Organocatalysis

DOI: 10.1002/anie.201103555

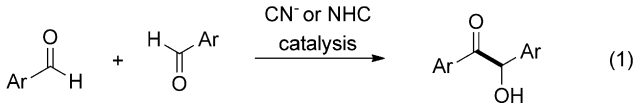
N-Heterocyclic Carbene Catalyzed Umpolung of Michael Acceptors for Intermolecular Reactions**

*Akkattu T. Biju, Mohan Padmanaban, Nathalie E. Wurz, and Frank Glorius**

Dedicated to Dr. Vijay Nair on the occasion of his 70th birthday

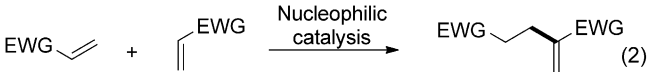
The benzoin reaction, the coupling of two aromatic aldehydes [Eq. (1)], is one of the most important transformations catalyzed by N-heterocyclic carbenes (NHCs).[1] It proceeds through a unique umpolung strategy, which is widely used to provide unconventional access to various target molecules.[2] Intriguingly, however, in most cases this strategy is limited to aldehydes,[3] and the umpolung of other electrophiles in this realm of NHC organocatalysis is very rare. In 2006, Fu and co-workers developed an elegant NHC-catalyzed umpolung of Michael acceptors and applied this strategy in an intramolecular β-alkylation of Michael acceptors, the equivalent of a Heck reaction.[4] Although the coupling of an activated olefin/latent enolate with a second Michael acceptor to create a new C–C bond at the α position of the former is well documented [Rauhut–Currier reaction, Eq. (2); EWG = electron-withdrawing group],[5] the analogous transformation for the β functionalization of Michael acceptors is less developed,[6] and an organocatalytic approach that utilizes an umpolung strategy remains to be explored.[7] Herein, we report the NHC-catalyzed umpolung of Michael acceptors, followed by an intermolecular addition to activated olefins that leads to the β-selective formation of linear dimers, which are potential precursors for the synthesis of fine chemicals and polymer intermediates [Eq. (3)].[8]

Benzoin condensation: union of two aldehydes



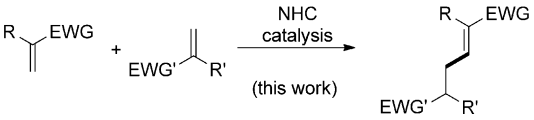
(1)

Dimerization of activated olefins: Rauhut-Currier reaction



(2)

Umpolung of Michael acceptors: coupling of two activated olefins



(3)

In the context of our sustained interest in developing organocatalytic transformations using NHCs,[3b–d,9] we recently initiated a research program on the NHC-catalyzed umpolung of activated alkenes followed by intermolecular addition reactions. The underlying principle behind this program is to extend NHC catalysis beyond the umpolung of aldehydes. Our current study commenced with the NHC-catalyzed umpolung of the β position of *n*-butyl methacrylate (**1a**) to give dibutyl 2,5-dimethylhex-2-enedioate (**2a**; Table 1). After extensive investigation, we found that treatment of **1a** with the carbene generated by deprotonation of the 1,3,4-triphenyltriazolium salt **3**[10] with DBU resulted in the smooth formation of hex-2-enedioate **2a** in 71% yield and an excellent *E*/*Z* ratio of 97:3 (based on ^{1}H NMR spectroscopy; Table 1, entry 1). Remarkably, other common NHCs derived from the precursors **4**–**7** are ineffective (Table 1, entries 2–5). Control experiments showed that no umpolung reactivity is observed if the carbene precursor **3** or DBU is omitted (Table 1, entries 6 and 7). Additionally, a variety of phosphines and amines are essentially inactive as catalysts (Table 1, entries 8 and 9), thus emphasizing the essential role of NHCs in the umpolung of Michael acceptors.[11] Bases such as KO*t*Bu, K_2CO_3, and K_3PO_4 furnished the desired product in reduced yields (Table 1, entries 10–12), and solvents other than 1,4-dioxane resulted in inferior reactivity (Table 1, entries 13–15). The reaction is sluggish at lower temperatures (Table 1, entry 16), and the yield of the product was reduced considerably when the amount of DBU was halved (Table 1, entry 17). Delightfully, increasing the amount of DBU led to full conversion, which led to the formation of **2a** in 96% yield and an excellent diastereoselectivity of 96:4 (Table 1, entry 18).[12]

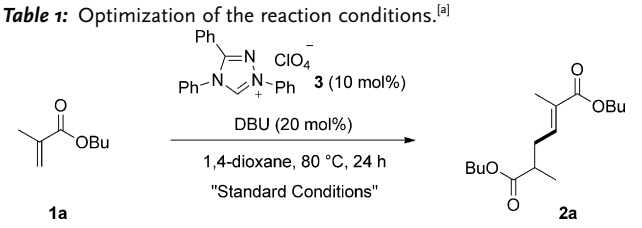
With these optimized reaction conditions in hand, we examined the scope of this unique NHC-organocatalyzed umpolung/dimerization reaction (Scheme 1). A variety of

[*] Dr. A. T. Biju
Organic Chemistry Division
National Chemical Laboratory (CSIR)
Dr. Homi Bhabha Road, Pune—411008 (India)
M. Padmanaban, N. E. Wurz, Prof. Dr. F. Glorius
Westfälische Wilhelms-Universität Münster, NRW Graduate School of Chemistry, Organisch-Chemisches Institut
Corrensstrasse 40, 48149 Münster (Germany)
E-mail: glorius@uni-muenster.de

[**] Generous financial support by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, the Alexander von Humboldt Foundation (A.T.B.), the International NRW Graduate School of Chemistry (M.P.), and the Deutsche Telekom Stiftung (N.E.W.) is gratefully acknowledged. The research of F.G. has been supported by the Alfried Krupp Prize for Young University Teachers of the Alfried Krupp von Bohlen und Halbach Foundation.

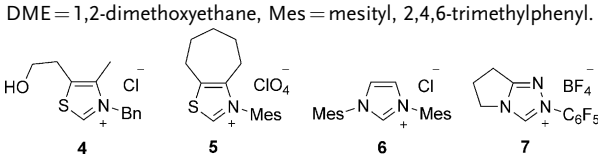
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201103555.

Table 1: Optimization of the reaction conditions.[a]



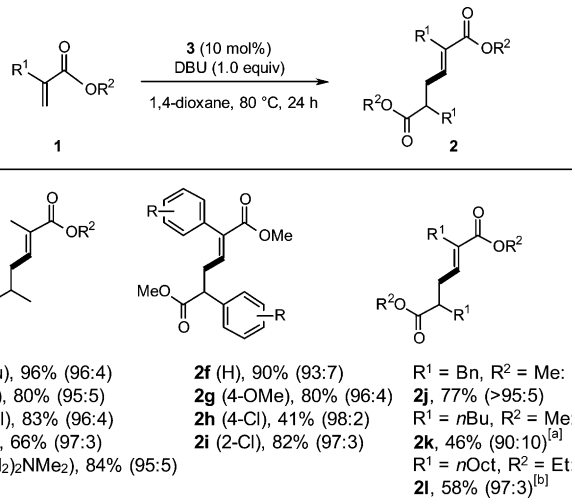
Entry	Variation of the standard conditions[a]	Yield [%][b]	*E*/*Z*[c]
1	none	71 (70)[d]	97:3
2	**4** instead of **3**	<1	n.d.
3	**5** instead of **3**	<1	n.d.
4	**6** instead of **3**	<1	n.d.
5	**7** instead of **3**	<1	n.d.
6	no **3**, 40 mol% DBU	<1	n.d.
7	no DBU	<1	n.d.
8	10 mol% PPh_3 instead of **3** and DBU	<1	n.d.
9	10 mol% DMAP instead of **3** and DBU	<1	n.d.
10	KO*t*Bu instead of DBU	<1	n.d.
11	K_2CO_3 instead of DBU	6	96:4
12	K_3PO_4 instead of DBU	17	98:2
13	THF instead of 1,4-dioxane	57	97:3
14	toluene instead of 1,4-dioxane	50	94:4
15	DME instead of 1,4-dioxane	64	97:3
16	run at 40°C, 1.0 equiv of DBU	<1	n.d.
17	10 mol% **3** and 10 mol% DBU	31	97:3
18	10 mol% **3** and 1.0 equiv of DBU	98 (96)[d]	96:4

[a] Standard conditions: **1a** (0.25 mmol), NHC·HX **3** (10 mol%), DBU (20 mol%), 1,4-dioxane (0.5 mL), 80°C, and 24 h. [b] The yields were determined by ^{1}H NMR spectroscopic analysis of crude products using CH_2Br_2 as the internal standard. [c] Determined by ^{1}H NMR spectroscopy. [d] Yield of isolated product in parentheses. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-dimethylaminopyridine, DME = 1,2-dimethoxyethane, Mes = mesityl, 2,4,6-trimethylphenyl.



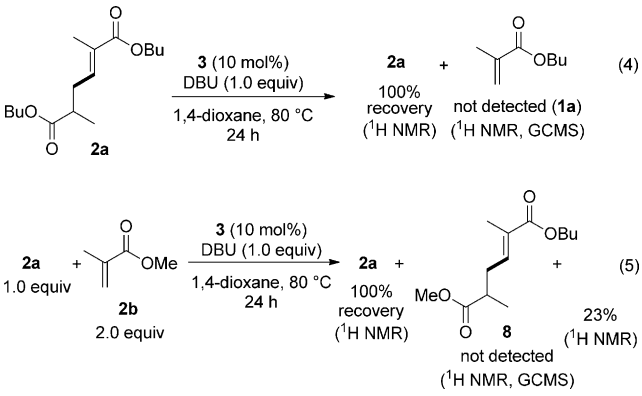
methacrylate derivatives showed superb reactivity and led to the formation of hex-2-enedioates in 66–96% yield and excellent diastereoselectivities (**2a–e**). Moreover, 2-phenyl acrylate underwent smooth dimerization to afford **2f** in 90% yield. Electron-donating and electron-withdrawing groups on the aromatic ring of the 2-aryl acrylates were well tolerated (**2g–i**). Furthermore, 2-alkyl acrylates furnished the desired products in good yields and excellent diastereoselectivities (**2j–l**). It is important to note, however, that in preliminary experiments, α,β-unsaturated aldehydes such as 2-ethylacrolein and cinnamaldehyde failed to undergo this transformation under the standard reaction conditions, presumably because of irreversible binding of the carbene with these substrates, as evident from our inhibition experiments.[11]

We carried out a series of experiments to probe the mechanism of this unique transformation. To get insight into the reversibility of the reaction and to test the stability of the product **2a** under the reaction conditions, **2a** was treated with triazolium salt **3** and DBU [Eq. (4)]. The reaction returned **2a** quantitatively without the formation of any detectable amount of butyl methacrylate. Moreover, when **2a** was

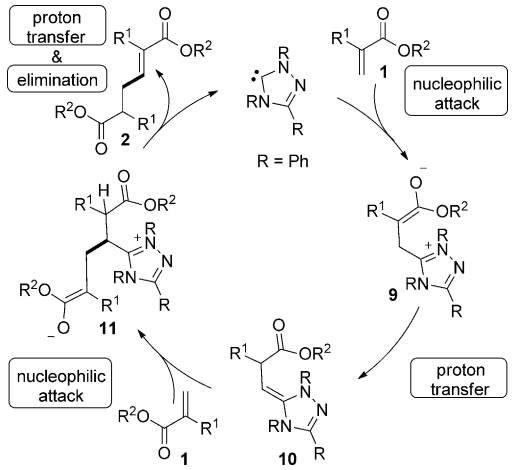


Scheme 1. NHC-catalyzed umpolung of Michael acceptors: Substrate scope. General conditions: **1** (1.0 mmol), **3** (10 mol%), DBU (1.0 equiv), 1,4-dioxane (2.0 mL), 80°C, and 24 h. Yields of isolated products are given. *E*/*Z* ratio determined by ^{1}H NMR spectroscopic analysis of crude products is given in parentheses. Bn = benzyl. [a] 0.25 mmol scale. [b] Using 20 mol% of **3** on 0.5 mmol scale.

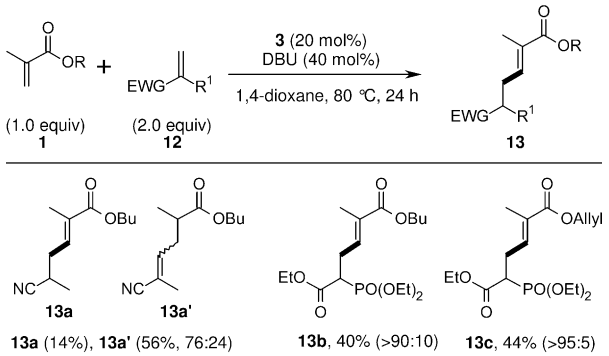
treated with methyl methacrylate in the presence of **3** and DBU no cross-over product **8** or its isomer was detected, and **2a** was recovered quantitatively [Eq. (5)].[11] These observations indicate that the dimerization occurs irreversibly under the optimized conditions. It is noteworthy in this context that the NHC-catalyzed formation of benzoin is reversible in most cases.[13]



The mechanistic rationale for this transition-metal-free transformation is shown in Scheme 2. The reaction is likely initiated by the conjugate addition of the NHC generated from **3** to the activated alkene **1** to form the ester enolate **9**, which undergoes proton transfer to form the enamine intermediate **10**. It is noteworthy that similar enamines have been isolated by the 1:1 addition of the NHC derived from **3** to activated alkenes, including dimethyl maleate, dimethyl fumarate, and fumaric dinitrile.[14] Intermediate **10** bears a strong resemblance to the Breslow intermediate,[15] which is usually formed by the addition of an NHC to aldehydes and is

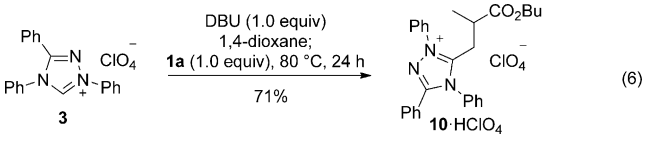


Scheme 2. Proposed mechanism of the reaction.

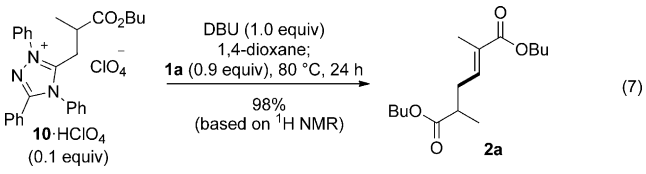


Scheme 3. NHC-catalyzed cross-coupling of Michael acceptors. General conditions: **1** (1.0 mmol), **12** (2.0 mmol), **3** (20 mol%), DBU (40 mol%), 1,4-dioxane (2.0 mL), 80 °C, and 24 h. Yields of isolated products are given. *E*/*Z* ratio determined by GC-MS analysis of crude reaction mixture is given in parentheses.

nucleophilic at the β-carbon atom (umpolung). This deoxy Breslow intermediate[16] **10** adds to another molecule of **1** to form the ester enolate **11**, which undergoes proton transfer and elimination of the NHC to form the observed product **2**. A strong indication for the presence of **10** comes from the fact that the stoichiometric reaction of NHC precursor **3**, DBU, and butyl methacrylate **1a** in a 1:1:1 ratio resulted in the smooth formation of the corresponding protonated species **10**·$HClO_4$ [Eq. (6)].[17] Moreover, adding more DBU and **1a** to **10**·$HClO_4$ and heating the mixture to 80 °C resulted in full conversion to the desired coupling product **2a** [Eq. (7)].



(6)



(7)

Monitoring the kinetics of the reaction on varying the amount of DBU indicated that in addition to shifting the equilibrium towards the generation of more free NHC, the base may also be involved in the deprotonation events in the catalytic cycle.[11] This is in accordance with the observation of Fu and co-workers,[4a] where the base is involved in the catalytic cycle and is also supported by computational mechanistic studies.[4b]

Encouraged by the NHC-catalyzed homocoupling of Michael acceptors by using the umpolung strategy, we then focused our attention on the cross-coupling of two different Michael acceptors (Scheme 3). Gratifyingly, treatment of butyl methacrylate with methacrylonitrile under modified reaction conditions resulted in the formation of a mixture of the cross-coupling products **13a** and **13a′** in 70% yield.[18] In addition, phosphoryl acrylate can also be employed as the coupling partner, which leads to the formation of **13b** and **13c** in moderate yields but excellent diastereoselectivities.

In conclusion, we have developed a transition-metal-free NHC-organocatalyzed umpolung of Michael acceptors ("Michael umpolung") and their addition to Michael acceptors. It is conceivable that the present study will trigger increased interest in the umpolung of Michael acceptors. Further elucidation of the mechanism of this transformation, expanding the scope to challenging cross-coupling reactions, and the development of an asymmetric variant seem to be rewarding goals.

Experimental Section

Triazolium salt **3** (39.7 mg, 0.1 mmol) was added to a Schlenk tube with a teflon screw cap inside a glovebox. Dry 1,4-dioxane (2.0 mL) was then introduced into the tube by syringe outside of the glovebox but under a positive pressure of argon, and the mixture was stirred at RT. The Michael acceptor **1** (1.0 mmol) followed by DBU (152 mg, 149 μL, 1.0 mmol) were then added. The resulting mixture was then stirred in a preheated oil bath at 80 °C for 24 h, and then cooled to RT. Evaporation of the solvent followed by column chromatography afforded the corresponding products **2**.

Received: May 24, 2011
Published online: July 21, 2011

Keywords: carbenes · Michael acceptors · nitrogen heterocycles · organocatalysis · umpolung

[1] For reviews of NHC organocatalysis, see a) V. Nair, S. Vellalath, B. P. Babu, *Chem. Soc. Rev.* **2008**, *37*, 2691; 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) E. M. Phillips, A. Chan, K. A. Scheidt, *Aldrichimica Acta* **2009**, *42*, 55; e) J. L. Moore, T. Rovis, *Top. Curr. Chem.* **2009**, *291*, 77; f) P.-C. Chiang, J. W. Bode in *RSC Catalysis Series*, Royal Society of Chemistry, Cambridge, **2010**, p. 339; g) C. D. Campbell, K. B. Ling, A. D. Smith, *Catal. Metal Complexes* **2011**, *32*, 263; h) A. T.

Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.* **2011**, DOI: 10.1021/ar2000716; for recent reviews on the physicochemical properties of NHCs, see i) T. Dröge, F. Glorius, *Angew. Chem.* **2010**, *122*, 7094; *Angew. Chem. Int. Ed.* **2010**, *49*, 6940; j) T. Dröge, F. Glorius, *Nachr. Chem.* **2010**, *58*, 112.

[2] For selected examples of the benzoin reaction, see a) D. Enders, U. Kallfass, *Angew. Chem.* **2002**, *114*, 1822; *Angew. Chem. Int. Ed.* **2002**, *41*, 1743; b) D. Enders, O. Niemeier, T. Balensiefer, *Angew. Chem.* **2006**, *118*, 1491; *Angew. Chem. Int. Ed.* **2006**, *45*, 1463; c) H. Takikawa, Y. Hachisu, J. W. Bode, K. Suzuki, *Angew. Chem.* **2006**, *118*, 3572; *Angew. Chem. Int. Ed.* **2006**, *45*, 3492.

[3] For initial reports on the conjugate umpolung of α,β-unsaturated aldehydes, see a) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370; b) C. Burstein, F. Glorius, *Angew. Chem.* **2004**, *116*, 6331; *Angew. Chem. Int. Ed.* **2004**, *43*, 6205; see also: c) C. Burstein, S. Tschan, X. Xie, F. Glorius, *Synthesis* **2006**, 2418; d) K. Hirano, I. Piel, F. Glorius, *Adv. Synth. Catal.* **2008**, *350*, 984; e) V. Nair, S. Vellalath, M. Poonoth, E. Suresh, S. Viji, *Synthesis* **2007**, 3195; f) M. He, J. W. Bode, *Org. Lett.* **2005**, *7*, 3131; g) N. Duguet, C. D. Campbell, A. M. Z. Slawin, A. D. Smith, *Org. Biomol. Chem.* **2008**, *6*, 1108; see also: h) N. T. Reynolds, J. Read deAlaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 9518; i) K. Y.-K. Chow, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 8126; j) G.-Q. Li, L.-X. Dai, S.-L. You, *Org. Lett.* **2009**, *11*, 1623.

[4] a) C. Fischer, S. W. Smith, D. A. Powell, G. C. Fu, *J. Am. Chem. Soc.* **2006**, *128*, 1472; for a computational mechanistic study of this reaction, see b) L. Zhao, X. Y. Chen, S. Ye, Z.-X. Wang, *J. Org. Chem.* **2011**, *76*, 2733; c) for a related umpolung of acrylamide using stoichiometric amounts of PBu_3, see J. H. Gong, Y. J. Im, K. Y. Lee, J. N. Kin, *Tetrahedron Lett.* **2002**, *43*, 1247.

[5] a) C. E. Aroyan, A. Dermenci, S. J. Miller, *Tetrahedron* **2009**, *65*, 4069. For an NHC-catalyzed example of a Aza–Morita—-Baylis—-Hillman reaction, see: b) L. He, T.-Y. Jian, S. Ye, *J. Org. Chem.* **2007**, *72*, 7466. For an interesting NHC-catalyzed rearrangement of vinyl sulfones by conjugate addition of the NHC, see: c) R. L. Atienza, H. S. Roth, K. A. Scheidt, *Chem. Science* **2011**, DOI: 10.1039/c1sc00194a.

[6] For a recent Ru-catalyzed tail to tail dimerization of methyl methacrylate, see M. Hirano, Y. Hiroi, N. Komine, S. Komiya, *Organometallics* **2010**, *29*, 3690.

[7] When our study was in progress, we became aware of an abstract on the NHC-catalyzed tail to tail dimerization of methyl methacrylate, see S. Matsuoka, A. Washio, Z. Ohta, A. Katada, K. Ichioka, K. Takagi, M. Suzuki, Abstracts of Papers, the 90th Annual Meeting of the Chemical Society of Japan, Osaka, **2010**, 3F703. The corresponding publication appeared online on June 23, 2011: S.-i. Matsuoka, Y. Ota, A. Washio, A. Katada, K. Ichioka, K. Takagi, M. Suzuki, *Org. Lett.* **2011**, *13*, 3722.

[8] a) G. M. DiRenzo, P. S. White, M. Brookhart, *J. Am. Chem. Soc.* **1996**, *118*, 6225; b) M. Brookhart, E. Hauptman, *J. Am. Chem. Soc.* **1992**, *114*, 4437; c) M. Brookhart, S. Sabo-Etienne, *J. Am. Chem. Soc.* **1991**, *113*, 2777.

[9] a) X. Bugaut, F. Liu, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 8130; b) I. Piel, M. Steinmetz, K. Hirano, R. Fröhlich, S. Grimme, F. Glorius, *Angew. Chem.* **2011**, *123*, 5087; *Angew. Chem. Int. Ed.* **2011**, *50*, 4983; c) T. Jousseaume, N. E. Wurz, F. Glorius, *Angew. Chem.* **2011**, *123*, 1446; *Angew. Chem. Int. Ed.* **2011**, *50*, 1410; d) M. Padmanaban, A. T. Biju, F. Glorius, *Org. Lett.* **2011**, *13*, 98; e) N. Kuhl, F. Glorius, *Chem. Commun.* **2011**, *47*, 573; f) A. T. Biju, F. Glorius, *Angew. Chem.* **2010**, *122*, 9955; *Angew. Chem. Int. Ed.* **2010**, *49*, 9761; g) A. T. Biju, N. E. Wurz, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 5970; h) K. Hirano, A. T. Biju, I. Piel, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 14190.

[10] a) D. Enders, K. Breuer, G. Raabe, J. Runsink, J. H. Teles, J.-P. Melder, K. Ebel, S. Brode, *Angew. Chem.* **1995**, *107*, 1119; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1021; for the electronic effects on the reactivity of triazole-derived carbenes, see b) J. H. Teles, J.-P. Melder, K. Ebel, R. Schneider, E. Gehrer, W. Harder, S. Brode, D. Enders, K. Breuer, G. Raabe, *Helv. Chim. Acta* **1996**, *79*, 61.

[11] See the Supporting Information for details.

[12] The same yield was obtained from a 10 mmol scale reaction.

[13] a) D. Enders, J. Han, A. Henseler, *Chem. Commun.* **2008**, 3989; b) P.-C. Chiang, J. Kaeobamrung, J. W. Bode, *J. Am. Chem. Soc.* **2007**, *129*, 3520; c) G.-Q. Li, L.-X. Dai, S.-L. You, *Chem. Commun.* **2007**, 852; for a report on an irreversible benzoin formation, see d) J. A. Murry, D. E. Frantz, A. Soheili, R. Tillyer, E. J. J. Grabowski, P. J. Reider, *J. Am. Chem. Soc.* **2001**, *123*, 9696.

[14] a) D. Enders, K. Breuer, J. H. Teles, K. Ebel, *J. Prakt. Chem.* **1997**, *339*, 397; b) D. Enders, K. Breuer, J. Runsink, J. H. Teles, *Liebigs Ann.* **1996**, 2019.

[15] R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719.

[16] For insightful reports and applications of deoxy-Breslow intermediates, see a) C. E. I. Knappke, J. M. Neudörfl, A. Jacobi von Wangelin, *Org. Biomol. Chem.* **2010**, *8*, 1695; b) N. Kuhn, M. Göhner, M. Steimann, *Z. Naturforsch. B* **2002**, *57*, 631; c) G. H. Alt, *J. Org. Chem.* **1968**, *33*, 2858.

[17] The identity of the ClO_4 counterion in **10**·$HClO_4$ could not be unequivocally determined.

[18] Two experiments support the notion that **13a′** is formed from the initial reaction product **13** by double-bond migration. First, in our previous experiments (Scheme 1), methacrylonitrile (**12a**) was not found to be suitable for this umpolung, not providing any homocoupling product. Moreover, resubjecting isolated product **13** to the reaction conditions (without additional olefin **12a**) resulted in the formation of double bond isomerization product **13a′**.

