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N-Heterocyclic Carbene Catalyzed Aza-Morita−Baylis−Hillman Reaction of Cyclic Enones with *N*-Tosylarylimines

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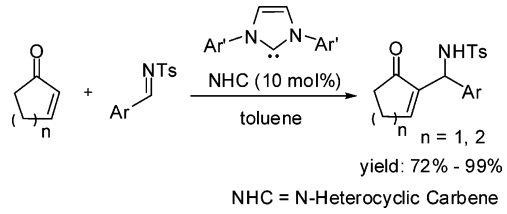
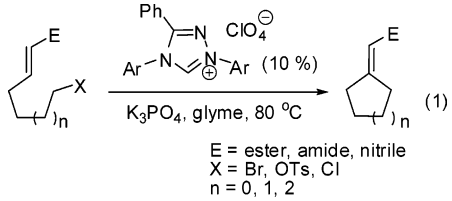


N-Heterocyclic carbenes (NHCs) prove to be efficient catalysts for the aza-Morita−Baylis−Hillman (aza-MBH) reaction of cyclopent-2-en-1-one or cyclohex-2-en-1-one with a variety of *N*-tosylarylimines to give the aza-MBH adduct in high yields. Crossover experiments show NHC can add to *N*-tosylarylimines in a reversible manner, which allows the addition of NHC to cyclic enones and thus catalyzes the aza-Mortia−Baylis−Hillman reaction.

The chemistry of N-heterocyclic carbenes (NHCs) has grown dramatically since the first isolation of the stable NHCs by Arduengo in 1991.[1] They have been widely applied for the synthesis of heterocycles,[2] used as ligands for organometallic catalysts,[3] and recently developed into nucleophilic organocatalysts.[4] Owing to their nucleophilic attack to the carbon−oxygen double bond of aldehydes, not only the NHC-catalyzed classical umpolung of aldehydes for the Benzoin reactions[5] and the Stetter reactions[6] but also the NHC-catalyzed "extended-umpolung" of functionalized aldehydes,[7] such as α,β-unsaturated aldehydes,[8] α-haloaldehydes,[9] α,β-epoxyaldehydes,[10] and cyclopropanecarboxaldehydes,[11] were demonstrated very successfully in the past few years. However, the catalytic reactions triggered by the carbon-nucleophilic NHC to attack unsaturated carbon−carbon bonds are rarely investigated, for these reactions are typically catalyzed by heteroatom-nucleophilic catalysts, such as amines and phosphines.[12] In view of the importance and wide application of nucleophilic catalysis in organic synthesis,[13] we are very interested in exploring the nucleophilic activity of NHCs to attack unsaturated carbon−carbon bond to trigger a catalytic cycle. Being atom economic and able to generate functional groups, the aza-Morita−Baylis−Hillman (aza-MBH) reaction[14] was chosen as the model reaction for our research. We were pleased to find that NHCs could catalyze the reaction of cyclic enones with *N*-tosylarylimines to give the aza-MBH adducts in high yields. Recently, Fu et al. reported a NHC-catalyzed umpolung of Michael acceptors through an addition−tautomerization sequence, thus furnishing an intramolecular β-alkylation of Michael acceptors (eq 1).[15] Herein we report our results of the NHC-catalyzed intermolecular aza-MBH reaction.



Initially, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (**1**),[16] a stable NHC, was investigated as a catalyst for the aza-MBH reaction of cyclopent-2-en-1-one (**8a**) with *N*-tosylphenylimine (**9a**). It was found that imine **9a** was fully consumed when the reaction was carried out in THF at room temperature in 24 h, and the corresponding aza-MBH product was obtained in 39% yield (entry 1, Table 1).

Encouraged by this result, various NHCs, generated from the corresponding precursors and 1 equiv of base, were screened. It was found that all the NHCs screened, including imida-

(1) Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.

(2) (a) Cheng, Y.; Meth-Cohn, O. *Chem. Rev.* **2004**, *104*, 2507. (b) Nair, V.; Bindu, S.; Sreekumar, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 5130.

(3) (a) *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Glorius, F., Ed.; Topics in Organometallic Chemistry, Vol. 28; Springer-Verlag: Berlin/Heidelberg, 2007. (b) *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Weinheim, 2006. (c) César, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619.

(4) (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (b) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988 and references cited therein.

(5) (a) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719. (b) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1463. (c) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492. (d) Li, G. Q.; Dai, L. X.; You, S. L. *Chem. Commun.* **2007**, 852.

(6) (a) Kerr, M. S.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 1029. (b) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876. (c) Mennen, S. M.; Blank, J. T.; Tran-Dubé, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195. (d) de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284. (e) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552.

(7) (a) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506.

(8) (a) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. (b) Chow, K. Y. K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126. (c) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736. (d) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334. (e) Chiang, P. C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520. (f) Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3107.

(9) (a) Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406. (b) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088.

(10) Chow, K. Y. K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126.

(11) Sohn, S. S.; Bode, J. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 6021.

(12) For recent reviews, see: (a) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985. (b) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542. (c) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (d) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035.

(13) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520.

(14) Shi, Y.-L.; Shi, M. *Eur. J. Org. Chem.* **2007**, 2905. (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

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

(16) Arduengo, A. J., III; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, *55*, 14523.

10.1021/jo071247i CCC: $37.00
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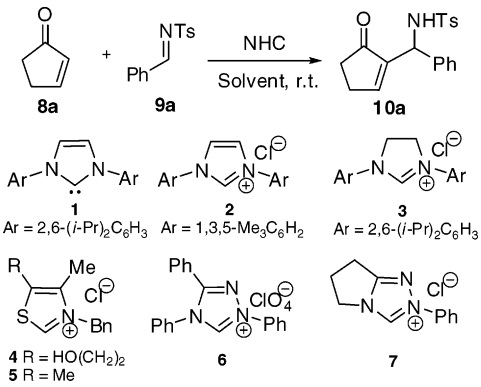
TABLE 1. NHC-Catalyzed Aza-MBH Reaction of Cyclopent-2-en-1-one (8a) with *N*-Tosylphenylimine (9a)[a]



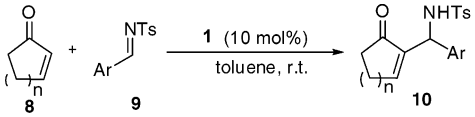
entry	NHC[b]	solvent	time (h)	yield[c] (%)
1	**1** (20 mol %)	THF	24	39
2	**2**, Cs_2CO_3 (20 mol %)	THF	24	50
3	**3**, Cs_2CO3 (20 mol %)	THF	24	38
4	**4**, Cs_2CO_3 (20 mol %)	THF	24	38
5	**5**, Cs_2CO_3 (20 mol %)	THF	24	38
6	**6**, Cs_2CO_3 (20 mol %)	THF	24	5
7	**7**, Cs_2CO_3 (20 mol %)	THF	24	22
8	**2**, *t*-BuOK (20 mol %)	toluene	12	99
9	**3**, *t*-BuOK (20 mol %)	toluene	12	81
10	**4**, *t*-BuOK (20 mol %)	toluene	12	62
11	**5**, *t*-BuOK (20 mol %)	toluene	12	78
12	**2**, *t*-BuOK(10 mol %)	toluene	15	96
13	**1** (10 mol %)	toluene	15	94
14	**2**, *t*-BuOK(5 mol %)	toluene	12	23
15	**2** (20 mol %)	toluene	24	NR[d]
16	*t*-BuOK (20 mol %)	toluene	24	complex

[a] Enone **8a** (0.36 mmol) and imine **9a** (0.3 mmol) were used for entries 1−7, while **8a** (0.3 mmol) and **9a** (0.45 mmol) for entries 8−16. [b] The NHCs, except **1**, were generated in situ by stirring the suspension of the corresponding precursors in the presence of 1 equiv of base for 30 min at room temperature. [c] Isolated yield. [d] No reaction.

zolylidene (entry 2), imidazolinylidene (entry 3), thiazolylidenes (entries 4 and 5), and triazolylidenes (entries 6 and 7), could catalyze the aza-MBH reaction but in only low to moderate yields. Careful examination showed that decomposition of imine **9a** was the possible reason for low yields. The yield was improved to 99% when the reaction was carried out in toluene and 1.5 equiv of imine **9a** was used (entry 8). Under these conditions, all of the reactions catalyzed by NHCs afforded aza-MBH adduct in good to high yields (entries 9−11). When the loading of catalyst **2** or **1** was reduced to 10 mol %, the yield of the aza-MBH product remained excellent (entries 12 and 13), while 5 mol % loading resulted in dramatical loss of yield (entry 14). Controlled experiments showed that the aza-MBH reaction could not proceed without azonium salt or *t*-BuOK (entries 15 and 16).

The scope of the imines was then investigated (Table 2). It was found that the arylimines with either electron-donating groups (4-Me and 4-MeO) or electron-withdrawing groups (4-Cl, 4-F and 4-NO_2) worked well to give the aza-MBH adducts in high yields (entries 1−6). 2-Furylimine **9g** was also a suitable substrate (entry 7). The substituent on the meta position (3-MeO and 3-Cl) or ortho position (2-MeO) of arylimines has no significant effect on the aza-MBH reaction (entries 8−10). The substrate for aza-MBH reaction could be extended to cyclohex-2-en-1-one when 20 mol % of NHC **1** was employed and the reaction was carried at 50 °C. All the reactions of cyclohex-2-en-1-one with the four tested *N*-tosylarylimines proceeded

TABLE 2. NHC-Catalyzed Aza-MBH Reaction of Cyclic Enones with Arylimines



Entry	Enone **8**	Imine **9**	Ar	Time (h)	**10,** Yield (%) [a]
1		**9a**	C_6H_5	15	**10a**, 96
2		**9b**	4-MeC_6H_4	24	**10b**, 85
3		**9c**	4-$MeOC_6H_4$	36	**10c**, 82
4		**9d**	4-ClC_6H_4	15	**10d**, 82
5		**9e**	4-FC_6H_4	24	**10e**, 77
6		**9f**	4-$NO_2C_6H_4$	24	**10f**, 75
7		**9g**	2-Furyl	24	**10g**, 80
8		**9h**	3-$MeOC_6H_4$	36	**10h**, 85
9		**9i**	3-ClC_6H_4	20	**10i**, 99
10		**9j**	2-$MeOC_6H_4$	36	**10j**, 76
11 [b]		**9a**	C_6H_5	36	**10k**, 86
12 [b]		**9d**	4-ClC_6H_4	36	**10l**, 98
13 [b]		**9e**	4-FC_6H_4	36	**10m**, 74
	8b				
14 [b]		**9c**	4-$MeOC_6H_4$	36	**10n**, 72

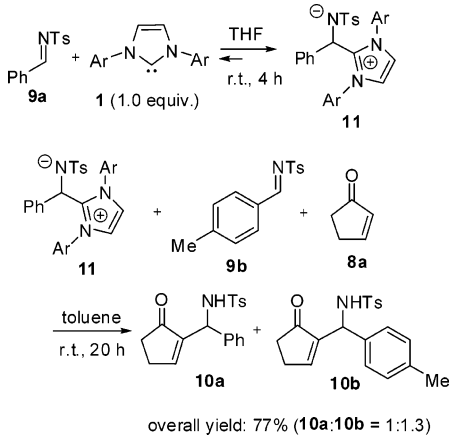
[a] Isolated yield. [b] 20 mol % of NHC **1** was employed, and the reaction was carried out at 50 °C.

smoothly and gave the corresponding aza-MBH product in good to excellent yields (entries 11−14).

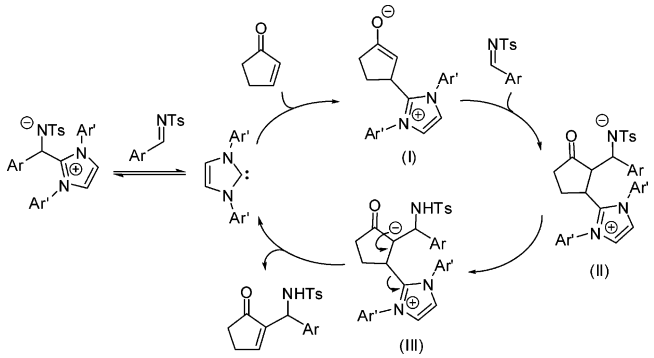
It has been reported that NHC could readily add to *N*-tosylarylimine according to NMR investigation,[17] and we isolated adduct **11** by the reaction of NHC **1** with imine **9a** in 82% yield. A crossover experiment showed the mixture of cyclopent-2-en-1-one, adduct **11** (1.0 equiv), and imine **9b** (1.0 equiv) affords both aza-MBH products **10a** and **10b** (1:1.3) in 77% overall yield (Scheme 1). This result suggests that the addition of NHC **1** with *N*-tosylimines is reversible and indicates that adduct **11** may decompose to the free NHC **1** and imine **9a**, followed by NHC-catalyzed aza-MBH reaction of enone **8a** with **9a** and **9b** to afford products **10a** and **10b**, respectively. The first step of the MBH reaction is generally proposed as the nucleophilic addition of catalyst to Michael acceptor. Therefore, the mixture of 1 equiv of NHC **1** and cyclopent-2-en-1-one in toluene was stirred at room temperature in order to identify the addition intermediate. TLC showed cyclopent-2-en-1-one was consumed slowly. We failed to isolate the proposed intermediate, and only some unidentified compounds are detectable.

(17) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131.

SCHEME 1. Addition of NHC to Imine and the Crossover Experiment



SCHEME 2. Proposed Catalytic Cycle



A proposed catalytic cycle for the NHC-catalyzed aza-MBH reaction is depicted in Scheme 2. The free NHC is added to Michael acceptor to give enolate I and Mannich reaction of the enolate with imine to give the intermediate II, followed by protonation and deprotonation to give intermediate III. The aza-MBH adduct is afforded by elimination from intermediate III, and NHC is released to finish the catalytic cycle.

In summary, we have shown that NHCs catalyze the aza-MBH reaction of cyclopent-2-en-1-one and cyclohex-2-en-1-one with a variety of *N*-tosylarylimines. This reaction represents the first example of NHC-triggered intermolecular reaction of cyclic enones. The unique feature of NHCs and the importance of nucleophilic catalysis make the concept of NHCs as nucleophilic catalysts to attack unsaturated carbon−carbon bonds potentially useful in organic synthesis. The detailed mechanistic investigations and chiral NHC-catalyzed aza-MBH reactions are underway in our lab.

Experimental Section

Representative Procedure for the NHC-Catalyzed Aza-MBH Reaction of Cycloenones with *N*-Tosylarylimines. To a solution of *N*-tosylphenylimine **9a** (116.6 mg, 0.45 mmol) in 2.0 mL of toluene was added cyclopent-2-en-1-one (25 μL, 0.30 mmol,) via a syringe, followed by addition of 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene (**1**) (11.7 mg, 0.03 mmol). The resulting mixture was stirred for 15 h at room temperature, and TLC indicated complete consumption of cyclopent-2-en-1-one. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (EtOAc/petroleum ether, 1:2) to give the aza-MBH adduct product **10a** as a white solid[18] (98 mg, 96% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 8.3 Hz, 2H), 7.34 (t, J = 2.7 Hz, 1H), 7.21−7.15 (m, 7H), 6.17 (d, J = 8.4 Hz, 1H), 5.28 (d, J = 8.4 Hz, 1H), 2.52−2.05 (m, 4H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 160.5, 143.5, 143.2, 138.6, 137.4, 129.3, 128.6, 127.8, 127.3, 126.7, 55.2, 34.9, 26.7, 21.4.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Shi, M.; Xu, Y.-M.; Zhao, G.-L.; Wu, X.-F. *Eur. J. Org. Chem.* **2002**, 3666.