Organocatalysis

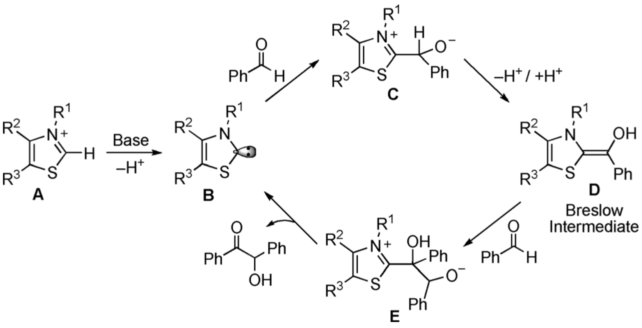
DOI: 10.1002/anie.201204524

Structures and Reactivities of O-Methylated Breslow Intermediates[**]

*Biplab Maji and Herbert Mayr**

Dedicated to Professor Dieter Seebach on the occasion of his 75th birthday

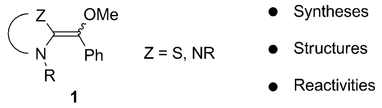
Since the report by Ukai et al. in 1943,[1] thiamine and related thiazolium ions **A** have been known to be catalysts for the umpolung[2] of aldehydes. The mechanism generally accepted for these reactions was proposed by Breslow in 1958,[3] when he described that the thiazolium ring first undergoes deprotonation at the most acidic position to give an ylide or carbene **B** (Scheme 1). The subsequent nucleophilic addition of **B** to an aldehyde generates the zwitterion **C**, which undergoes a proton shift to give the Breslow intermediate **D**, a nucleophilic acyl anion equivalent. The reaction of **D** with a second molecule of aldehyde followed by a proton shift and release of **B** generates the benzoin.[3]



Scheme 1. Breslow's mechanistic proposal for thiazole–ylidene-catalyzed benzoin condensation reaction.

The first isolation and characterization of stable N-heterocyclic carbenes (NHCs) by Arduengo et al. in 1991[4] triggered extensive investigations on the use of these species for umpolung reactions of aldehydes and also for the umpolung of α,β-unsaturated aldehydes and related Michael systems.[5,6] However, our knowledge of the structure and reactivity of Breslow intermediates has so far been based predominantly on theoretical investigations[7] since attempts to isolate Breslow intermediates or their O-protected derivatives have been unsuccessful.[7c,8] In 1987, O-protected Breslow intermediates derived from thiazoles were generated by Jordan et al. in [D_5]pyridine solution and characterized by ^{1}H NMR spectroscopy.[9a] Three years later, Bordwell, Jordan, and co-workers determined the pK_a values of the conjugate acids.[9b] Recently, Berkessel et al. characterized the keto form of the Breslow intermediate derived from 1,2,4-triphenyltriazol-5-ylidene.[7c] While the authors succeeded in identifying a spirodioxolane as the resting state of the catalytic cycle, the enol form of the Breslow intermediate could be neither detected nor trapped.[7c]

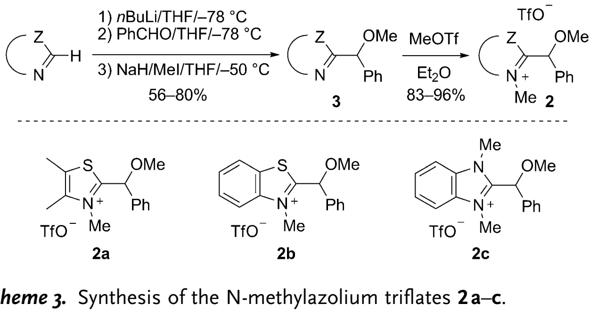
The presence of the enol group makes the intermediates **D** inherently unstable and difficult to isolate or characterize. Rovis et al. recently succeeded in isolating and characterizing aza analogues of the Breslow intermediates derived from chiral triazole carbenes, in which the hydroxy group of the Breslow intermediates is formally replaced by a methylphenylamino group.[10] We now report on the synthesis of O-methylated Breslow intermediates **1** derived from thiazole, imidazole, and triazole carbenes and benzaldehyde, which can be considered to be the closest relatives of Breslow intermediates that can be isolated as stable entities (Scheme 2).



1

Scheme 2. O-methylated Breslow intermediates **1**.

The N-methylated azolium triflates **2a–c**, precursors of **1a–c**, are readily accessible by quaternization of the nitrogen atom of **3** with MeOTf in Et_2O (Scheme 3).[11]



Scheme 3. Synthesis of the N-methylazolium triflates **2a–c**.

The N-aryl substituted azolium chlorides **2d,e** were synthesized by slow addition of diluted *n*-pentane/toluene solutions of the corresponding carbenes into *n*-pentane/

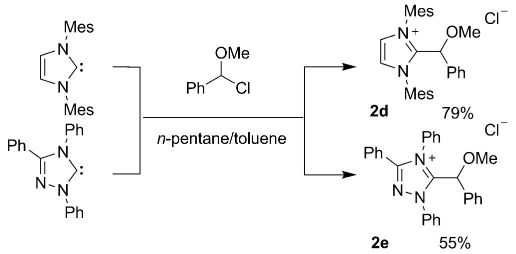
---

[*] M. Sc. B. Maji, Prof. Dr. H. Mayr
Department Chemie, Ludwig-Maximilians-Universität München
Butenandtstrasse 5–13 (Haus F), 81377 München (Germany)
E-mail: herbert.mayr@cup.uni-muenchen.de
Homepage: http://www.cup.lmu.de/oc/mayr

[**] We thank the Deutsche Forschungsgemeinschaft (SFB 749) for financial support, Dr. Peter Mayer for the determination of the X-ray structures, and Dr. Sami Lakhdar, Dr. Jörg Bartl, and Dr. Armin R. Ofial for helpful discussions.

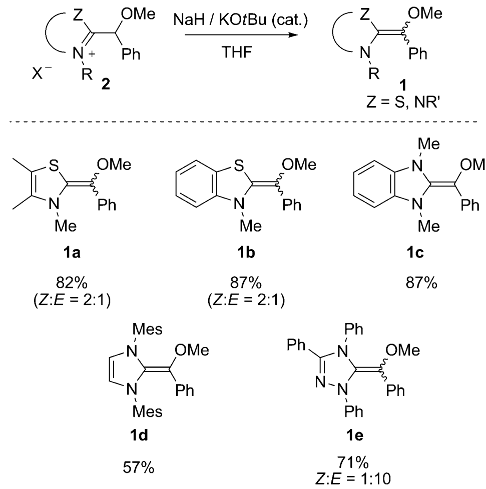
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201204524.

toluene solutions of [chloro(methoxy)methyl]benzene, which was generated from benzaldehyde dimethyl acetal and acetyl chloride in toluene (Scheme 4).



Scheme 4. Synthesis of the N-aryl-substituted azolium chlorides **2d**,**e**.

Treatment of the azolium salts **2** with NaH in the presence of catalytic amounts of KO*t*Bu in anhydrous THF followed by evaporation of the solvent and extraction of the organic materials with anhydrous toluene yielded the O-methylated Breslow intermediates **1a**–**e**, which can be stored in an argon-filled glove box at −30 °C for several weeks without significant decomposition (Scheme 5).



Scheme 5. Synthesis of the O-methylated Breslow intermediates **1a**–**e**.

The thiazole derivatives **1a**,**b** are formed as mixtures of *Z* and *E* isomers (ratio $Z/E = 2{:}1$ in C_6D_6 solution, NOESY)[9a] and the triazole derivative **1e** is formed as $Z/E = 1{:}10$ mixture. The olefinic character of these species is revealed by ^{13}C NMR signals at $\delta = 135$–145 ppm for N*C*Z and at $\delta = 114$–128 ppm for *C*-OMe. X-ray crystallographic analyses of (*Z*)-**1a** and (*E*)-**1e**[12] (Figure 1) show that the exocyclic double bond adopts a planar geometry with bond lengths (**1a**: 134.9 pm, **1e**: 135.8 pm) similar to those of the corresponding deoxy-Breslow intermediates (ca. 136 pm)[13] and their aza analogues (136 pm).[10] The S⋯O distance in **1a** (285.0 pm) is shorter than the sum of the corresponding van der Waals radii (332 pm) suggesting an intramolecular nonbonding 1,4-S–O interaction which might be responsible for the preferred configuration (*Z* isomer) in the solid state.[14] In both compounds, the phenyl ring is slightly twisted (28° in **1a** and 37° in **1e**), and the O-methyl group is oriented almost perpendicular to the exocyclic double bond, as is seen for the OH group in the quantum chemically calculated structures of their nonprotected analogues.[15]

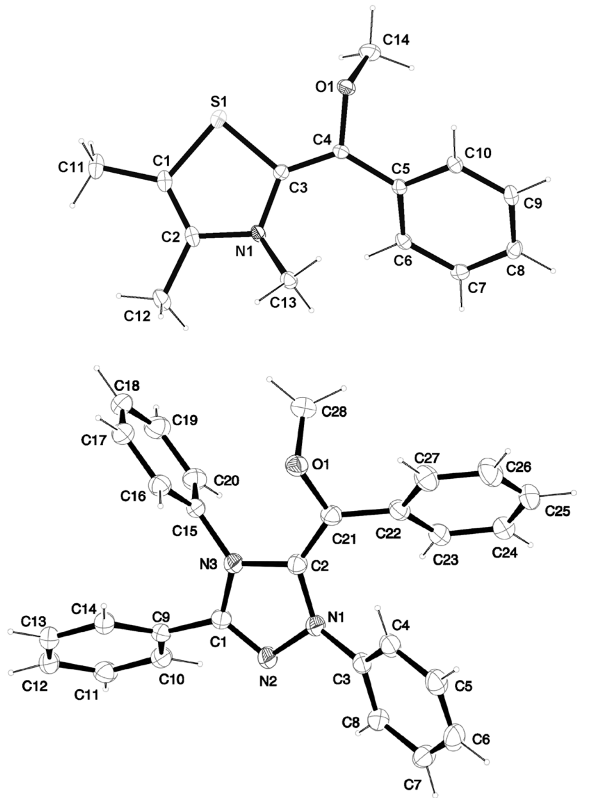
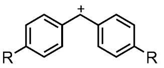
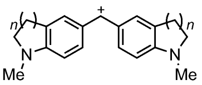
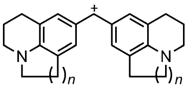


Figure 1. Crystal structures of (*Z*)-**1a** (top) and (*E*)-**1e** (bottom). Ellipsoids at the 50% probability level.

In order to elucidate the relationship between structure and reactivity we have studied the kinetics of the reactions of the O-methylated Breslow intermediates **1** with the stabilized benzhydrylium ions **4a**–**g** (Table 1), which have been used as reference electrophiles to develop the most comprehensive

Table 1: Benzhydrylium ions **4a**–**g** employed as reference electrophiles in this work.

Electrophile			$E^{[a]}$
	$R = N(CH_2CH_2)_2O$	**4a**	−5.53
	$R = NMe_2$	**4b**	−7.02
	$R = N(CH_2)_4$	**4c**	−7.69
	$n = 2$	**4d**	−8.22
	$n = 1$	**4e**	−8.76
	$n = 2$	**4f**	−9.45
	$n = 1$	**4g**	−10.04

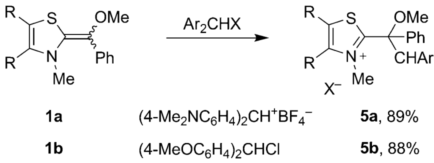
[a] Electrophilicity parameters *E* for **4a**–**g** from Ref. [16a].

nucleophilicity scale presently available on the basis of Equation (1).[16] Herein, nucleophiles are characterized by

$$\lg k = s_N(N + E) \qquad (1)$$

two solvent-dependent parameters (nucleophilicity parameter N and sensitivity parameter s_N), electrophiles are characterized by one solvent-independent parameter (electrophilicity E), and k is the second-order rate constant [$M^{-1}s^{-1}$] at 20 °C.[16]

Representative combinations of the O-methylated Breslow intermediates **1a**,**b** with diarylcarbenium tetrafluoroborates or chlorides **4**[17] showed that the electrophiles attack at the exocyclic double bond of **1** to give the azolium salts **5a,b** (Scheme 6), which were isolated and characterized as described in the Supporting Information.



Scheme 6. Reactions of **1a**,**b** with diarylcarbenium ions.

The rates of the reactions of **1** with the electrophiles **4** were measured photometrically by following the decay of the absorbances of **4** in anhydrous THF at 20 °C by using a stopped-flow instrument as described previously[16] and specified on page S21 of the Supporting Information. A large excess of **1** was used in order to achieve pseudo-first-order conditions. Except for the reaction of **1b** with **4b** and **4c**, the benzhydrylium ions **4** were consumed completely in all reaction investigated. The end absorbances of **4b** and **4c** observed with variable concentrations of **1b** were used to calculate the equilibrium constants given in footnotes [b] and [c] of Table 2.

The plots of lg$k$ against the empirical electrophilicity parameters E of the diarylcarbenium ions **4** are linear (Figure 2), indicating that Equation (1) can be used to derive the N and s_N parameters of the O-methylated Breslow intermediates **1** (Table 2).

The different slopes of the correlation lines in Figure 2 imply that the relative reactivities of the electron-rich π-systems **1** depend slightly on the electrophilicity of the reaction partners. As none of the reference electrophiles **4a–g** has been combined with all nucleophiles listed in Table 2, the correlations for **1a** and **1c** have been extrapolated to obtain rate constants for their reactions with **4c**, which are compared with directly measured rate constants for the other π-nucleophiles in Scheme 7.

Scheme 7 shows that the methyl-protected Breslow intermediate **1b** is 163 times less reactive than its deoxy analogue **6**[18] owing to the inductive electron-withdrawing effect of the methoxy group, which destabilizes the positively charged thiazolium ion **5** formed by electrophilic attack. Thus, the mesomeric electron-donating effect of the methoxy group,

Table 2: Second-order rate constants k [$M^{-1}s^{-1}$] for the reactions of the O-methylated Breslow intermediates **1a–e** and the deoxy-Breslow intermediate **6** with the reference electrophiles **4** (counterions: BF_4^-, in THF at 20 °C).

Nucleophile	N, s_N[a]	Electrophile	k [$M^{-1}s^{-1}$]
1a	14.77, 0.80	**4d**	1.93×10^5
		4e	5.22×10^4
		4f	2.28×10^4
		4g	5.67×10^3
1b	10.45, 0.81	**4a**	9.26×10^3
		4b	5.63×10^2[b]
		4c	1.71×10^2[c]
1c	16.61, 0.68	**4d**	5.88×10^5
		4e	1.64×10^5
		4f	8.48×10^4
		4g	2.89×10^4
1e	15.65, 0.52	**4c**	1.16×10^4
		4d	9.85×10^3
		4e	2.67×10^3
		4f	1.52×10^3
		4g	8.61×10^2
6	15.58, 0.57	**4c**	2.79×10^4
		4d	2.20×10^4
		4e	6.09×10^3
		4f	3.31×10^3

[a] N and s_N as defined by Equation (1). [b] Equilibrium constant $K = (3–5)\times10^3\ M^{-1}$. [c] Equilibrium constant $K = (1–5)\times10^2\ M^{-1}$.

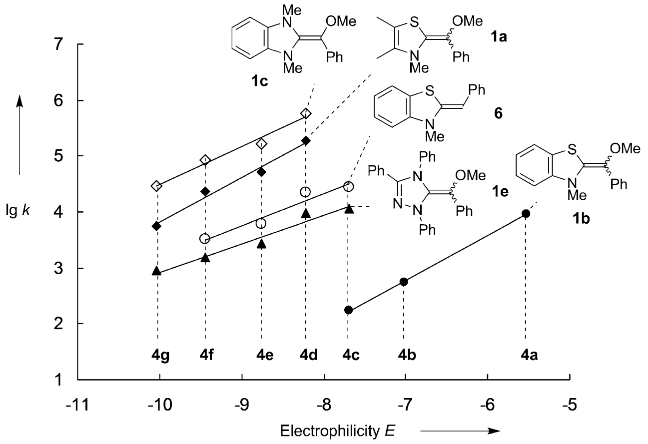
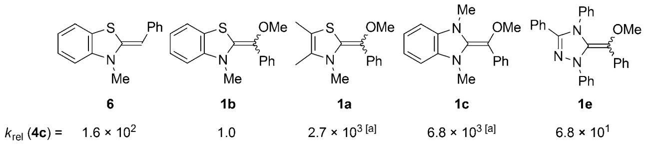


Figure 2. Plot of lg$k$ (Table 2) for the reactions of **1** with the electrophiles **4** in THF at 20 °C versus the corresponding electrophilicity parameters E (Table 1).



Scheme 7. Relative reactivities of the O-methylated Breslow intermediates **1** and comparison with **6** (towards **4c**, THF, 20 °C). [a] From rate constant calculated by using Equation (1), N and s_N from Table 2, and E(**4c**) from Table 1.

which raises the HOMO of **1b** relative to **6**, does not lead to an increase of $k_{\rm rel}$ (and of N) but to an increase of the sensitivity $s_{\rm N}$, which implies that the reactivity ratio **6**/**1b** decreases with increasing electrophilicity of the reaction partner. Analogous effects have been observed previously for ordinary alkenes[16c,19] and enol ethers.[16f]

Scheme 7 also shows that replacement of the benzoannelated ring by two methyl groups (**1b**→**1a**) increases the nucleophilic reactivity by a factor of 2700. An even higher activation (factor 6800) is observed when the sulfur atom in **1b** is replaced by the better mesomeric electron donor NMe (**1b**→**1c**). The 100-fold lower reactivity of the triazole-derived Breslow intermediate (**1c**→**1e**) may be due to the electron-withdrawing effect of the extra nitrogen or the exchange of NMe by the NPh groups.

In summary, we have developed a method to synthesize and isolate stable O-methylated Breslow intermediates **1** by deprotonation of the corresponding azolium salts **2**. This allowed us to perform X-ray analyses of these compounds and to derive their nucleophilic reactivities from the kinetics of their reactions with stabilized benzhydrylium ions **4**. If the ratios **1b**/**6** and **1c**/**1b** are considered to be representative, one can conclude that O-methylated Breslow intermediates are 10^2 times less nucleophilic than the corresponding deoxy-Breslow intermediates and that O-methylated Breslow intermediates derived from thiazoles are 10^3–10^4 times less reactive than those derived from structurally analogous imidazoles.

Received: June 11, 2012

Keywords: benzoin condensation · kinetics · N-heterocyclic carbenes · structure–reactivity relationship · umpolung

---

[1] a) T. Ukai, R. Tanaka, T. Dokawa, *J. Pharm. Soc. Jpn.* **1943**, *63*, 296 – 300; b) For an excellent review of asymmetric benzoin condensations (from 1966 to 2003) see: D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534 – 541.

[2] a) D. Seebach, *Angew. Chem.* **1979**, *91*, 259 – 278; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239 – 258; b) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511 – 3522.

[3] R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719 – 3726.

[4] a) First isolation: A. J. Arduengo III, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.* **1991**, *113*, 361 – 363; b) for physicochemical data of NHCs see: T. Dröge, F. Glorius, *Angew. Chem.* **2010**, *122*, 7094 – 7107; *Angew. Chem. Int. Ed.* **2010**, *49*, 6940 – 6952; c) for studies on nucleophilicities and Lewis basicities of NHCs see: B. Maji, M. Breugst, H. Mayr, *Angew. Chem.* **2011**, *123*, 7047 – 7052; *Angew. Chem. Int. Ed.* **2011**, *50*, 6915 – 6919.

[5] For reviews of NHC catalyzed reactions see: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606 – 5655; b) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 3046 – 3058; *Angew. Chem. Int. Ed.* **2007**, *46*, 2988 – 3000; c) P.-C. Chiang, J. W. Bode in *N-Heterocyclic Carbenes: From Laboratory Curiosities to Efficient Synthetic Tools* (Ed.: S. S. Díez-González), Royal Society of Chemistry, Cambridge, **2010**, pp. 399 – 435; d) K. Zeitler, *Angew. Chem.* **2005**, *117*, 7674 – 7678; *Angew. Chem. Int. Ed.* **2005**, *44*, 7506 – 7510; e) J. L. Moore, T. Rovis, *Top. Curr. Chem.* **2010**, *291*, 77 – 144; f) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose, V. Sreekumar, *Chem. Soc. Rev.* **2011**, *40*, 5336 – 5346; g) A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.* **2011**, *44*, 1182 – 1195; h) C. D. Campbell, K. B. Ling, A. D. Smith in *N-Heterocyclic Carbenes in Transition Metal Catalysis* (Ed.: C. S. J. Cazin), Springer, Dordrecht, **2011**, pp. 263 – 297; i) J. Douglas, G. Churchill, A. D. Smith, *Synthesis* **2012**, *44*, 2295 – 2309.

[6] For umpolung of Michael acceptors see: a) C. Fischer, S. W. Smith, D. A. Powell, G. C. Fu, *J. Am. Chem. Soc.* **2006**, *128*, 1472 – 1473; b) S. Matsuoka, Y. Ota, A. Washio, A. Katada, K. Ichioka, K. Takagi, M. Suzuki, *Org. Lett.* **2011**, *13*, 3722 – 3725; c) A. T. Biju, M. Padmanaban, N. E. Wurz, F. Glorius, *Angew. Chem.* **2011**, *123*, 8562 – 8565; *Angew. Chem. Int. Ed.* **2011**, *50*, 8412 – 8415; d) R. L. Atienza, H. S. Roth, K. A. Scheidt, *Chem. Sci.* **2011**, *2*, 1772 – 1776; e) Y. Zhang, E. Y. X. Chen, *Angew. Chem.* **2012**, *124*, 2515 – 2519; *Angew. Chem. Int. Ed.* **2012**, *51*, 2465 – 2469.

[7] For selected examples see: a) T. Dudding, K. N. Houk, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5770 – 5775; b) J. M. Um, D. A. DiRocco, E. L. Noey, T. Rovis, K. N. Houk, *J. Am. Chem. Soc.* **2011**, *133*, 11249 – 11254; c) A. Berkessel, S. Elfert, K. Etzenbach-Effers, J. H. Teles, *Angew. Chem.* **2010**, *122*, 7275 – 7279; *Angew. Chem. Int. Ed.* **2010**, *49*, 7120 – 7124; d) K. J. Hawkes, B. F. Yates, *Eur. J. Org. Chem.* **2008**, 5563 – 5570; e) P. Verma, P. A. Patni, R. B. Sunoj, *J. Org. Chem.* **2011**, *76*, 5606 – 5613; f) M. Schumacher, B. Goldfuss, *Tetrahedron* **2008**, *64*, 1648 – 1653; g) L. R. Domingo, M. J. Aurell, M. Arnó, *Tetrahedron* **2009**, *65*, 3432 – 3440; h) O. Hollóczki, Z. Kelemen, L. Nyulászi, *J. Org. Chem.* **2012**, *77*, 6014 – 6022.

[8] a) A. E. Mattson, A. R. Bharadwaj, A. M. Zuhl, K. A. Scheidt, *J. Org. Chem.* **2006**, *71*, 5715 – 5724; b) L. Pignataro, T. Papalia, A. M. Z. Slawin, S. M. Goldup, *Org. Lett.* **2009**, *11*, 1643 – 1646; c) J. H. Teles, J.-P. Melder, K. Ebel, R. Schneider, E. Gehrer, W. Harder, S. Bode, D. Enders, K. Breuer, G. Raabe, *Helv. Chim. Acta* **1996**, *79*, 61 – 83; d) R. Breslow, R. Kim, *Tetrahedron Lett.* **1994**, *35*, 699 – 702.

[9] a) F. Jordan, Z. H. Kudzin, C. B. Rios, *J. Am. Chem. Soc.* **1987**, *109*, 4415 – 4416; b) F. G. Bordwell, A. V. Satish, F. Jordan, C. B. Rios, A. C. Chung, *J. Am. Chem. Soc.* **1990**, *112*, 792 – 797.

[10] D. A. DiRocco, K. M. Oberg, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 6143 – 6145.

[11] Use of MeOTf is superior to the use of $Me_3O^+BF_4^-$ which has previously been described: G. L. Barletta, A. C. Chung, C. B. Rios, F. Jordan, J. M. Schlegel, *J. Am. Chem. Soc.* **1990**, *112*, 8144 – 8145.

[12] a) Single-crystal X-ray structure of (*Z*)-**1a** (crystallized from *n*-pentane): B. Maji, H. Mayr, P. Mayer, *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2012**, 68, o2644; b) single-crystal X-ray structure of (*E*)-**1e** (crystallized from MeCN): B. Maji, G. Berionni, H. Mayr, P. Mayer, *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2012**, accepted.

[13] a) B. Maji, M. Horn, H. Mayr, *Angew. Chem.* **2012**, *124*, 6335 – 6339; *Angew. Chem. Int. Ed.* **2012**, *51*, 6231 – 6235; b) C. E. I. Knappke, J. M. Neudörfl, A. Jacobi von Wangelin, *Org. Biomol. Chem.* **2010**, *8*, 1695 – 1705; c) C. E. I. Knappke, A. J. Arduengo III, H. Jiao, J.-M. Neudörfl, A. Jacobi von Wangelin, *Synthesis* **2011**, 3784 – 3795.

[14] a) P. Franchetti, L. Cappellacci, M. Grifantini, A. Barzi, G. Nocentini, H. Yang, A. O'Connor, H. N. Jayaram, C. Carrell, B. M. Goldstein, *J. Med. Chem.* **1995**, *38*, 3829 – 3837; b) Y. Nagao, T. Hirata, S. Goto, S. Sano, A. Kakehi, K. Iizuka, M. Shiro, *J. Am. Chem. Soc.* **1998**, *120*, 3104 – 3110.

[15] See pages S32 and S33 in the Supporting Information for the comparison of the calculated structures of **1a**-OH and **1e**-OH with the crystal structures of **1a** and **1e**.

[16] a) H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, H. Schimmel, *J.*

Am. Chem. Soc. **2001**, *123*, 9500–9512; b) R. Lucius, R. Loos, H. Mayr, *Angew. Chem.* **2002**, *114*, 97–102; *Angew. Chem. Int. Ed.* **2002**, *41*, 91–95; c) H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66–77; d) H. Mayr, A. R. Ofial, *Pure Appl. Chem.* **2005**, *77*, 1807–1821; e) H. Mayr, *Angew. Chem.* **2011**, *123*, 3692–3698; *Angew. Chem. Int. Ed.* **2011**, *50*, 3612–3618; f) for a comprehensive listing of nucleophilicity parameters *N* and electrophilicity parameters *E*, see http://www.cup.lmu.de/oc/mayr/DBintro.html.

[17] For thiazole–ylidene catalyzed cross-coupling of aromatic aldehydes with activated alkyl halides see: M. Padmanaban, A. T. Biju, F. Glorius, *Org. Lett.* **2011**, *13*, 98–101.

[18] Compound **6** was synthesized by deprotonation of the corresponding azolium triflate (see page S17 of the Supporting Information).

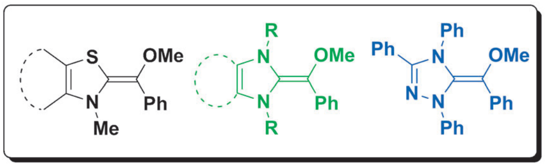
[19] H. Mayr, A. R. Ofial, *Angew. Chem.* **2006**, *118*, 1876–1886; *Angew. Chem. Int. Ed.* **2006**, *45*, 1844–1854.

Communications

Organocatalysis

B. Maji, H. Mayr* ________ ▮▮▮▮–▮▮▮▮

Structures and Reactivities of O-Methylated Breslow Intermediates



- Syntheses
- Structures
- Reactivities

As close as you can get: Since Breslow intermediates usually exist in their keto form, their O-protected tautomers may be considered as their closest isolable relatives. A series of these compounds have been synthesized, their structures determined, and the kinetics of their reactions with electrophiles investigated.