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Formal Diels–Alder Reactions of Chalcones and Formylcyclopropanes Catalyzed by Chiral N-Heterocyclic Carbenes

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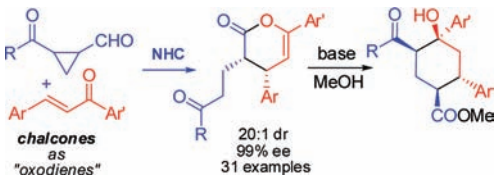
ABSTRACT



Highly enantioselective (formal) hetero-Diels–Alder reactions between chalcones and formylcyclopropanes are disclosed. The challenging N-heterocyclic carbene (NHC)-bounded enolate intermediates from formylcyclopropanes were captured for new C–C bond forming reactions. The reaction products were obtained with high diastereo- and enantioselectivities and could be easily transformed to optically pure multisubstituted cyclohexane derivatives.

The catalytic generation of chiral ester enolates or their equivalents with small organic catalysts for enantioselective carbon–carbon bond-forming reaction is a powerful strategy in reaction discovery and synthesis.[1−4] One well-studied approach is to generate enolates from ketenes by employing nucleophilic catalysts, such as planar-chiral DMAP derivatives,[2] cinchona alkaloids,[3] and chiral N-heterocyclic carbenes (NHCs).[4] With NHCs as the catalysts, the chiral ester enolate equivalents can also be generated from α-heteroatom-functionalized aldehydes (such as α-chloro aldehydes) and recently simple enals.[5] These NHC-bounded enolate equivalents have been explored as dienophiles for (formal) reverse-electron-demand Diels–Alder reactions.[5c−e] Highly activated heterodienes, such as ketoenones[5d,e,6] and α,β-unsaturated *N*-sulfonylimines,[5c,7] were widely used for the Diels–Alder reactions (eq 1).[8] However, chalcones were rarely used in NHC-mediated[5f,9] or other catalytic intermolecular

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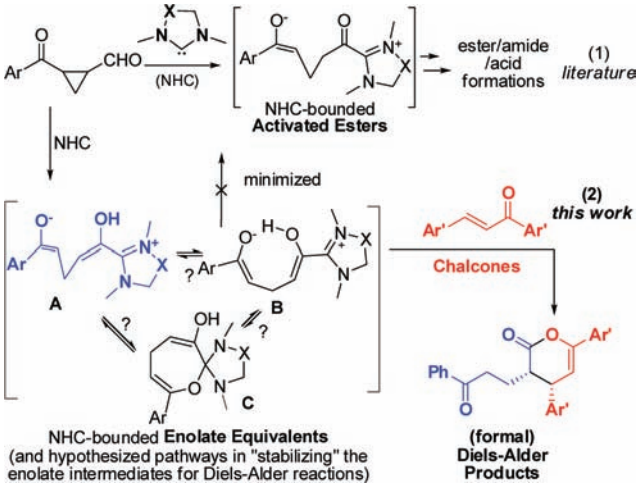
hetero-Diels–Alder reactions, as indicated through literature survey and recently pointed out by Feng and coworkers.[10]

We reasoned that one difficulty of using the relatively less-activated chalcones as oxodienes for NHC-catalyzed intermolecular Diels–Alder reactions might be that the catalytically generated enolates could undergo rapid conversions to the corresponding activated esters and subsequently end up as carboxylic acids (when trace water was present) or their derivatives such as amides and esters when alcohols and amines were present.[11] When enals were used as the enolate precursors, additional complications came from the competing NHC-bounded homoenolate equivalent intermediates.[5f,9,12] One solution to overcome this difficulty is perhaps to minimize the conversion of the enolate to the activated ester intermediates through some kind of stabilizing or buffering.

Our attention was turned to formylcyclopropanes as enolate precursors for formal Diels–Alder reactions with chalcones. In 2006, Bode et al. reported the pioneering NHC-mediated ring opening of formylcyclopropanes to give activated carboxylate esters that were trapped *intermolecularly* by alcohols or amines to afford the corresponding esters and amides (eq 1).[13] The groups of You and Wang have then applied this chemistry to synthesize heterocyclic compounds *via* intra- or intermolecular trapping of the activated ester intermediates (eq 1).[14] To the best of our knowledge, no reaction through trapping of the possible enolate intermediates **A** (eq 2) has been developed.[14d] At first glance trapping the enolate intermediates seemed to be difficult especially given the fact that You et al.[14a] had reported the facile intramolecular trapping of the activated ester by the ketone enol oxygen. However, a further evaluation of the system let us hypothesize that the reactivity (and/or stability) of the enolate **A** might be modulated through intramolecular noncovalent interactions (**B**) and/or formation of cyclic adduct **C**.[15] Our efforts with ^{1}H NMR studies did not detect these interactions or intermediates; nevertheless we decided to evaluate the reactions of formylcyclopropanes with chalcones and other electrophiles. Described here are our highly enantioselective intermolecular Diels–Alder reactions between simple chalcones and formylcyclopropanes (eq 2).



Our condition optimization for a model reaction between formylcyclopropane **1a** and chalcone **2a** is summarized in Table 1. The reaction using 10 mol % of **4a** NHC precatalyst and 30 mol % DBU successfully afforded product **3a** with 68% yield but poor dr (Table 1, entry 1). Additional studies revealed that the low dr was mainly caused by the base (DBU)-induced postreaction epimerization of **3a**. Thus decreasing the DBU loading from 30 to 10 mol % led to a higher dr (14:1; Table 1, entry 2) without loss of the yield. The use of a slight excess of aldehyde **1a** (1.2 to 1.5 equiv) was necessary to ensure high yields as side reactions *via* the previously reported activated ester intermediates[14a] could not be completely suppressed. Further screenings of solvents and bases suggested that the combination of DBU and THF gave the best results in terms of both yields and stereoselectivities (Table 1, entries 3–8).The use of 4A molecular sieve could improve the reaction yield but with a dropped dr (Table 1, entry 10). Finally, switching the counteranions[16] of the NHC precursors from Cl^- (**4a**) to BF_4^- (**4b**) could consistently afford the product with high yields and excellent enantioselectivities (Table 1, entries 11–12).

With the optimized conditions (Table 1, entry 12) in hand, the scope of the chalcone substrates was examined

(7) Jian, T.-Y.; Shao, P.-L.; Ye, S. *Chem. Commun.* **2011**, *47*, 2381.

(8) The same type of highly activated heterodiene substrates were also widely used in other catalytic hetero-Diels–Alder reactions. See: (a) Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498. (b) Han, B.; He, Z.-Q.; Li, J.-L.; Li, R.; Jiang, K.; Liu, T.-Y.; Chen, Y.-C. *Angew. Chem.* **2009**, *121*, 5582–5589. (c) *Angew. Chem., Int. Ed.* **2009**, *58*, 5474.

(9) For examples of NHC-bounded enolates involved in *intramolecular* Diels–Alder reactions (or possible Michael additions) with chalcones, see ref 5f and Fang, X.; Jiang, K.; Xing, C.; Hao, L.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 1910.

(10) For one example of guanidine-catalyzed intermolecular Diels–Alder reactions with chalcones, see: Dong, S.; Liu, X.; Chen, X.; Mei, F.; Zhang, Y.; Gao, B.; Lin, L.; Feng, X. *J. Am. Chem. Soc.* **2010**, *132*, 10650. It should be noted that stepwise pathways *via* Michael-type additions to chalcones followed by enol ester formatons cannot be ruled out. So these (ref 5c–5e, 6, 7, 10) and our reactions might be considered as "formal" Diels–Alder reactions.

(11) (a) Rovis, T.; Reynolds, N. T.; Read de Alaniz, J. *J. Am. Chem. Soc.* **2004**, *126*, 9518. (b) Rovis, T.; Vora, H. U. *J. Am. Chem. Soc.* **2007**, *129*, 13796. (c) Bode, J. W.; Chow, K. Y.-K. *J. Am. Chem. Soc.* **2004**, *126*, 8126.

(12) (a) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736. (b) Bode, J. W.; Chiang, P.-C.; Kaeobamrung, J. *J. Am. Chem. Soc.* **2007**, *129*, 3520.

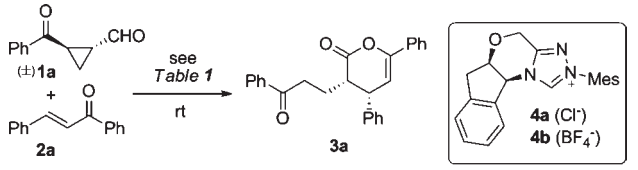
(13) (a) Bode, J. W.; Sohn, S. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6021. (b) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798. (c) Vesely, J.; Zhao, G.-L.; Bartoszewicz, A.; Córdova, A. *Tetrahedron Lett.* **2008**, *49*, 4209.

(14) (a) You, S.-L.; Li, G.-Q.; Dai, L.-X. *Org. Lett.* **2009**, *11*, 1623. (b) Du, D.; Li, L.; Wang, Z. *J. Org. Chem.* **2009**, *74*, 4379. (c) Li, L.; Du, D.; Ren, J.; Wang, Z. *Eur. J. Org. Chem.* **2011**, *2011*, 614. (d) Du, D.; Wang, Z. *Eur. J. Org. Chem.* **2008**, *2008*, 4949. In Wong's work (ref 14d) the formation of an ester intermediate (*via* trapping of the NHC-bounded activated ester) was followed by an intramolecular condensation of the ester with an aldehyde to form the product; no direct trapping of an NHC-bounded enolate intermediate was observed/proposed.

(15) For a recent example of related intramolecular nucleophilic addition to triazoliums in an NHC-catalyzed living polymerization, see: Guo, L.; Zhang, D. *J. Am. Chem. Soc.* **2009**, *131*, 18072.

(16) For a discusion on counteranion effects, see: Wei, S.; Wei, X.-G.; Su, X.; You, J.; Ren, Y. *Chem.—Eur. J.* **2011**, *17*, 5965.

Table 1. Optimization of Reaction Conditions[a]



entry	cat.	conditions	yield, %[b]	dr[c]	ee[d]
1	**4a**	DBU (30 mol %), THF	68	2:3	>99[e]
2	**4a**	DBU, THF	68	14:1	>99
3	**4a**	DBU, Toluene	39	12:1	>99
4	**4a**	DBU, DCM	52	4:1	>99
5	**4a**	KO^{t}Bu, THF	50	16:1	>99
6	**4a**	Cs_2CO_3, THF	28	12:1	>99
7	**4a**	NMM, THF	12	>20:1	>99
8	**4a**	DMAP, THF	20	>20:1	>99
9[f]	**4a**	DBU, THF	83	13:1	>99
10[f]	**4a**	DBU, THF, 4A MS	93	4:1	>99
11[f]	4b	**DBU, THF, 4A MS**	**81**	**>20:1**	**>99**
12[g]	4b	**DBU, THF, 4A MS**	**86**	**>20:1**	**>99**

[a] Reaction conditions: **1a** (1.2 equiv), **2a** (0.2 mmol, 1 equiv), **4a** (10 mol %; for entries 11–12, 12 mol % **4b**), 10 mol % base (except entry 1), 1 mL of solvent, 2–3 h. [b] Isolated yield based on **2a**. [c] Diastereoselectivtiy of **3a**, determined *via* ^{1}H NMR analysis of unpurified reaction mixtures. Absolute configuration of products was determined *via* X-ray of **3p** (see Table 2 and SI). [d] Enantiomeric excess of **3a**, determined *via* chiral-phase HPLC analysis. [e] >99% ee for both diastereomers. [f] 1.5 equiv **1a**. [g] **1a** (1.5 equiv) was added in two portions (see Supporting Information (SI)).

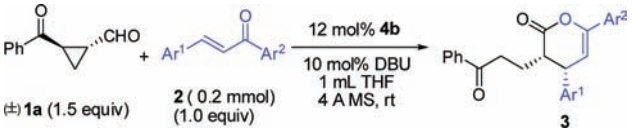
(Table 2). The diastereo- and enantioselectivities were excellent in all the cases. The yields of the lactone products **3** could be influenced by the electronic properties of the chalcones. Generally, chalcones with electron-withdrawing substituents on Ar^1 and/or Ar^2 led to higher yields (e.g., Table 2, entries 2–4, 10–12, 18–19); chalcones with electron-donating substituents gave lower but still acceptable yields with a slightly longer reaction time (e.g., Table 2, entries 5–7, 13–14). Replacing the aryl groups of **2** with heteroaryl groups (Table 2, entries 8 and 15) and swapping the phenyl to a cinnamyl group (Table 2, entry 9) were all tolerated.

The scope of the formylcyclopropanes was also explored (Table 3). It appeared the reaction yields and stereoselectivities were not sensitive to the formylcyclopropanes examined here. Formylcyclopropanes with an electron-withdrawing group and electron-donating substituents on the R^1 aryls all reacted smoothly (Table 3, entries 1–7). Formylcyclopropane with bulky R^1 groups, such as napthyl and ^{t}Bu groups, were also tolerated (Table 3, entries 8–9, 11).[17]

The postulated reaction pathways are summarized in Scheme 1. The formation of Breslow intermediate **I** is followed by a ring opening and subsequent protonation and enal-ketone tautomerization to give enolate **III** as a

(17) A few other formylcyclopropanes with various substitution patterns that were examined in this study but did not work well are briefed in the Supporting Information.

Table 2. Scope of Chalcones[a]

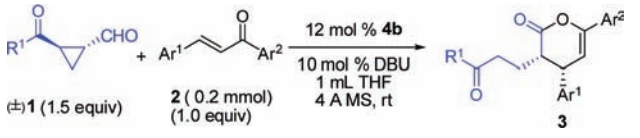


entry	Ar^1	Ar^2	yield %	ee (dr)
1	Ph	Ph	86(**3a**)	>99(20:1)
2	*p*-ClC_6H_4	Ph	95(**3b**)	>99(12:1)
3	*p*-BrC_6H_4	Ph	95(**3c**)	>99(11:1)
4	*m*-BrC_6H_4	Ph	95(**3d**)	>99(10:1)
5	*o*-BrC_6H_4	Ph	32(**3e**)	>99(20:1)
6	*p*-$MeOC_6H_4$	Ph	44(**3f**)	>99(20:1)
7	*p*-MeC_6H_4	Ph	57(**3g**)	>99(15:1)
8	3-Py	Ph	93(**3h**)	>99(12:1)
9	Ph	Cinnamyl	83(**3i**)	>99(20:1)
10	Ph	*p*-ClC_6H_4	95(**3j**)	>99(11:1)
11	Ph	*p*-BrC_6H_4	95(**3k**)	99(14:1)
12	Ph	*m*-BrC_6H_4	92(**3l**)	>99(19:1)
13	Ph	*p*-$MeOC_6H_4$	39(**3m**)	>99(20:1)
14	Ph	*p*-MeC_6H_4	52(**3n**)	>99(17:1)
15	Ph	3-Py	94(**3o**)	>99(19:1)
16	*p*-BrC_6H_4	*p*-BrC_6H_4	99(**3p**)	>99(6:1)
17	*p*-ClC_6H_4	*p*-ClC_6H_4	93(**3q**)	>99(11:1)
18	*p*-MeC_6H_4	*p*-MeC_6H_4	37(**3r**)	>99(13:1)
19	*p*-BrC_6H_4	*p*-MeC_6H_4	81(**3s**)	>99(12:1)
20	*p*-MeC_6H_4	*p*-BrC_6H_4	86(**3t**)	>99(15:1)

[a] Conditions as in Table 1 (entry 12); reaction time: 3–24 h (see SI).

key intermediate. The enolate **III** then undergoes a reverse-electron-demand Diels–Alder reaction with chalcone **2a** to give intermediate **IV** that eventually leads to product **3a**

Table 3. Scope of Formylcyclopropanes[a]

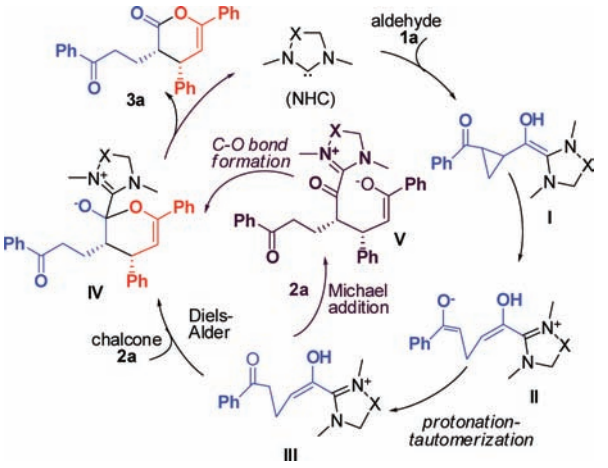


entry	R^1	Ar^1, Ar^2	yield %	ee (dr)
1	*p*-$MeOC_6H_4$	Ph, Ph	66(**3u**)	>99(20:1)
2	*p*-MeC_6H_4	Ph, Ph	59(**3v**)	>99(20:1)
3	*p*-FC_6H_4	Ph, Ph	62(**3w**)	99(20:1)
4	*p*-ClC_6H_4	Ph, Ph	66(**3x**)	>99(20:1)
5	*p*-BrC_6H_4	Ph, Ph	71(**3y**)	>99(20:1)
6	3,4-$Cl_2C_6H_3$	Ph, Ph	65(**3z**)	>99(20:1)
7	3-$NO_2C_6H_4$	Ph, Ph	69(**3aa**)	99(20:1)
8	2-Naphthyl	Ph, Ph	74(**3ab**)	>99(20:1)
9	^{t}Bu *n*-C_5H_{11}	Ph, Ph	49(**3ac**)	>99(20:1)
10	*p*-$MeOC_6H_4$	Ph, *p*-ClC_6H_4	87(**3ad**)	>99(12:1)
11	2-Naphthyl	Ph, *p*-ClC_6H_4	89(**3ae**)	>99(20:1)

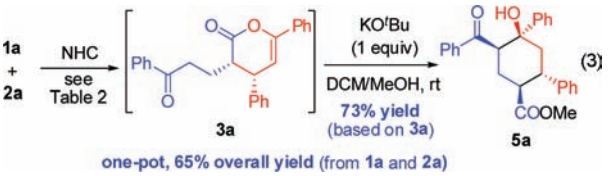
[a] Conditions as in Table 1 entry 12 (see SI).

and the NHC catalyst. A stepwise pathway *via* intermediate **V** cannot be ruled out.

Scheme 1. Postulated Reaction Pathways



The Diels–Alder products **3** bearing ketone groups are amenable for further transformations under simple conditions. For example, compound **3a** could undergo a transesterification followed by a regio- (>9:1 regioselectivity; see SI) and stereoselective aldol reaction in the same reaction mixture to give highly functionalized cyclohexane **5a** as a single stereoisomer with 73% isolated yield (eq 3). Two new chiral centers were formed with nearly complete stereocontrols. The NHC catalysis step before any workup could be combined with the transesterification and aldol reaction steps in a single-pot operation to give **5a** with 65% overall isolated yield under unoptimized conditions. In this way, starting from **1a** and **2a**, product **5a** was obtained as a formal [3 + 3] annulation product in a single operation with good yield and essentially 100% optical purity (eq 3).



In summary, we have captured the likely challenging NHC-bounded enolate intermediates from formylcyclopropanes for highly diastereo- and enantioselective (formal) reverse-electron-demand hetero-Diels–Alder reactions with chalcones. The resulting functionalized δ-lactone products can be easily transformed to highly substituted cyclohexanes with good regio- and stereoselectivities. The scope of NHC-catalyzed (formal) hetero-Diels–Alder reactions, previously mainly limited to highly activated heterodienes, is expanded by using chalcone substrates. Mechanistic studies and new reaction developments of NHC-mediated activation of other constrained rings are being pursued in our laboratory.

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Supporting Information Available. Experimental details. This material is available free of charge via Internet at http://pubs.acs.org.