Organic LETTERS
Letter
pubs.acs.org/OrgLett

N-Heterocyclic Carbene Catalyzed Umpolung of Styrenes: Mechanistic Elucidation and Selective Tail-to-Tail Dimerization

Michael Schedler, Nathalie E. Wurz,[†] Constantin G. Daniliuc, and Frank Glorius*

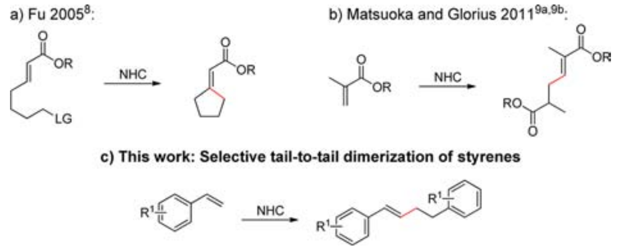
Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstraße 40, 48149 Münster, Germany

Ⓢ *Supporting Information*

ABSTRACT: The reaction between N-heterocyclic carbenes (NHCs) and styrenes yields alkyl-substituted azolium salts, which are able to form nucleophilic deoxy Breslow intermediates by simple deprotonation. This hitherto unknown reaction of NHCs represents a new way to generate deoxy Breslow intermediates and paves the way for the selective NHC-catalyzed tail-to-tail homodimerization of styrenes. This reaction significantly broadens the scope of the Michael umpolung and provides a new method to generate 1,4-diaryl compounds.

The use of NHCs[1] as organocatalysts[2] is mainly founded on their ability to attack the electrophilic aldehyde moiety and form the so-called Breslow intermediate,[3] a nucleophilic acyl anion equivalent, which leads to an umpolung of this moiety.[4] This umpolung of aldehydes led to extensive research on the benzoin condensation and the Stetter reaction.[5] While the electrophilic reaction partner of the Breslow intermediate has been widely varied, only limited variation of the aldehyde has been yet realized. The scope was significantly extended by the introduction of α,β-unsaturated aldehydes and the "conjugate umpolung" in 2004.[6] Recently, the area of conjugate umpolung was further broadened by the group of Y. R. Chi, who introduced saturated esters as suitable substrates with the β-position of these compounds being rendered nucleophilic.[7] Additionally, Fu and co-workers showed in 2005 that NHCs are also able to add to α,β-unsaturated esters and to perform an umpolung of this Michael acceptor, which they used in an intramolecular reaction to form cyclopentenones (Scheme 1a).[8] Six years later, the intermolecular Michael umpolung of acrylates was independently reported by Matsuoka and our group, leading to a tail-to-tail homocoupling of two Michael acceptors (Scheme 1b).[9] These first intermolecular Michael umpolung reactions constitute a groundbreaking proof of principle but suffered from the fact that only α-substituted acrylates were suitable substrates and the limited scope of the cross-coupling of two different Michael acceptors. The combination of NHCs with Michael acceptors also led to further interesting reactions, similar to the Morita–Baylis–Hillman reaction.[10] In addition, the group of Scheidt has shown that NHCs add to vinyl sulfones, turning these into reactive nucleophiles.[10,11]

Scheme 1. NHC-Catalyzed Reactions of Acrylates and Styrenes



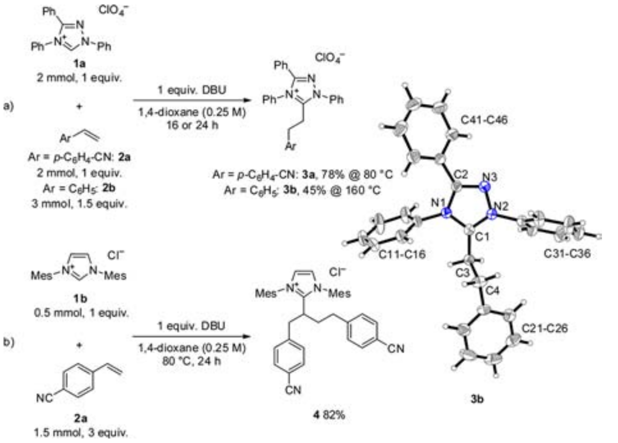
In a recent communication we presented the first intermolecular NHC-catalyzed hydroacylation of unactivated alkenes, namely, styrenes,[12] demonstrating the feasibility of a reaction of the Breslow intermediate[13] with styrenes. Adding to our previous research, we now report the ability of NHCs to add directly to styrenes, turning them into transient nucleophiles and enabling the homocoupling of styrenes as well as the cross-coupling of different styrenes (Scheme 1c). In order to investigate the reactivity of NHCs toward styrenes, we conducted a stoichiometric reaction of the NHC precursor **1a**, which was the most potent catalyst for the acrylate dimerization,[9a] with the electron-poor styrene **2a** under basic conditions (Scheme 2a). At a temperature of 80 °C, only the adduct of the NHC to styrene was formed and could be isolated in a good yield of 78%. Motivated by this successful reaction of **2a**, we repeated the same reaction with unsubstituted styrene **2b**, which surprisingly also gave the addition product **3b** in a yield of 45%, but only at an increased temperature of 160 °C and using a slight excess of styrene. The structure of this adduct **3b** could be confirmed by X-ray crystallography (Scheme 2). This reaction shows for the first time that NHCs are capable of adding to unactivated double bonds and even to an electron-rich double bond, a reaction typically known for carbenes or metal-bound carbenoids, which add readily to alkenes to form cyclopropanes.[14]

When repeating the stoichiometric reaction of p-cyanostyrene **2a** with other NHCs, only traces of the NHC-styrene adduct were observed. Notably, the reaction of IMes **1b** with p-cyanostyrene **2a** yielded a mixture of the NHC-styrene adduct

Received: May 1, 2014
Published: May 14, 2014

dx.doi.org/10.1021/ol501256d | *Org. Lett.* 2014, 16, 3134–3137

Scheme 2. Stoichiometric Reactions of NHCs with Styrenes and Molecular Structure of 3b (Counterion Omitted for Clarity)



and a 2:1 adduct of styrene and NHC (Scheme 2b). Using an excess of **2a**, the 2:1 adduct became the main product, which could be isolated and identified as **4**. The formation of **4** can be explained by deprotonation of the methylene group adjacent to the azolium salt and the formation of a so-called deoxy Breslow intermediate,[15] which then acts as a nucleophile and attacks another molecule of **2a**. In order to confirm this hypothesis, we mixed the adducts **3a** and **3b** with 1.5 equiv of NaH in d_8-THF in an NMR tube, which led to full deprotonation of the CH_2 group, which is directly connected to the triazolium moiety and the expected formation of the deoxy Breslow intermediates, which were stable under O_2- and H_2O-free conditions. These intermediates were fully characterized by 1D and 2D NMR spectroscopy, showing that a mixture of (*E*)- and (*Z*)-deoxy Breslow intermediates was formed, in a ratio of about 1:3 in favor of the (*Z*)-intermediate. The formation of the two deoxy Breslow intermediates could be followed by ^1H and ^{13}C NMR spectroscopy, and the assignment of the (*E*)- and (*Z*)-geometry was achieved by NOE experiments (Figure 1).[16] Previous research on the structures of deoxy Breslow intermediates was based on the reaction of NHCs with activated alkyl halides, leading to compounds similar to **5**, and deprotonation of these compounds also led to the formation of deoxy Breslow intermediates.[15] The isolation of these intermediate **3** allowed us to investigate the reactivity of the deoxy Breslow intermediates **5** toward electrophilic styrenes. Under basic conditions and at high temperatures, a reaction of the adduct **3a** with four different electron-poor styrenes led selectively to the tail-to-tail dimers (**6a**−**d**) in moderate yields, whereas the adducts were formed as approximately 1:1 mixtures of the two shown double-bond regioisomers (Scheme 3). Encouraged by these remarkable stoichiometric reactions, we focused on the possibility of a *catalytic* dimerization of styrenes and investigated the homodimerization of **2a** with **1a** as the catalyst. Under the previously established conditions for the Michael umpolung of acrylates[9a] the dimer **7a** could not be observed (Table 1, entry 1), but increasing the temperature to 120 °C (21% yield, entry 2) and subsequently to 140 °C (77%, entry 4) facilitated the product formation. Using an increased amount of base was helpful to a

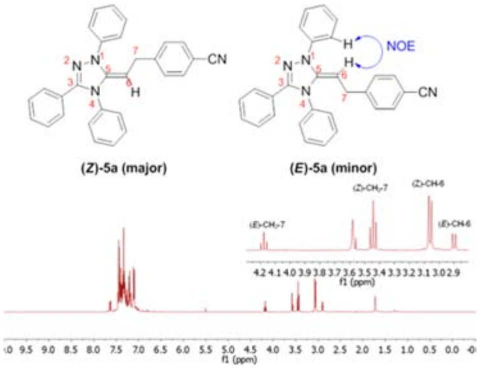
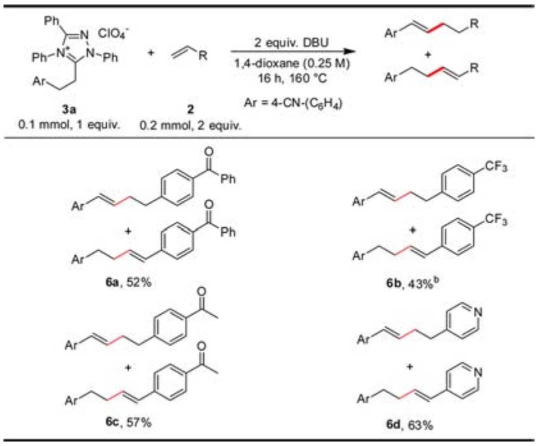


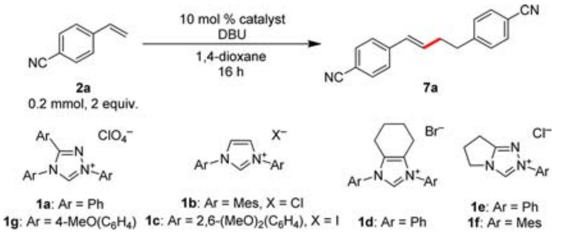
Figure 1. ^1H NMR spectrum of deoxy Breslow intermediate **5a**.

Scheme 3. Stoichiometric Cross-Coupling of Styrenes[a]



[a] Standard conditions: 1 equiv ≙ 0.1 mmol, 2 equiv of DBU, 1,4-dioxane (0.25 M, 0.4 mL), 16 h, 160 °C. Yields of isolated products. [b] Contains another inseparable isomer (about 5%).

Table 1. Optimization of the Catalytic Dimerization of Styrenes[a]



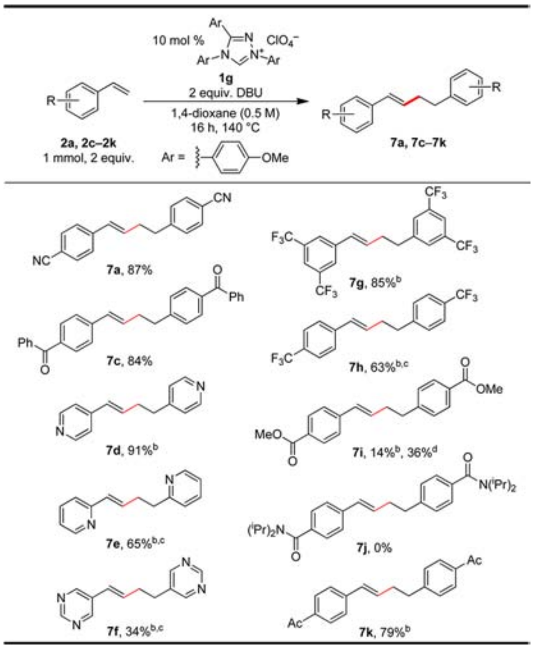
entry	catalyst	DBU (equiv)	temp (°C)	yield[b] (%)
1	**1a**	1	80	0
2	**1a**	1	120	21
3	**1a**	2	120	81
4	**1a**	1	140	77
5	**1a**	2	140	78
6	**1b**	2	140	61
7	**1c**	2	140	0
8	**1d**	2	140	5
9	**1e**	2	140	0
10	**1f**	2	140	0
11	**1g**	2	140	99 (87)[c]

[a] Standard conditions: 1 equiv ≙ 0.1 mmol, 10 mol % NHC·HX, DBU, 1,4-dioxane (0.5 M, 400 μL), 16 h. [b] Yield was determined by ^1H NMR spectroscopy with CH_2Br_2 as the internal standard. [c] Yield of isolated product, 2 equiv of **2a** (1 mmol).

degree (entries 3 and 5), but full conversion was achieved only after a screening of carbenes. IMes **1b**, which had earlier been shown to be capable of adding to styrenes, gave only a reduced yield of 61% (Entry 6). Variations of IMes, such as the more electron-rich NHC precursor **1c**[17] or the phenyl-substituted imidazolium salt **1d**, gave no or a very low yield (entries 7 and 8). The same can be said for other triazolium-based catalysts, such as **1e** and **1f** (entries 9 and 10). Only a more electron-rich variation of the previously used NHC **1a** gave a better yield, and its use in fact led to full conversion into the dimer **2a** (99%, entry 11).

Having established these conditions, we were curious about the scope and the functional group tolerance of this dimerization and hence tested different styrenes with electron-withdrawing substituents. A carbonyl-based electron-withdrawing group as a ketone was well tolerated and gave the corresponding dimer **7c** in a good yield (Scheme 4). However, for most of the other styrenes that were tested, the conversion into the dimer was quite low; we thus optimized the conditions again and found that an increased temperature of 160 °C and an increased concentration (2 M instead of 0.5 M) were beneficial.[18] Under these conditions, heteroaromatic compounds, such as 4-vinylpyridine **2d**, 2-vinylpyridine **2e**, and 5-vinylpyrimidine **2f**, could be used as substrates and gave the corresponding products in good to moderate yields. When the reaction was performed at 140 °C, no product was formed at all, but the adduct of the NHC to the product could be detected by ESI mass spectrometry, indicating that the final elimination of the carbene to liberate the product is not proceeding at 140 °C and only occurs, as is typical for an elimination, at sufficiently high temperatures and at high concentrations of a base. The same is true for trifluoromethyl-substituted styrenes, and the high-temperature conditions gave the dimers of 3,5-bis(trifluoromethyl)-styrene **2g** and of 4-trifluoromethyl-styrene **2h** in good and moderate yields, respectively. The structure of **7g**, especially the *E*-configuration of the double bond, could be confirmed by X-ray crystallography.[18] However, a strongly electron-withdrawing group is essential for the reactivity, which can be seen by the low yield of the ester-substituted styrene **2i**, which yielded only 36% of the dimer **7i** even with increased catalyst loading. Furthermore, the amide-substituted styrene **2j** did not give any product. Surprisingly, the acetyl-substituted styrene **7k** yielded 79% of the dimer, showing that acidic protons, such as the ones in the acetyl moiety, are well tolerated under the harsh and basic conditions. For most substrates, nearly full conversion of the styrene, even at a low yield of **7**, was observed, indicating a decomposition of the styrene, probably via oligo- or polymerization, as a competing process.

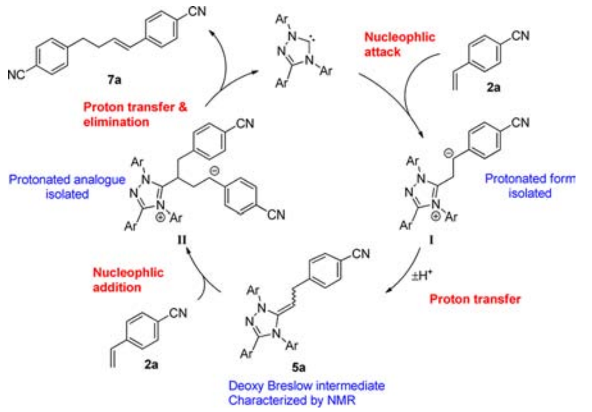
Scheme 4. Scope of the Catalytic Dimerization of Styrenes[a]



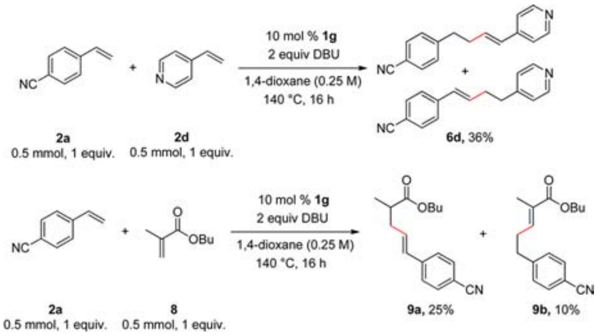
[a] Standard conditions: 1 equiv $\triangleq$ 0.5 mmol, 10 mol % **1g**, 2 equiv of DBU, 1,4-dioxane (0.5 M, 2 mL), 16 h. Yields of isolated products. [b] Reaction performed at 160 °C in 1,4-dioxane (2 M, 0.5 mL). [c] Contains an inseparable isomer (about 5%). [d] Reaction performed with 20 mol % **1g** at 160 °C.

Based on the stoichiometric reactions and the characterization of the deoxy Breslow intermediates, the following mechanism for the dimerization of styrenes is proposed (Scheme 5). Addition of the NHC to the β-position of the styrene leads to a first adduct **I**, which was isolated and characterized in its protonated form. A 1,2-migration of a proton transforms the zwitterionic adduct into the deoxy Breslow intermediate **5a**, which performs a nucleophilic attack on a second molecule of styrene, forming the adduct **II**. Now, another proton shift is needed to generate an anionic charge in the β-position of the NHC, enabling the elimination of the NHC and the formation of **7a**. While the addition of the NHC to the styrene already proceeds smoothly at 80 °C (Scheme 2a), the attack of the deoxy Breslow intermediate on a second molecule of styrene also happens for the challenging substrates at 140 °C (*vide supra*). Therefore, only the elimination of the NHC from **II** requires the high temperature of 160 °C, indicating that this last step is the turnover-limiting step of the catalytic cycle. Finally, we also performed preliminary experiments concerning the coupling of two different styrenes. Submitting a 1:1 mixture of styrenes **2a** and **2d** to the established conditions yielded 36% of the cross-coupled product **6d** alongside the products of homocoupling. Product **6d** was isolated as an approximately 1:1 mixture of two double-bond regioisomers. Preliminary experiments on combining the styrene umpolung with acrylates revealed the formation of the cross-coupled product **9** in a yield of 35%, while remaining starting materials formed the homocoupling products. In this case, the two double-bond isomers were formed in a 2.5:1 ratio and could be separated by column chromatography (Scheme 6).

Scheme 5. Proposed Mechanism for the Dimerization of 2a



Scheme 6. Catalytic Cross-Coupling of Styrenes and Acrylates



In summary, we have investigated the reaction of N-heterocyclic carbenes with styrenes and demonstrated that NHCs are capable of adding to these comparatively electron-neutral alkenes. Furthermore, we showed that the deprotonation of these adducts yielded nucleophilic deoxy Breslow intermediates, which enabled the previously unknown tail-to-tail dimerization of styrenes. This surprising expansion of the Michael umpolung provides a new synthetically useful method to generate 1,4-diaryl compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental data on formation of the stoichiometric adducts, their reactions, and the catalytic reactions. NMR spectra and information on the single crystal X-ray structures. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: glorius@uni-muenster.de.

Present Address

†Wiley-VCH, Boschstrasse 12, 69469 Weinheim, Germany.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Generous financial support by the Fond der Chemischen Industrie (M.S.), the Deutsche Forschungsgemeinschaft and the Deutsche Telekom Stiftung (N.E.W.) is gratefully acknowledged. Dr. Mohan Padmanaban (Inst. für Org. Chem./University of Vienna) is acknowledged for the synthesis of NHC precursors. Karin Gottschalk (Org.-Chem. Inst./WWU Münster) is acknowledged for skillful technical support.

■ REFERENCES

(1) For reviews on the chemistry of NHCs, see: (a) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39. (b) Hahn, F. E.; Jahnke, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3122. For reviews on the properties of NHCs, see: (c) Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 6940. (d) Nelson, D. J.; Nolan, S. P. *Chem. Soc. Rev.* **2013**, *42*, 6723. For recent work on the nucleophilicity of NHCs, see: (e) Maji, B.; Breugst, M.; Mayr, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6915. (f) Mayr, H.; Lakhdar, S.; Maji, B.; Ofial, A. R. *Beilstein J. Org. Chem.* **2012**, *8*, 1458.

(2) For reviews on NHC organocatalysis, see: (a) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506. (b) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (c) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (d) Rovis, T. *Chem. Lett.* **2008**, *37*, 2. (e) Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichimica Acta* **2009**, *42*, 55. (f) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2010**, *291*, 77. (g) Vora, H. U.; Rovis, T. *Aldrichimica Acta* **2011**, *44*, 3. (h) Hirano, K.; Piel, I.; Glorius, F. *Chem. Lett.* **2011**, *40*, 786. (i) Chiang, P.-C.; Bode, J. W. *TCIMAIL*; Tokyo Chemical Industry Co., Ltd.: Tokyo, 2011; Vol. *149*, p 2 (j) Cohen, D. T.; Scheidt, K. A. *Chem. Sci.* **2012**, *3*, 53. (k) Mahatthananchai, J.; Bode, J. W. *Chem. Sci.* **2012**, *3*, 192. (l) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314. (m) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 11686. (n) Fèvre, M.; Pinaud, J.; Gnanou, Y.; Vignolle, J.; Taton, D. *Chem. Soc. Rev.* **2013**, *42*, 2142. For reviews on NHC organocatalysis beyond umpolung, see: (o) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182. (p) Vora, H. U.; Wheeler, P.; Rovis, T. *Adv. Synth. Catal.* **2012**, *354*, 1617. (q) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906. (r) Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res.* **2014**, *47*, 696.

(3) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

(4) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239. (b) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511.

(5) (a) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407. (b) Read de Alaniz, J.; Rovis, T. *Synlett* **2009**, 1189.

(6) (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (b) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. For a review, see: (c) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691. (d) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336.

(7) (a) Fu, Z.; Xu, J.; Zhu, T.; Leong, W. W. Y.; Chi, Y. R. *Nat. Chem.* **2013**, *5*, 597. (b) Bode, J. W. *Nat. Chem.* **2013**, *5*, 813.

(8) Fischer, C.; Smith, S. W.; Powel, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 1472.

(9) (a) Biju, A. T.; Padmanaban, M.; Wurz, N. E.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 8412. (b) Matsuoka, S.-i.; Ota, Y.; Wahio, A.; Katada, A.; Ichioka, K.; Tagaki, K.; Suzuki, M. *Org. Lett.* **2011**, *13*, 3722. (c) Matsuoka, S.-i.; Namera, S.; Wahio, A.; Tagaki, K.; Suzuki, M. *Org. Lett.* **2013**, *15*, 5916. (d) Kato, T.; Matsuoka, S.-i.; Suzuki, M. *J. Org. Chem.* **2014**, DOI: 10.1021/jo500514e.

(10) (a) Atienza, R. L.; Roth, H. R.; Scheidt, K. A. *Chem. Sci.* **2011**, *2*, 1772. (b) Atienza, R. L.; Scheidt, K. A. *Aust. J. Chem.* **2011**, *64*, 1158.

(11) For a review on NHC-catalyzed reactions with C−C multiple bonds, see: Chen, X.-Y.; Ye, S. *Org. Biomol. Chem.* **2011**, *11*, 7991.

(12) Schedler, M.; Wang, D.-S.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 2585.

(13) For recent studies on the properties of the Breslow intermediate, see: (a) Berkessel, A.; Elfert, S.; Yatham, V. R.; Neudörfl, J.-M.; Schlörer, N.; Teles, J. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 12370. (b) Berkessel, A.; Yatham, V. R.; Elfert, S.; Neudörfl, J.-M. *Angew. Chem., Int. Ed.* **2013**, *52*, 11158.

(14) For a review on the addition of carbenes to alkenes (cyclopropanation), see: (a) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1. For the more typical addition of NHCs to electron-poor double bonds, see: (b) Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J. P.; Ebel, K.; Brode, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1021. For a recent work on the reaction of diamidocarbenes with olefins, see: (c) Moerdyk, J. P.; Bielawski, C. W. *Nat. Chem.* **2012**, *4*, 275.

(15) For recent work on the properties of deoxy Breslow intermediates, see: (a) Knappke, C. E. I.; Neudörfl, J.-M.; Jacobi von Wangelin, A. *Org. Biomol. Chem.* **2010**, *8*, 1695. (b) Knappke, C. E. I.; Arduengo, A. J., III; Jiao, H.; Neudörfl, J.-M.; Jacobi von Wangelin, A. *Synthesis* **2011**, 3784. (c) Maji, B.; Horn, M.; Mayr, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 6231. (d) Maji, B.; Mayr, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 10408. (e) Berkessel, A.; Elfert, S. *Adv. Synth. Catal.* **2014**, *356*, 571.

(16) See the Supporting Information for the NMR spectra of **5b**.

(17) Schedler, M.; Fröhlich, R.; Daniliuc, C.-G.; Glorius, F. *Eur. J. Org. Chem.* **2012**, 4164.

(18) See the Supporting Information for details.