2 = OMe; **g**: R^1 = Me, R^2 = Me; **h**: R^1 = Me, R^2 = Et; **i**: R^1 = Me, R^2 = Ph

entry	α-dicarbonyl compound	reac. temp. °C	yield[a] %	ee %
1	**1a**	−78	**3a** − 80	93[b]
2	**1b**	−78	**3b** − 74	83[c]
3	**1c**	−15	**3c** − 70	77[c]
4	**1d**	−15	**3d** − 58	80[c]
5	**1e**	−15	**3e** − 55	53[c]
6	**1f**	−78	**3f** − 80	85[b]
7	**1g**	−15	**3g** − 71	95[d]
8	**1h**	−15	**3h** − 70	90[d]
9	**1i**	−15	**3i** − 58	90[b]

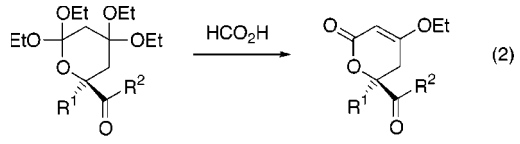
[a] Isolated yield. [b] ee determined by HPLC using an OD or AD column. [c] ee determined after hydrolysis of **3** by HPLC using an OD or AD column. [d] ee determined by GC−MS using a Chromopack Chiralsil-Dex CB column.

to high isolated yields and high enantioselectivity as 77−93% ee's are obtained (entries 1−4, 6), while **3e** is formed in moderate yield and 53% ee (entry 5). The byproducts in these reactions are the corresponding mono-addition products which are isolated in ∼10% yield. It is notable that the reactions proceed with both good yields and high ee's with such different R^1-substituents as phenyl, methyl, ethyl, *i*-propyl, bromo-methyl, and (*E*)-styryl. The catalytic enantioselective reaction for the formation of *δ*-lactone derivatives can be extended to symmetrical and unsymmetrical α-diketones without loss of selectivity. 2,3-Butanedione **1g** reacts with **2** to give **3g** in 71% yield and 95% ee (entry 7). The (*S*)-**5a**-Cu(OTf)$_2$ catalyst can distinguish between a methyl ketone and ethyl ketone as shown by the reaction of the unsymmetrical 2,3-pentanedione **1h** which reacts with **2** by addition to the methyl ketone exclusively, giving **3h** in 70% yield and 90% ee (entry 8). The high regioselectivity of the reaction is further demonstrated by the reaction of an α-diketone substituted with a methyl and phenyl substituent. For this substrate (**1i**) the methyl ketone reacts exclusively, and 58% of **3i** is isolated having 90% ee (entry 9).

The optically active *δ*-lactone acetals (**3a**−**i**) obtained from reaction of the α-dicarbonyl compounds with **2** can be hydrolyzed to highly functionalized *δ*-lactones. Different acidic conditions have been tried for the hydrolysis of the ketal groups, and the results obtained for **1b**−**e** using HCO_2H in a mixture of pentane and CH_2Cl_2 are presented in eq 2. The *δ*-lactones **4** obtained by hydrolysis contain attractive functional groups/building blocks which can be used for further organic transformations.

The formation of the functionalized *δ*-lactone acetals **3** proceeds as a sequential-aldol reaction as outlined in Scheme 1 for ethyl benzoylformate **1a**. The determination of the absolute configuration of **3a** is based on the known absolute configuration of **6a** (Scheme 1).[9] On this basis, it is proposed that **1a** coordinates to (*S*)-**5a**-Cu(II) in a bidentate fashion leading to a square-planar complex[10] to which the ketene diethylacetal **2** adds to the *si*-face

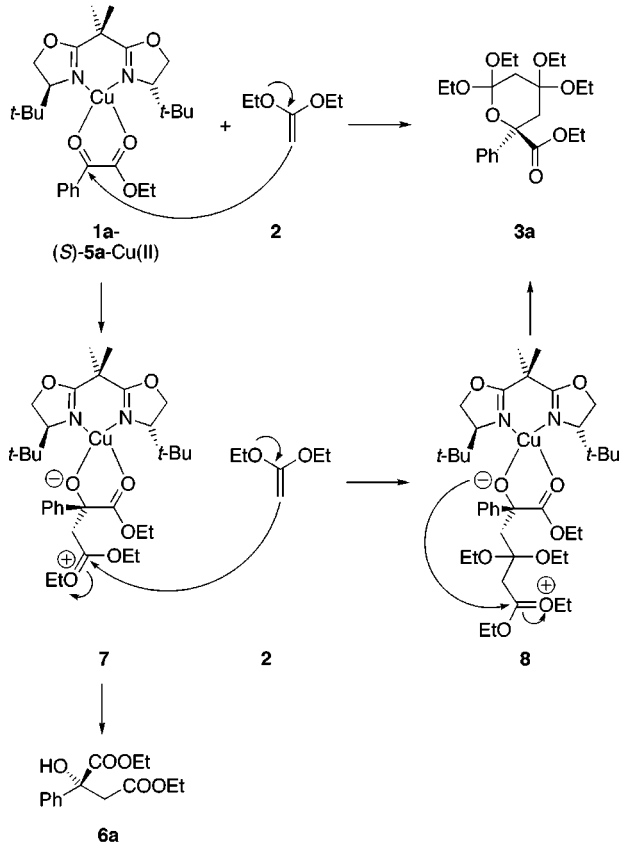
(9) Moorlag, H.; Kellog, R. *Tetrahedron: Asymmetry* **1991**, *2*, 705.
(10) See e.g. refs 7b, c for a discussion of the structure of the intermediate.



(2)

of the carbonyl functionality. This leads to **7** from which **6a**, the byproduct of the reaction, is formed. It is suggested that **2** adds in the second reaction as outlined in Scheme 1, giving **8** from which the *δ*-lactone acetals **3** are formed. We cannot distinguish if the last part of the reaction is an off- or on-metal process.

Scheme 1



In summary, the catalytic enantioselective synthesis of functionalized optically active *δ*-lactones by a new reaction of α-keto esters and symmetrical and unsymmetrical α-diketones with ketene diethylacetal is described. The reaction proceeds in good yield and up to 95% ee for the functionalized *δ*-lactone acetals which are hydrolyzed by HCO_2H to highly functionalized optically active *δ*-lactones.

Acknowledgment. We are indebted to The Danish National Research Foundation for financial support.

Supporting Information Available: Complete experimental procedure and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

JA003097Y