Organocatalysis

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Asymmetric Synthesis of Pyrroloindolones by N-Heterocyclic Carbene Catalyzed [2+3] Annulation of α-Chloroaldehydes with Nitrovinylindoles**

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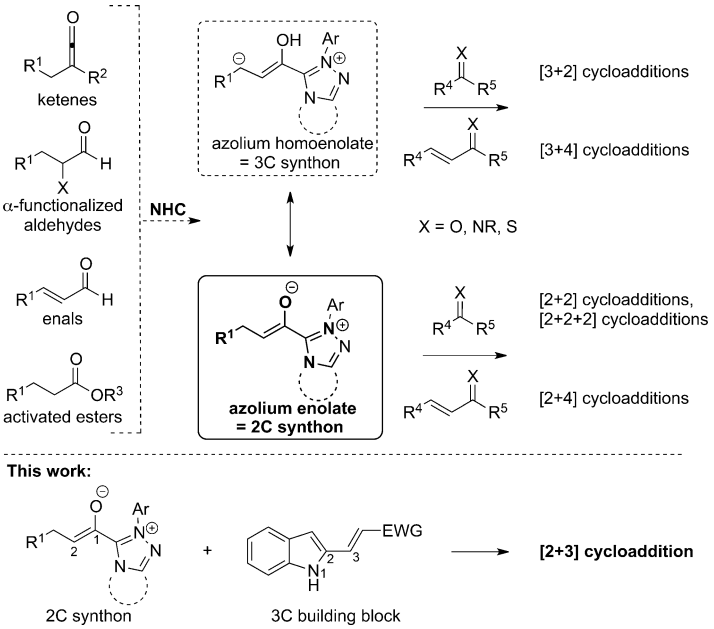
Dedicated to Professor M. T. Reetz on the occasion of his 70th birthday

N-heterocyclic carbenes (NHCs) are an outstanding class of organocatalysts because of their unique ability to reverse the polarity of aldehydes.[1] However, despite this unprecedented reactivity, for quite some time the domain of NHC organocatalysis was limited to the simple a^1-d^1 umpolung represented in such prominent transformations as the benzoin and the Stetter reactions. As there are still some challenging issues associated with these pioneering reactions, they are still subjects of the research.[2,3] In fact, a tremendous breakthrough in NHC catalysis in the past decade was the discovery of the a^3-d^3 umpolung and interlinked NHC transformations.[1g–o] Independently, the groups of Glorius, Bode, and Rovis presented homoenolates and acyl azolium species generated from α-functionalized aldehydes as new reactive NHC-derived intermediates in 2004.[4] Furthermore, just one year later, Reynolds and Rovis reported azolium enolates as new reactive NHC-based species which were formed from α-chloroaldehydes.[5] Importantly, recent work gives more and more evidence that all three reactive intermediates can be generated from the same substrates such as ketenes, α-functionalized aldehydes, enals, and activated esters (Scheme 1).[1] In addition, this diversity was extended by the discovery of the oxidative interconversion of NHC adducts.[1r,6] This concept enabled the use of unfunctionalized aldehydes as precursors for homoenolates, azolium enolates, and acyl azolium species in the presence of an external oxidant. The conclusion is that the desired NHC intermediate can be generated selectively depending on the reaction conditions but independent of the chosen substrate.



Scheme 1. NHC-catalyzed cycloadditions. EWG = electron-withdrawing group.

Within the broad range of reaction modes formal cycloadditions are an important subfield of NHC catalysis and can be used to synthesize different N- and O-heterocycles with significant biological activities.[1] In this context, each NHC-based intermediate leads to distinct reactions. For instance, α,β-unsaturated acyl azolium species are predestined for Claisen-type [3+3] additions,[7] while with homoenolate intermediates usually [3+2] and very recently [3+4] cycloadditions have been observed (Scheme 1).[8] However, the broadest diversity is enabled by the azolium enolate resulting in various [2+2],[9] [2+2+2],[10] and [2+4] cycloadditions[11] (Scheme 1). On the other hand, the [2+3] cycloadditions[12] with NHC enolates are rare. This is because, in contrast to the homoenolate intermediate, the NHC enolate exhibits no polarity reversal. Hence, such [2+3] products with an unevenly sized ring are only possible if the 3C building block has reversed polarity. In fact, to the best of our knowledge, there are only two publications addressing this

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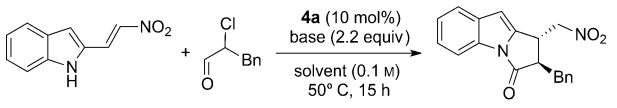
topic. Ye et al. reported a highly enantioselective [2+3] cycloaddition of ketenes to oxaziridines forming oxazolin-4-ones.[12a] Furthermore, Wang et al. showed the reaction of indol-2-carbaldehydes with α-cyclopropyl aldehydes yielding racemic pyrroloindolones.[12b] Therefore, this class of reactions has been rarely represented in the literature. In the course of our own studies on NHC-catalyzed reactions we envisaged that 2-nitrovinylindoles would be suitable substrates for a formal [2+3] cycloaddition with an NHC enolate generated from a α-functionalized chloroaldehyde (Scheme 1, bottom). In this context, the electron-withdrawing nitrovinyl group reverses the polarity at C3, leading to an umpolung of this NCC unit. Herein we report our results on this very rare, highly enantioselective [2+3] annulation resulting in valuable 1*H*-pyrrolo[1,2-*a*]indol-3-(2*H*)-ones.

We began to evaluate the reaction conditions by screening various bases (Table 1, entries 1–8). With inorganic bases such as NaOAc, K_2CO_3, and K_3PO_4 the desired product was obtained with excellent diastereo- and enantioselectivity (Table 1, entries 1–4). Similar results were obtained with organic amine bases such as DMAP, DIPEA, and NEt_3 with the latter being the best of the tested bases with respect to yield (Table 1, entries 6–8). DBU was an the only base that afforded no product at all (Table 1, entry 5). Next, a number of solvents were tested utilizing NEt_3 as the base. Although the diastereoselectivities and *ee* values were excellent in all cases, the highest yield remained that for the reaction in toluene (Table 1, entries 10–13).

In order to determine the absolute configuration of the products, we performed an X-ray crystallographic analysis on compound **3e** and we could unambiguously confirm that the outlined 1*H*-pyrrolo[1,2-*a*]indol-3(2*H*)-ones **3** are 1*S*,2*R* configured (see the Supporting Information).[13] Interestingly, the observed *trans* configuration is opposite to that in our previous report on the TMS-prolinol-based synthesis of this class of compounds.[14] Finally, we tested the best reaction conditions from this optimization on a gram scale (Table 1, entry 14). Indeed, 1.2 g (73% yield) of the desired product **3a** with good diastereo- and enantioselectivity (>20:1 d.r., 93% *ee*).

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

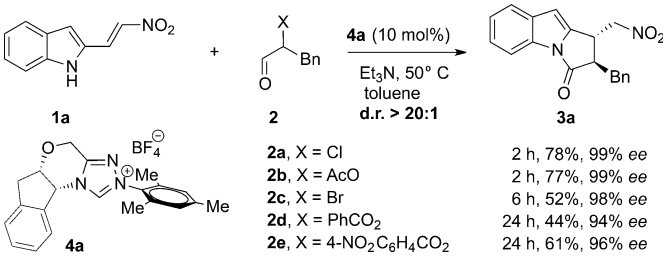


1a 2a 3a

Entry	Solvent	Base	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	toluene	NaOAc	56	15:1	99
2	toluene	K_2CO_3	58	>20:1	99
3	toluene	Cs_2CO_3	26	>20:1	99
4	toluene	K_3PO_4	50	>20:1	99
5	toluene	DBU	n.r.	–	–
6	toluene	DMAP	42	>20:1	92
7	toluene	DIPEA	38	>20:1	98
8[e]	toluene	NEt_3	78	>20:1	99
9[f]	toluene	NEt_3	61	>20:1	99
10	CH_2Cl_2	NEt_3	62	>20:1	98
11	THF	NEt_3	33	>20:1	98
12	$CHCl_3$	NEt_3	66	>20:1	96
13	EtOAc	NEt_3	52	>20:1	99
14[g]	toluene	NEt_3	73	>20:1	93

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), **4c** (10 mol%), base (2.2 equiv), solvent (2 mL), at 50°C for 15 h. [b] Yield of isolated product **3** after column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] The *ee* value was determined by HPLC on a chiral stationary phase. [e] Reaction time: 2 h. [f] 5 mol% **4c** was used. [g] Reaction was performed on a 5 mmol scale. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, Mes = 2,4,6-trimethylphenyl, DIPEA = *N*,*N*-diisopropylethylamine, DMAP = 4-dimethylaminopyridine, TBDPS = *tert*-butyldiphenylsilyl, n.r. = no reaction.

With the optimized reaction conditions in hand we investigated whether variation of the leaving group in α-position to the aldehyde carbonyl group would influence the reactivity and selectivity.[15] Indeed, the reaction of 2-nitrovinylindole **1a** with different α-functionalized aldehydes **2a**–**e** furnished the same product **3a**. As shown in Scheme 2,

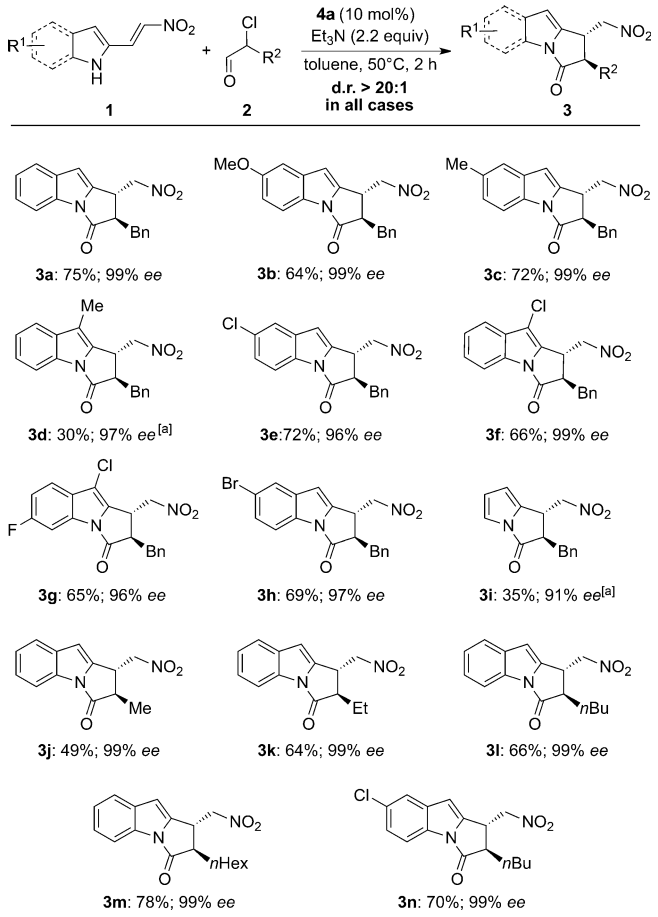


Scheme 2. Influence of the functional group of **2** on yield and diastereo- and enantioselectivity.

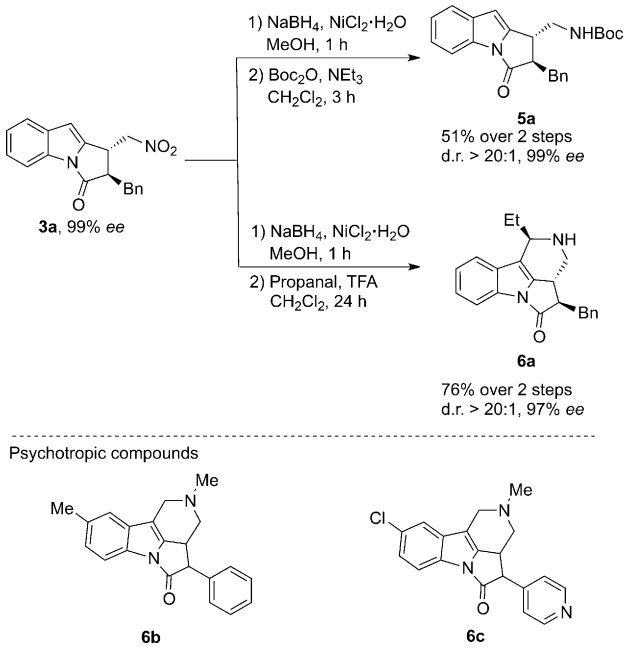
all reactions proceeded smoothly with excellent diastereoselectivity (>20:1) and *ee* values (94–99% *ee*), while a significant deviation in yield was observed. In the case of **2a** and **2b** the same good yield was obtained after a reaction time of just 2 h. However, when aldehydes **2c**–**e** were employed as substrates, even with a prolonged reaction time of up to 24 h only moderate yields (44–61% yield) were obtained.

Next we evaluated the substrate scope of the nitrovinylindoles **1**. As shown in Scheme 3, the reaction proceeded smoothly for a variety of indole substrates **1** bearing either electron-withdrawing or electron-donating groups. In most cases the corresponding products **3a**–**h** were obtained in good yields and excellent diastereo- (>20:1) and enantioselectivities (96–99% *ee*). The only exception was the formation of the product **3d**, where only a low yield of 30% was observed. The low yield was probably due to the steric hindrance of the methyl group on the C3 position. Notably, pyrrole derivative **1i** was also suitable for the outlined reaction affording 1*H*-pyrrolizin-3(2*H*)-one **3i** in excellent selectivities, however, with rather low yield. Additionally, *N*-Me-protected nitrovinylindole was also tested, but no reaction was observed; even the Michael addition did not occur. We finalized the substrate scope with regard to α-chloroaldehydes **2** and fortunately, all aldehydes with unbranched alkyl chains generated the desired product in 49–78% yield with excellent diastereo- and enantioselectivities (**3j**–**n**).

The pyrrolo[1,2-*a*]indole scaffold is a crucial substructure in many bioactive molecules.[16] With the *trans*-disubstituted **3a** in hand, we conducted several transformations (Scheme 4). For instance, the nitro group was converted into a primary amine and protected with a *tert*-butoxycarbonyl (Boc) group in moderate yield while maintaining



Scheme 3. Scope of the nitrovinylindoles **1**. All reactions were performed on a 0.5 mmol scale. Yields of isolated products **3** after column chromatography. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy. The *ee* values were determined by HPLC analysis on a chiral stationary phase. [a] Reaction time: 24 h.

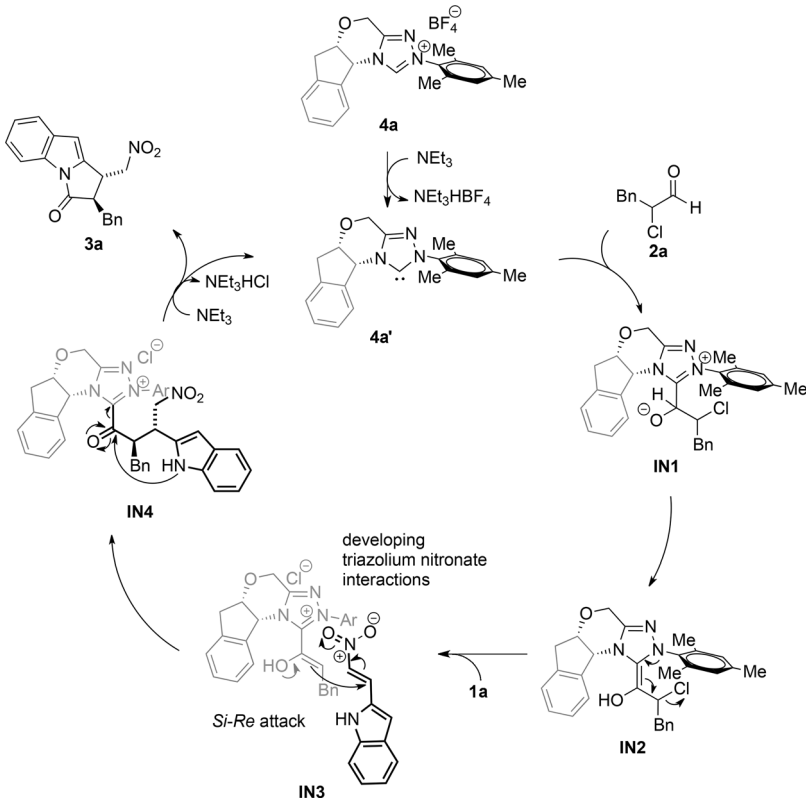


Scheme 4. Top: Derivatization of **3a**; bottom: examples of psychotropic compounds with this scaffold.

excellent diastereomeric and enantiomeric ratios. Remarkably, the tetracyclic pyrrolo[1,2-*a*]indole skeleton **6a** was synthesized by the reduction of the nitro group and a subsequent Pictet–Spengler reaction in 76% overall yield and excellent diastereo- and enantioselectivity (d.r. $>$20:1, 97% *ee*).[17] This class of compounds has received attention recently because they have been tested as psychotropic drugs[18] as well as for treatment of cardiovascular and renal disorders (Scheme 4, bottom).[19]

Regarding the mechanism of the reaction, a proposed catalytic cycle is illustrated in Scheme 5. First, the free carbene **4a′** is generated by deprotonation of the triazolium salt **4a**. The nucleophilic addition of the NHC organocatalyst **4a′** to the α-chloroaldehyde **2a** results in the formation of the zwitterionic species **IN1**. It is well established that this adduct generates the Breslow intermediate **IN2**[20] by a [1,2] H-shift, which is a consequence of two intermolecular proton-exchange processes.[21] The elimination of chloride leads to the formation of the enol structure presented in the intermediate **IN3**. We do not exclude completely that the corresponding enolate structure may be also generated directly from the zwitterionic intermediate **IN1** by a base-mediated elimination. However, it is likely that the formation of the Breslow intermediate is faster than the elimination of chloride by a weak base such as triethylamine. In agreement with previous reports on formal [2+2] and [2+4] cycloadditions with NHC-enolates, we postulate that the enol structure in the intermediate **IN3** is *Z*-configured.[9,11] This may be due to the strong 1,3-allylic strain between the N-heterocyclic carbene and the moiety on the enol.[22] In the intermediate **IN3** the chiral backbone of the NHC efficiently shields the *Re* face of the enolate species to force the Michael addition from the *Si* face. The nitrovinylindol approaches with its *Re* face.[23] During this Michael addition a certain additional stabilization can be rationalized by the positive charge of the triazolium ring and the developing negative charge of the nitronate.[24] The consequence is the observed *trans* selectivity of the outlined reaction. Finally, the catalytic cycle is completed by the intramolecular lactamization of the intermediate **IN4** liberating the catalyst and 1*H*-pyrrolo-[1,2-*a*]indol-3(2*H*)-ones **3a** as the final product. This can occur either directly after the protonation of the nitronate formed in the meantime or by passing through a [4+2] cycloaddition giving an oxazine-type intermediate.[25]

In conclusion, we have developed an asymmetric, NHC-catalyzed approach towards *trans*-disubstituted pyrroloindolones **3**. The desired products were obtained in moderate to good yields with excellent diastereo- and enantioselectivities. Further derivatizations of the products **3** resulted in new scaffolds with potential bioactivity. Mechanistically, this unprecedented [2+3] annulation method involves the Michael addition of the in situ generated enolate species from α-functionalized aldehydes **2** to nitroalkenes **1**, followed by a ring-closing reaction between indole nitrogen and the acyl azolium carboxyl surrogate. We are currently investigating the scope and applications of this reaction.



Scheme 5. Proposed mechanism.

Experimental Section

A dried and argon-filled Schlenk flask was charged with (*E*)-2-(2-nitrovinyl)-1*H*-indole **1** (0.5 mmol, 1.0 equiv) and triazolium salt **4a** (0.05 mmol, 10 mol%) in 5 mL toluene. Subsequently, 2-chloroaldehyde **2** (1 mmol, 2.0 equiv) and triethylamine (1.1 mmol, 2.2 equiv) were added. The mixture was stirred at 50 °C until the reaction was complete according to TLC. After purification by column chromatography on silica gel (pentane/ether 10:1) the desired product **3** was obtained as a yellow oil or solid.

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[1] For reviews and highlights on NHC catalysis, see: a) H. Stetter, *Angew. Chem.* **1976**, *88*, 695 – 704; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 639 – 647; b) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534 – 541; c) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606 – 5655; d) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 3046 – 3058; *Angew. Chem. Int. Ed.* **2007**, *46*, 2988 – 3000; e) V. Nair, S. Vellalath, B. P. Babu, *Chem. Soc. Rev.* **2008**, *37*, 2691 – 2698; f) M. J. Fuchter, *Chem. Eur. J.* **2010**, *16*, 12286 – 12294; g) A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.* **2011**, *44*, 1182 – 1195; h) K. Hirano, I. Piel, F. Glorius, *Chem. Lett.* **2011**, *40*, 786 – 791; i) 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; j) D. A. DiRocco, T. Rovis, *Angew. Chem.* **2011**, *123*, 8130 – 8132; *Angew. Chem. Int. Ed.* **2011**, *50*, 7982 – 7983; k) N. T. Patil, *Angew. Chem.* **2011**, *123*, 1797 – 1799; *Angew. Chem. Int. Ed.* **2011**, *50*, 1759 – 1761; l) D. T. Cohen, K. A. Scheidt, *Chem. Sci.* **2012**, *3*, 53 – 57; m) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511 – 3522; n) J. Douglas, G. Churchill, A. D. Smith, *Synthesis* **2012**, *44*, 2295 – 2309; o) A. Grossmann, D. Enders, *Angew. Chem.* **2012**, *124*, 320 – 332; *Angew. Chem. Int. Ed.* **2012**, *51*, 314 – 325; p) J. Izquierdo, G. E. Hutson, D. T. Cohen, K. A. Scheidt, *Angew. Chem.* **2012**, *124*, 11854 – 11866; *Angew. Chem. Int. Ed.* **2012**, *51*, 11686 – 11698; q) H. U. Vora, P. Wheeler, T. Rovis, *Adv. Synth. Catal.* **2012**, *354*, 1617 – 1639; r) C. E. I. Knappke, A. Imami, A. Jacobi von Wangelin, *ChemCatChem* **2012**, *4*, 937 – 941; s) S. J. Ryan, L. Candish, D. W. Lupton, *Chem. Soc. Rev.* **2013**, *42*, 4906 – 4917.

[2] For publications on benzoin reactions in the last two years, see: a) D. A. DiRocco, T. Rovis, *Angew. Chem.* **2012**, *124*, 6006 – 6008; *Angew. Chem. Int. Ed.* **2012**, *51*, 5904 – 5906; b) D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 8094 – 8097; c) L.-H. Sun, Z.-Q. Liang, W.-Q. Jia, S. Ye, *Angew. Chem.* **2013**, *125*, 5915 – 5918; *Angew. Chem. Int. Ed.* **2013**, *52*, 5803 – 5806; d) K. Thai, S. M. Langdon, F. Bilodeau, M. Gravel, *Org. Lett.* **2013**, *15*, 2214 – 2217.

[3] For publications on Stetter reactions in the last two years, see: a) X. Fang, X. Chen, H. Lv, Y. R. Chi, *Angew. Chem.* **2011**, *123*, 11986 – 11989; *Angew. Chem. Int. Ed.* **2011**, *50*, 11782 – 11785; b) M. Gravel, E. Sanchez-Larios, K. Thai, F. Bilodeau, *Org. Lett.* **2011**, *13*, 4942 – 4945; c) D. A. DiRocco, E. L. Noey, K. N. Houk, T. Rovis, *Angew. Chem.* **2012**, *124*, 2441 – 2444; *Angew. Chem. Int. Ed.* **2012**, *51*, 2391 – 2394; d) A. Bhunia, S. R. Yetra, S. S. Bhojgude, A. T. Biju, *Org. Lett.* **2012**, *14*, 2830 – 2833; e) N. E. Wurz, C. G. Daniliuc, F. Glorius, *Chem. Eur. J.* **2012**, *18*, 16297 – 16301; f) M.-Q. Jia, C. Liu, S.-L. You, *J. Org. Chem.* **2012**, *77*, 10996 – 11001; g) T. Soeta, Y. Tabatake, Y. Ukaji, *Tetrahedron* **2012**, *68*, 10188 – 10193; h) M.-Q. Jia, S.-L. You, *Chem. Commun.* **2012**, *48*, 6363 – 6365.

[4] a) C. Burstein, F. Glorius, *Angew. Chem.* **2004**, *116*, 6331 – 6334; *Angew. Chem. Int. Ed.* **2004**, *43*, 6205 – 6208; b) K. Y.-K. Chow, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 8126 – 8127; c) N. T. Reynolds, J. R. deAlaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 9518 – 9519; d) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370 – 14371.

[5] N. T. Reynolds, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 16406 – 16407.

[6] For NHC catalysis in the presence of an external oxidant, see: a) B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, *Org. Lett.* **2007**, *9*, 371 – 374; b) J. Guin, S. De Sarkar, S. Grimme, A. Studer, *Angew. Chem.* **2008**, *120*, 8855 – 8858; *Angew. Chem. Int. Ed.* **2008**, *47*, 8727 – 8730; c) S. De Sarkar, A. Studer, *Angew. Chem.* **2010**, *122*, 9452 – 9455; *Angew. Chem. Int. Ed.* **2010**, *49*, 9266 – 9269; d) S. D. Sarkar, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2010**, *132*, 1190 – 1191; e) S. De Sarkar, A. Studer, *Org. Lett.* **2010**, *12*, 1992 – 1995; f) Y.-C. Xin, S.-H. Shi, D.-D. Xie, X.-P. Hui, P.-F. Xu, *Eur. J. Org. Chem.* **2011**, 6527 – 6531; g) A. Biswas, S. D. Sarkar, R. Fröhlich, A. Studer, *Org. Lett.* **2011**, *13*, 4966 – 4969; h) P.-C. Chiang, J. W. Bode, *Org. Lett.* **2011**, *13*, 2422 – 2425; i) R. S. Reddy, J. N. Rosa, L. F. Veiros, S. Caddick, P. M. P. Gois, *Org. Biomol. Chem.* **2011**, *9*, 3126 – 3129; j) S. Kuwano, S. Harada, R. Oriez, K.-i. Yamada, *Chem. Commun.* **2012**, *48*, 145 – 147; k) P. Arde, B. T. Ramanjaneyulu, V. Reddy, A. Saxena, R. V.

Anand, *Org. Biomol. Chem.* **2012**, *10*, 848 – 851; l) A. Biswas, S. De Sarkar, L. Tebben, A. Studer, *Chem. Commun.* **2012**, *48*, 5190 – 5192; m) S. Iwahana, H. Iida, E. Yashima, *Chem. Eur. J.* **2011**, *17*, 8009 – 8013; n) T. Uno, T. Inokuma, Y. Takemoto, *Chem. Commun.* **2012**, *48*, 1901 – 1903; o) E. E. Finney, K. A. Ogawa, A. J. Boydston, *J. Am. Chem. Soc.* **2012**, *134*, 12374 – 12377; p) J. Mo, R. Yang, X. Chen, B. Tiwari, Y. R. Chi, *Org. Lett.* **2013**, *15*, 50 – 53; q) X. Zhao, K. E. Ruhl, T. Rovis, *Angew. Chem.* **2012**, *124*, 12496 – 12499; *Angew. Chem. Int. Ed.* **2012**, *51*, 12330 – 12333; r) J. Mo, L. Shen, Y. R. Chi, *Angew. Chem.* **2013**, *125*, 8750 – 8753; *Angew. Chem. Int. Ed.* **2013**, *52*, 8588 – 8591; s) S. De Sarkar, A. Biswas, R. C. Samanta, A. Studer, *Chem. Eur. J.* **2013**, *19*, 4664 – 4678.

[7] For Claisen-type [3+3] additions, see: a) S. J. Ryan, L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2009**, *131*, 14176 – 14177; b) L. Candish, D. W. Lupton, *Org. Lett.* **2010**, *12*, 4836 – 4839; c) J. Kaeobamrung, J. Mahatthananchai, P. Zheng, J. W. Bode, *J. Am. Chem. Soc.* **2010**, *132*, 8810 – 8812; d) B. Wanner, J. Mahatthananchai, J. W. Bode, *Org. Lett.* **2011**, *13*, 5378 – 5381; e) Z.-Q. Zhu, X.-L. Zheng, N.-F. Jiang, X. Wan, J.-C. Xiao, *Chem. Commun.* **2011**, *47*, 8670 – 8672; f) L. Candish, D. W. Lupton, *Chem. Sci.* **2012**, *3*, 380 – 383; g) S. E. Allen, J. Mahatthananchai, J. W. Bode, M. C. Kozlowski, *J. Am. Chem. Soc.* **2012**, *134*, 12098 – 12103; h) J. Mahatthananchai, J. Kaeobamrung, J. W. Bode, *ACS Catal.* **2012**, *2*, 494 – 503.

[8] For [3+2] cycloadditions with homoenolates, see: a) Ref. [4a]; b) K. Hirano, I. Piel, F. Glorius, *Adv. Synth. Catal.* **2008**, *350*, 984 – 988; c) Y. Matsuoka, Y. Ishida, K. Saigo, *Tetrahedron Lett.* **2008**, *49*, 2985 – 2989; d) Y. Matsuoka, Y. Ishida, D. Sasaki, K. Saigo, *Chem. Eur. J.* **2008**, *14*, 9215 – 9222; e) O. Winkelmann, C. Nather, U. Luning, *Org. Biomol. Chem.* **2009**, *7*, 553 – 556; f) Y. Li, X.-Q. Wang, C. Zheng, S.-L. You, *Chem. Commun.* **2009**, 5823 – 5825; g) M. Rose, A. Notzon, M. Heitbaum, G. Nickerl, S. Paasch, E. Brunner, F. Glorius, S. Kaskel, *Chem. Commun.* **2011**, *47*, 4814 – 4816; h) L.-H. Sun, L.-T. Shen, S. Ye, *Chem. Commun.* **2011**, *47*, 10136 – 10138; i) P. Verma, P. A. Patni, R. B. Sunoj, *J. Org. Chem.* **2011**, *76*, 5606 – 5613; j) W. Yao, M. Bian, G. Wang, C. Ma, *Synthesis* **2011**, 1998 – 2002; k) D. T. Cohen, C. C. Eichman, E. M. Phillips, E. R. Zarefsky, K. A. Scheidt, *Angew. Chem.* **2012**, *124*, 7421 – 7425; *Angew. Chem. Int. Ed.* **2012**, *51*, 7309 – 7313; for a very recent example of [3+4]-cycloaddition, see: H. Lv, W.-Q. Jia, L.-H. Sun, S. Ye, *Angew. Chem.* **2013**, *125*, 8769 – 8772; *Angew. Chem. Int. Ed.* **2013**, *52*, 8607 – 8610.

[9] For [2+2] cycloadditions with NHC-enolates, see: a) Y.-R. Zhang, L. He, X. Wu, P.-L. Shao, S. Ye, *Org. Lett.* **2008**, *10*, 277 – 280; b) N. Duguet, C. D. Campbell, A. M. Z. Slawin, A. D. Smith, *Org. Biomol. Chem.* **2008**, *6*, 1108 – 1113; c) L. He, H. Lv, Y.-R. Zhang, S. Ye, *J. Org. Chem.* **2008**, *73*, 8101 – 8103; d) X.-L. Huang, X.-Y. Chen, S. Ye, *J. Org. Chem.* **2009**, *74*, 7585 – 7587; e) X.-N. Wang, P.-L. Shao, H. Lv, S. Ye, *Org. Lett.* **2009**, *11*, 4029 – 4031; f) P. V. G. Reddy, S. Tabassum, A. Blanrue, R. Wilhelm, *Chem. Commun.* **2009**, *0*, 5910 – 5912; g) C. Awasthi, L. D. S. Yadav, *Synlett* **2010**, 1783 – 1788; h) X.-N. Wang, Y.-Y. Zhang, S. Ye, *Adv. Synth. Catal.* **2010**, *352*, 1892 – 1895; i) T. Wang, X.-L. Huang, S. Ye, *Org. Biomol. Chem.* **2010**, *8*, 5007 – 5011; j) X.-N. Wang, L.-T. Shen, S. Ye, *Org. Lett.* **2011**, *13*, 6382 – 6385; k) T.-Y. Jian, L. He, C. Tang, S. Ye, *Angew. Chem.* **2011**, *123*, 9270 – 9273; *Angew. Chem. Int. Ed.* **2011**, *50*, 9104 – 9107.

[10] For a recent example of a [2+2+2] addition with NHC-enolates, see: X.-N. Wang, L.-T. Shen, S. Ye, *Chem. Commun.* **2011**, *47*, 8388 – 8390.

[11] For [2+4] cycloadditions with NHC-enolates, see: a) M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418 – 8420; b) M. He, G. J. Uc, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 15088 – 15089; c) T.-Y. Jian, P.-L. Shao, S. Ye, *Chem. Commun.* **2011**, *47*, 2381 – 2383; d) J. Kaeobamrung, M. C. Kozlowski, J. W. Bode, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20661 – 20665; e) P.-L. Shao, X.-Y. Chen, L.-H. Sun, S. Ye, *Tetrahedron Lett.* **2010**, *51*, 2316 – 2318; f) S. J. Ryan, L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2011**, *133*, 4694 – 4697; g) X. Fang, X. Chen, Y. R. Chi, *Org. Lett.* **2011**, *13*, 4708 – 4711; h) L. Hao, Y. Du, H. Lv, X. Chen, H. Jiang, Y. Shao, Y. R. Chi, *Org. Lett.* **2012**, *14*, 2154 – 2157; i) T.-Y. Jian, L.-H. Sun, S. Ye, *Chem. Commun.* **2012**, *48*, 10907 – 10909; j) L. Yang, F. Wang, P. J. Chua, Y. Lv, L.-J. Zhong, G. Zhong, *Org. Lett.* **2012**, *14*, 2894 – 2897; k) T.-Y. Jian, X.-Y. Chen, L.-H. Sun, S. Ye, *Org. Biomol. Chem.* **2013**, *11*, 158 – 163.

[12] For [2+3] cycloadditions with NHC-enolates, see: a) P.-L. Shao, X.-Y. Chen, S. Ye, *Angew. Chem.* **2010**, *122*, 8590 – 8594; *Angew. Chem. Int. Ed.* **2010**, *49*, 8412 – 8416; b) L. Li, D. Du, J. Ren, Z. Wang, *Eur. J. Org. Chem.* **2011**, 614 – 618.

[13] CCDC946742 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] D. Enders, C. Wang, X.-N. Yang, G. Raabe, *Synlett* **2011**, 469 – 472.

[15] a) K. B. Ling, A. D. Smith, *Chem. Commun.* **2011**, *47*, 373 – 375; b) Y.-M. Zhao, M. S. Cheung, Z. Lin, J. Sun, *Angew. Chem.* **2012**, *124*, 10505 – 10509; *Angew. Chem. Int. Ed.* **2012**, *51*, 10359 – 10363.

[16] a) A. P. Kozikowski, D. Ma, J. Brewer, S. Sun, E. Costa, E. Romeo, A. Guidotti, *J. Med. Chem.* **1993**, *36*, 2908 – 2920; b) J. L. Adams, R. S. Garigipati, M. Sorenson, S. J. Schmidt, W. R. Brian, J. F. Newton, K. A. Tyrrell, E. Garver, L. A. Yodis, M. Chabot-Fletcher, M. Tzimas, E. F. Webb, J. J. Breton, D. E. Griswold, *J. Med. Chem.* **1996**, *39*, 5035 – 5046; c) M. H. M. Sharaf, P. L. Schiff, A. N. Tackie, C. H. Phoebe, R. L. Johnson, D. Minick, R. C. Crouch, G. E. Martin, C. W. Andrews, *J. Heterocycl. Chem.* **1996**, *33*, 789 – 797; d) L. S. Fernandez, M. L. Sykes, K. T. Andrews, V. M. Avery, *Int. J. Antimicrob. Agents* **2010**, *36*, 275 – 279; e) J. Guellaumel, S. Leonce, A. Pierre, P. Renard, B. Pfeiffer, L. Peruchon, P. B. Arimondo, C. Monneret, *Oncol. Res.* **2003**, *13*, 537 – 549; f) G. A. Elmegeed, A. R. Baiuomy, O. M. E. Abdel-Salam, *Eur. J. Med. Chem.* **2007**, *42*, 1285 – 1292; g) I. Ngantchou, B. Nyasse, C. Denier, C. Blonski, V. Hannaert, B. Schneider, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3495 – 3498.

[17] The relative configuration of compound **5a** was established by NOE measurements; see the Supporting Information for details.

[18] A. A. Protter, S. Chakravarty (Medivation Technologies Inc.), Int. Patent WO2012/112961A1, August 23, **2012**.

[19] S. Chakravarty, P. B. Hart, R. P. Jain (Medivation Technologies Inc.), Int. Patent WO2011/103485A1, August 25, **2011**.

[20] a) A. Berkessel, S. Elfert, V. R. Yatham, J.-M. Neudörfl, N. E. Schlörer, J. H. Teles, *Angew. Chem.* **2012**, *124*, 12537 – 12541; *Angew. Chem. Int. Ed.* **2012**, *51*, 12370 – 12374; b) C. J. Collett, R. S. Massey, O. R. Maguire, A. S. Batsanov, A. C. O'Donoghue, A. D. Smith, *Chem. Sci.* **2013**, *4*, 1514 – 1522.

[21] K. J. Hawkes, B. F. Yates, *Eur. J. Org. Chem.* **2008**, 5563 – 5570.

[22] For computational calculations on NHC-enolates, see: a) K. Tang, J. Wang, X. Cheng, Q. Hou, Y. Liu, *Eur. J. Org. Chem.* **2010**, 6249 – 6255; b) K. Tang, J. Wang, Q. Hou, X. Cheng, Y. Liu, *Tetrahedron: Asymmetry* **2011**, *22*, 942 – 947.

[23] T. Dudding, K. N. Houk, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5770 – 5775.

[24] For a review on interactions among aromatic compounds, see: a) T. Rovis, J. M. Um, D. A. DiRocco, E. L. Noey, K. N. Houk, *J. Am. Chem. Soc.* **2011**, *133*, 11249 – 11254; b) E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem.* **2003**, *115*, 1244 – 1287; *Angew. Chem. Int. Ed.* **2003**, *42*, 1210 – 1250.

[25] For a somewhat related case, see: C.-Y. Zhu, X.-M. Deng, X.-L. Sun, J.-C. Zheng, Y. Tang, *Chem. Commun.* **2008**, 738 – 740.

