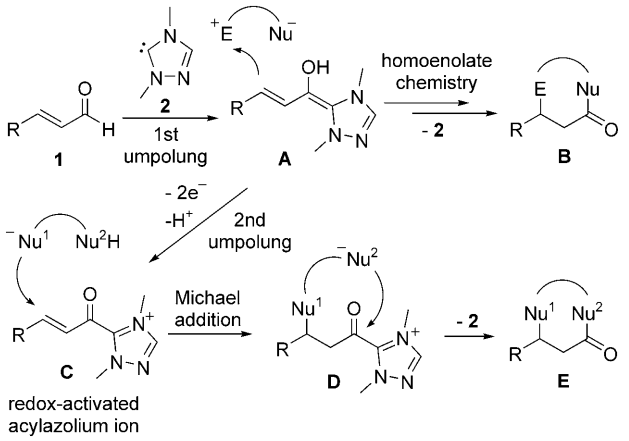
Organocatalysis

DOI: 10.1002/anie.201004593

NHC-Catalyzed Michael Addition to α,β-Unsaturated Aldehydes by Redox Activation**

*Suman De Sarkar and Armido Studer**

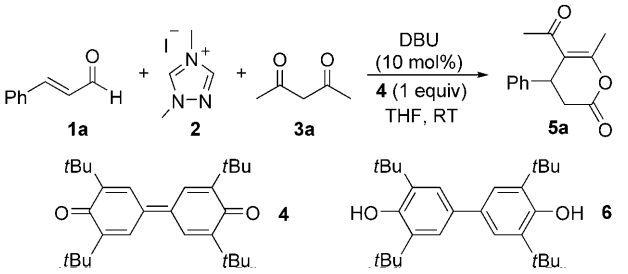
The formation of C–C bonds undoubtedly belongs to the most important transformations in organic chemistry, and Michael reactions are important examples thereof.[1] Two strategies have mainly been followed for the activation of Michael acceptors to conduct conjugate addition reactions: a) activation by using Lewis[2] or Brønsted[3] acids and b) activation by iminium ion generation.[4] It has been shown independently by Bode and Glorius[5] that α,β-unsaturated aldehydes **1** react with N-heterocyclic carbenes (NHCs) **2** to umpoled[6] intermediates of type **A**, which can then react as homoenolates at the β position with various electrophiles to give product **B** (Scheme 1).[7]



Scheme 1. Redox activation of α,β-unsaturated aldehydes and subsequent 1,4-addition.

We recently showed that Breslow intermediates **A** can be readily oxidized with mild organic oxidants to acylazolium ions of type **C**, which undergo efficient O acylation with various O nucleophiles to give the corresponding esters.[8–10] Based on these results we decided to use oxidatively generated intermediates **C** as Michael acceptors to conduct 1,4-addition reactions using soft C nucleophiles. There is precedence in biosynthesis for such processes, and very recently Lupton reported NHC-catalyzed 1,4-addition using activated α,β-unsaturated acid derivatives via intermediates of type **C**.[11–13] Starting with an α,β-unsaturated aldehyde our planned process would comprise two consecutive umpolung reactions at the β position of the α,β-unsaturated aldehyde by a redox-type activation. To liberate the NHC catalyst, the C nucleophile should bear an additional nucleophilic site (Nu^2) such that subsequent 1,2-addition to the acylazolium ion **D** releases the NHC catalyst. Herein we present initial results on this concept.

We first studied reaction of cinnamaldehyde (**1a**) with acetyl acetone (**3a**) by using triazolium salt **2** as a carbene precursor (10 mol%) and diazabicyclo[5.4.0]undecene (DBU, 10 mol%) in THF at room temperature. As an organic oxidant, the readily available quinone **4** (1 equiv)[14] was used. To our delight, the Michael addition/cyclization product **5a** was formed in 91% yield within 2 h along with bisphenol **6**, which can be readily transformed to **4** (Scheme 2, Table 1, entry 1). For optimization, the reaction was repeated under different conditions. The catalyst loading was reduced to 1 mol%, and the amount of **3a** was lowered to 1.5 equivalents without affecting the yield (Table 1, entries 2–4, 7). However,



Scheme 2. Reaction of cinnamaldehyde with acetyl acetone under oxidative NHC catalysis.

Table 1: Reaction of **1a** with **3a** under different conditions.

Entry	Cat. loading [mol%]	Acetyl acetone [equiv]	*t* [h]	Yield [%][a]
1	10	3.0	2.0	91
2	5	3.0	2.0	89
3	2	3.0	2.5	87
4	2	1.5	2.5	91
5[b]	2	1.5	6.0	86
6	2	1.1	2.5	78
7	1	1.5	6.0	89

[a] Yield of isolated product. [b] With 3 mol% DBU.

[*] S. De Sarkar, Prof. Dr. A. Studer
Organisch-Chemisches Institut, Westfälische Wilhelms-Universität
Corrensstrasse 40, 48149 Münster (Germany)
Fax: (+49) 281-83-36523
E-mail: studer@uni-muenster.de

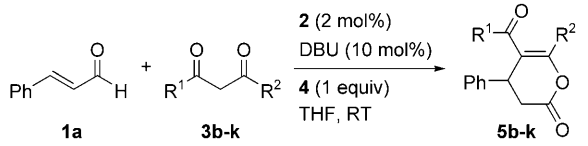
[**] We thank the DFG for supporting our work within the priority program "Organocatalysis" (SPP 1179). NHC = N-heterocyclic carbene.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201004593.

when a catalyst loading of 1 mol% was employed, the reaction time had to be increased to 6 h (Table 1, entry 7). The reaction was slowed by decreasing the amount of DBU (entry 5) and reducing the amount of acetyl acetone to 1.1 equiv also led to a lower yield (Table 1, entry 6). Therefore, most of the following experiments were conducted with 2 mol% of the catalyst and 1.5 equiv of the nucleophile.

To study the scope of the redox-activated Michael addition, we tested various 1,3-dicarbonyl compounds in the reaction with cinnamaldehyde (Table 2).[15] Symmetrical 1,3-

Table 2: Variation of the nucleophile.



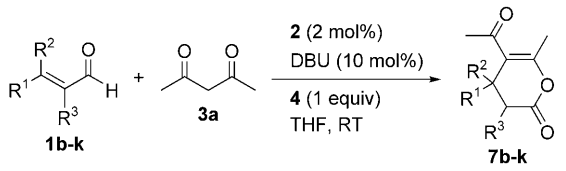
R^1	R^2	Product	*t* [h]	Yield [%][a]
Et	Et	**5b**	8.0	89
Ph	Ph	**5c**	4.0	82
Ph	Me	**5d**	2.5	86[b,c]
OEt	Me	**5e**	2.5	80
O*i*Pr	Me	**5f**	2.5	74
OMe	Et	**5g**	2.5	81
OMe	$CH_2CH_2CH{=}CH_2$	**5h**	2.5	76
OEt	Ph	**5i**	4.0	81
OMe	4-$MeOC_6H_4$	**5j**	8.0	76
N-morpholinyl[d]	Me	**5k**	12.0	51

[a] Yield of isolated product. [b] Combined yield of both regioisomers. [c] Regioisomer ratio 8:1. [d] With 5 mol% catalyst and 1.1 equiv DBU.

diketones bearing aliphatic and aromatic substituents afforded the corresponding products **5b** and **5c** in good yields. With these bulkier diketones the reaction was slower. When the unsymmetrical 1,3-diketone **3d** was used as a nucleophile, both product regioisomers were formed. However, good regioselectivity was achieved (ratio 8:1). Probably for steric reasons, the keto function next to the less bulky methyl substituent preferably acted as the nucleophile in the cyclization reaction to give **5d**. We found that β-keto esters are also efficient nucleophiles for NHC-catalyzed oxidative 1,4-additions (→**5e–j**, 74–81%). β-Alkyl β-keto esters reacted significantly faster than β-aryl β-keto esters. The reaction with β-keto amide **3k** was slower and more catalyst (5 mol%) and a stoichiometric amount of base were required (→**5k**, 51%).

We next examined the NHC-catalyzed Michael addition of acetyl acetone **3a** with various enals **1b–k** (Table 3). Electron-rich as well as electron-poor *para*-substituted cinnamaldehyde derivatives provided the corresponding dihydropyranones in high yields (→**7b-d**, 82–89%). *ortho*-Nitro cinnamaldehyde underwent smooth redox-mediated addition/cyclization with acetyl acetone (→**7e**, 86%) and a heteroaryl-substituted enal also worked well (→**7f**, 75%). The reaction with crotonal was efficient (→**7g**). With the sterically more hindered isopropyl enal **1h**, dihydropyranone **7h** was isolated in excellent yield (92%). Regioselective addition of **3a** at the β carbon was achieved with dienal **1i** to

Table 3: Variation of the enal.

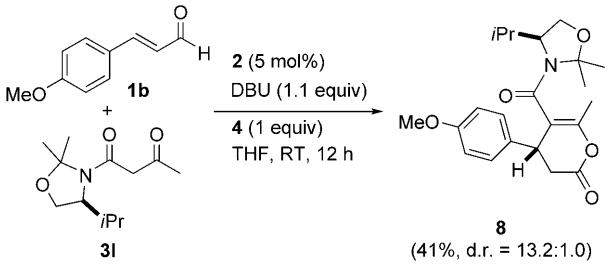


R^1	R^2	R^3	Product	*t* [h]	Yield [%][a]
4-$MeOC_6H_4$	H	H	**7b**	1.5	89
4-$Me_2NC_6H_4$	H	H	**7c**	4.0	85
4-$MeOCOC_6H_4$	H	H	**7d**	1.5	82
2-$NO_2C_6H_4$	H	H	**7e**	1.5	86
2-thienyl	H	H	**7f**	1.5	75
Me	H	H	**7g**	2.5	81
*i*Pr	H	H	**7h**	2.5	92
$CH{=}CHCH_3$	H	H	**7i**	2.5	91
Ph[b]	H	Me	**7j**	48.0	34[c,d]
Me[b]	Me	H	**7k**	36.0	73

[a] Yield of isolated product. [b] With 10 mol% catalyst and 15 mol% DBU. [c] Combined yield of both diastereoisomers. [d] Diastereoisomer ratio 1.5:1.

give **7i** (91%). The α-substituted α,β-unsaturated aldehyde **1j** afforded a lower yield even when a higher catalyst loading was used (→**7j**, 34%). In this reaction both diastereoisomers were formed (d.r. 1.5:1.0).[16] Importantly, the reaction of the β-disubstituted enal **1k** provided dihydropyranone **7k** in 73% yield, showing that our novel method can be used to build up quaternary carbon centers. Note that a higher catalyst loading and a longer reaction time were necessary in that case.

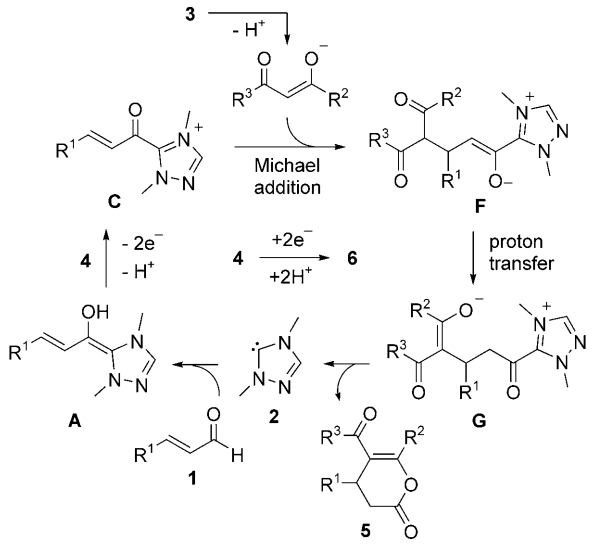
Importantly, we also found that a high stereoselectivity can be achieved using the chiral β-ketoamide **3l** as the nucleophile in the reaction with *para*-methoxy cinnamaldehyde **1b** (Scheme 3).[17]



Scheme 3. Diastereoselective Michael addition using a chiral β-keto amide.

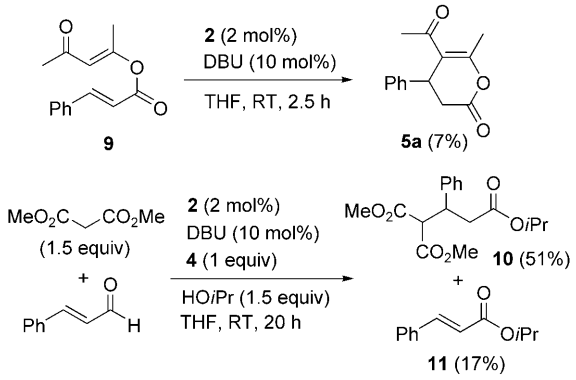
The suggested catalytic cycle is depicted in Scheme 4. The reaction between enal **1** and carbene **2** generates the electron-rich enaminol **A**. Two-electron oxidation and deprotonation of **A** with oxidant **4** provide the redox-activated Michael acceptor **C**.[8] Conjugate addition of the likely deprotonated 1,3-dicarbonyl compound affords **F**. Proton transfer (→**G**) and cyclization eventually lead to dihydropyranone **5** with liberation of carbene **2**.

To exclude other possible mechanisms we performed control experiments. The reaction might also proceed by kinetic O acylation of the enolate with **C** to form enol esters



Scheme 4. The proposed catalytic cycle.

of type **9** (Scheme 5). Subsequent NHC-mediated fragmentation would regenerate acylazolium ion **C** and the enolate,[12] which could then undergo 1,4-addition to **F** (thermodynamic addition product). We currently exclude kinetic O acylation, since the test reaction of preformed **9** under optimized reaction conditions afforded **5a** in only 7% yield; the reaction



Scheme 5. Control experiments.

starting with cinnamaldehyde gave 91% yield. Thus, acylated enolate **9** does not seem to be a kinetically competent intermediate. Furthermore, we showed that dimethyl malonate reacted under optimized conditions in the presence of isopropanol (1.5 equiv) within 20 h in a three-component reaction to give Michael product **10** (51%) along with ester **11** which arises from direct O acylation of isopropanol. Importantly, repeating this experiment in the absence of isopropanol did not lead to any product, showing that **10** was not formed through ring opening of the corresponding dihydropyranone derivative with isopropanol.[18] Reaction of **3a** with cinnamaldehyde in the absence of oxidant **4** under otherwise identical conditions did not occur. This clearly shows that the redox activation is necessary for conjugate addition.

In conclusion, we have shown that enals react with various 1,3-dicarbonyl compounds as redox-activated Michael acceptors under oxidative NHC catalysis to provide dihydropyranones. As the oxidant the readily available quinone **4** was used. Most of the substrates used are commercially available and only a low loading of a cheap carbene catalyst was required. The reactions were conducted under mild conditions and were easy to run. With a chiral β-keto amide, the product was formed with high diastereoselectivity.

Received: July 26, 2010
Published online: October 21, 2010

Keywords: carbenes · Michael addition · redox activation · stereoselectivity · umpolung

[1] Reviews on Michael addition: a) B. E. Rossiter, N. M. Swingle, *Chem. Rev.* **1992**, *92*, 771; b) J. Leonard, E. Diez-Barra, S. Merino, *Eur. J. Org. Chem.* **1998**, 2051; c) M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033; d) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171; e) S. C. Jha, N. N. Joshi, *ARKIVOC* **2002**, *VII*, 167; f) J. L. Vicario, D. Badia, L. Carrillo, *Synthesis* **2007**, 2065.

[2] a) J. Christoffers, *Eur. J. Org. Chem.* **1998**, 1259; b) S. Pelzer, T. Kauf, C. van Wüllen, J. Christoffers, *J. Organomet. Chem.* **2003**, *684*, 308; c) J. Comelles, M. Moreno-Manas, E. Pérez, A. Roglans, R. M. Sebastian, A. Vallribera, *J. Org. Chem.* **2004**, *69*, 6834; d) U. Kazmaier, *Angew. Chem.* **2009**, *121*, 5902; *Angew. Chem. Int. Ed.* **2009**, *48*, 5790.

[3] a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289; b) P. M. Pihko, *Angew. Chem.* **2004**, *116*, 2110; *Angew. Chem. Int. Ed.* **2004**, *43*, 2062; c) M. Rueping, C. Azap, *Angew. Chem.* **2006**, *118*, 7996; *Angew. Chem. Int. Ed.* **2006**, *45*, 7832; d) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999; e) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; f) J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416; g) W. J. Nodes, D. R. Nutt, A. M. Chippindale, A. J. A. Cobb, *J. Am. Chem. Soc.* **2009**, *131*, 16016.

[4] For leading references on secondary-amine-catalyzed conjugate addition to α,β-unsaturated aldehydes: a) J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172; b) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 7894; c) S. Brandau, A. Landa, J. Franzén, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2006**, *118*, 4411; *Angew. Chem. Int. Ed.* **2006**, *45*, 4305; d) A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen, *Chem. Commun.* **2006**, 4928; e) Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 9328; f) A. Carlone, S. Cabrera, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 1119; *Angew. Chem. Int. Ed.* **2007**, *46*, 1101; g) M. Rueping, E. Sugiono, E. Merino, *Chem. Eur. J.* **2008**, *14*, 6329; h) M. Rueping, A. Kuenkel, F. Tato, J. W. Bats, *Angew. Chem.* **2009**, *121*, 3754; *Angew. Chem. Int. Ed.* **2009**, *48*, 3699.

[5] a) C. Burstein, F. Glorius, *Angew. Chem.* **2004**, *116*, 6331; *Angew. Chem. Int. Ed.* **2004**, *43*, 6205; b) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370. Other selected papers: c) V. Nair, S. Vellalath, M. Poonoth, E. Suresh, *J. Am. Chem. Soc.* **2006**, *128*, 8736; d) E. M. Phillips, T. E. Reynolds, K. A. Scheidt, *J. Am. Chem. Soc.* **2008**, *130*, 2416; e) A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2008**, *130*, 2740.

[6] a) D. Seebach, *Angew. Chem.* **1979**, *91*, 259; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239; b) D. Seebach, R. Henning, J. Gonnermann, *Chem. Ber.* **1979**, *112*, 234. For a recent report on the characterization and isolation of a Breslow intermediate: c) A. Berkessel, S. Elfert, K. Etzenbach-Effers, J. H. Teles,

Angew. Chem. **2010**, *122*, 7275; *Angew. Chem. Int. Ed.* **2010**, *49*, 7120.

[7] Recent reviews on NHC-catalyzed transformations: a) K. Zeitler, *Angew. Chem.* **2005**, *117*, 7674; *Angew. Chem. Int. Ed.* **2005**, *44*, 7506; b) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; c) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 3046; *Angew. Chem. Int. Ed.* **2007**, *46*, 2988; d) V. Nair, S. Vellalath, B. P. Babu, *Chem. Soc. Rev.* **2008**, *37*, 2691.

[8] a) J. Guin, S. De Sarkar, S. Grimme, A. Studer, *Angew. Chem.* **2008**, *120*, 8855; *Angew. Chem. Int. Ed.* **2008**, *47*, 8727; b) S. De Sarkar, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2010**, *132*, 1190; c) S. De Sarkar, A. Studer, *Org. Lett.* **2010**, *12*, 1992.

[9] Selected examples of NHC-catalyzed esterifications using internal redox reactions: a) G. A. Grasa, T. Güveli, R. Singh, S. P. Nolan, *J. Org. Chem.* **2003**, *68*, 2812; b) K. Y.-K. Chow, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 8126; c) N. T. Reynolds, J. R. deAlaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 9518; d) S. S. Sohn, J. W. Bode, *Angew. Chem.* **2006**, *118*, 6167; *Angew. Chem. Int. Ed.* **2006**, *45*, 6021; e) E. M. Phillips, M. Wadamoto, A. Chan, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 3167; *Angew. Chem. Int. Ed.* **2007**, *46*, 3107; f) K. Zeitler, C. A. Rose, *J. Org. Chem.* **2009**, *74*, 1759; g) Y. Yamaki, A. Shigenaga, J. Li, Y. Shimohigashi, A. Otaka, *J. Org. Chem.* **2009**, *74*, 3278.

[10] NHC-catalyzed oxidative esterification using MnO_2 as the oxidant: a) B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, *Org. Lett.* **2007**, *9*, 371; b) B. E. Maki, K. A. Scheidt, *Org. Lett.* **2008**, *10*, 4331. Using organic oxidants: c) S. W. Tam, L. Jimenez, F. Diederich, *J. Am. Chem. Soc.* **1992**, *114*, 1503; d) A. Miyashita, Y. Suzuki, I. Nagasaki, C. Ishiguro, K.-I. Iwamoto, T. Higashino, *Chem. Pharm. Bull.* **1997**, *45*, 1254; e) C. Noonan, L. Baragwanath, S. J. Connon, *Tetrahedron Lett.* **2008**, *49*, 4003.

[11] S. J. Ryan, L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2009**, *131*, 14176. In contrast to the acyl fluorides and enol esters used by Lupton, our approach starts with readily available α,β-unsaturated aldehydes. Far lower catalyst loadings and milder reactions conditions are used for our process.

[12] 1,4-Addition to α,β-unsaturated acylazolium ions in biosynthesis: a) N. Khaleeli, R. Li, C. A. Townsend, *J. Am. Chem. Soc.* **1999**, *121*, 9223; b) M. Merski, C. A Townsend, *J. Am. Chem. Soc.* **2007**, *129*, 15750.

[13] During the preparation of this manuscript, Bode et al. reported on NHC-catalyzed Claisen-type rearrangement via intermediately formed α,β-unsaturated acylazolium ions: J. Kaeobamrung, J. Mahatthananchai, P. Zheng, J. W. Bode, *J. Am. Chem. Soc.* **2010**, *132*, 8810.

[14] M. S. Kharasch, B. S. Joshi, *J. Org. Chem.* **1957**, *22*, 1439. Compound **4** is readily prepared by treatment of *o,o'-di-tert*-butylphenol (Aldrich 29.1 US$ per 500 g) with O_2.

[15] Synthesis of dihydropyranones by NHC-catalyzed hetero-Diels–Alder reaction: a) M. He, G. J. Uc, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 15088; b) M. He, B. J. Beahm, J. W. Bode, *Org. Lett.* **2008**, *10*, 3817. For other methods see: c) D. A. Evans, R. J. Thomson, F. Franco, *J. Am. Chem. Soc.* **2005**, *127*, 10816; d) T. Tozawa, H. Nagao, Y. Yamane, T. Mukaiyama, *Chem. Asian J.* **2007**, *2*, 123; e) M. A. Calter, J. Wang, *Org. Lett.* **2009**, *11*, 2205.

[16] Relative configurations of the isomers were not assigned.

[17] The absolute configuration at the newly formed stereogenic center was assigned by derivatizing **8** and comparing this derivative with a similar compound, see the Supporting Information.

[18] This experiment shows that at least with dimethyl malonate as a nucleophile, a Claisen rearrangement as recently described by Bode et al. (see Ref. [13]) is not operative in our system.

