

Enantioselective Diels–Alder Reactions of Enals and Alkylidene Diketones Catalyzed by N-Heterocyclic Carbenes

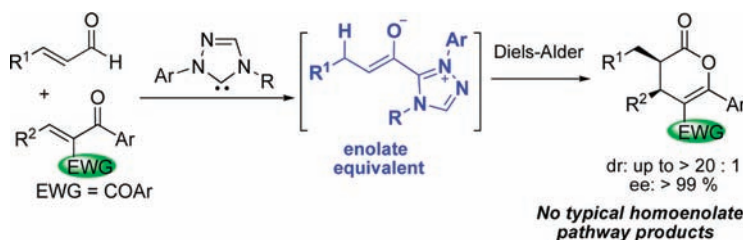
Xinqiang Fang, Xingkuan Chen, and Yonggui Robin Chi*

Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

robinchi@ntu.edu.sg

Received July 15, 2011

ABSTRACT



An electron-withdrawing group was introduced to the α -position of chalcones, and the resulting alkylidene diketones showed new reactivities with enals under the catalysis of N-heterocyclic carbenes (NHCs). Selective activation of enals affords enolate equivalents that undergo highly enantioselective intermolecular Diels–Alder reactions with the alkylidene diketones. No products that might have resulted from typical homoenolate pathways were observed.

The selective activation of readily available substrates with small organic molecule catalysts has become an increasingly promising approach in reaction discovery and synthesis.¹ In the arena of N-heterocyclic carbene (NHC) catalysis, the activation of aldehydes, α -functionalized aldehydes, ketenes, and enals has led to a diverse set of

unique reactive intermediates and new reactions.² In particular, enals have been used to generate homoenolate

(1) For recent reviews, see: (a) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580–591. (b) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621–631. (c) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416–5470. (d) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743. (e) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569. (f) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581. (g) Colby Davie, E. A.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759–5812. (h) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744–5758. (i) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638–4660. (j) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138–6171. (k) MacMillan, D. W. C. *Nature* **2008**, *455*, 304–308. (l) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178–2189. (m) Terada, M. *Synthesis* **2010**, 1929–1982.

(2) Reviews: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655. (b) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000. (c) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691–2698. (d) Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichimica Acta* **2009**, *42*, 55–66. (e) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, DOI: 10.1021/ar2000716. (f) Hirano, K.; Piel, I.; Glorius, F. *Chem. Lett.* **2011**, *40*, 786–791. (g) Chiang, P.-C.; Bode, J. W. *TCI MAIL* **2011**, *149*, 2–17.

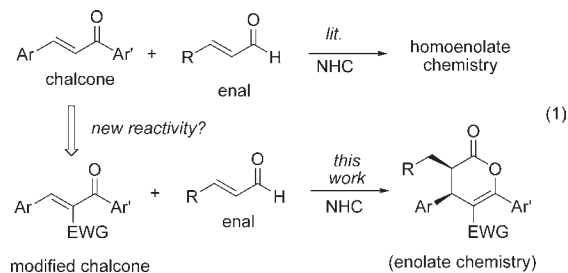
(3) For selected examples, see: (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370–14371. (b) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205–6208. (c) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507–509. (d) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334–5335. (e) Li, Y.; Zhao, Z.-A.; He, H.; You, S.-L. *Adv. Synth. Catal.* **2008**, *350*, 1885–1890. (f) Seayad, J.; Patra, P. K.; Zhang, Y.; Ying, J. Y. *Org. Lett.* **2008**, *10*, 953–956. (g) Yang, L.; Tan, B.; Wang, F.; Zhong, G. *J. Org. Chem.* **2009**, *74*, 1744–1746. For selected examples of NHC mediated enal/enone annulations affording cyclopentene products, see: (h) Nair, V.; Vellalath, S.; Poonoth, S.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736–8737. (i) Chiang, P.-C.; Kaebamrungs, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520–3521. (j) Cardinal-David, B.; Raup, D. E. A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 5345–5347. Also see reviews (ref 2) for additional examples.

(4) The ester enolate equivalents are typically generated from α -functionalized aldehydes and ketenes, as initially described by the groups of Bode, Rovis, Ye, and Smith; see: (a) Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518–9519. (b) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088–15089. (c) Zhang, Y. R.; Lv, H.; Zhou, D.; Ye, S. *Chem.—Eur. J.* **2008**, *14*, 8473–8476. (d) Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. M. *Org. Biomol. Chem.* **2008**, *6*, 1108–1113. (e) Wang, X. N.; Lv, H.; Huang, X. L.; Ye, S. *Org. Biomol. Chem.* **2009**, *7*, 346–350. The potential instability issue of using α -chloroaldehydes for enolate generations was addressed by Bode and co-workers through the use of bisulfite salts as precursors; see: (f) He, M.; Beahm, B. J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 3817–3820.

equivalents for effective reactions, such as enal/enone annulations affording cyclopentenones, as pioneered by the groups of Bode, Glorius, Scheidt, Nair, You, and others.³ The enal β -carbon is involved in the overall formation of the first C–C or carbon–heteroatom bond of the products (the “homoenolate” pathway).³ A selective protonation of the NHC-bound homoenolate β -carbon of enals leading to ester enolate equivalents⁴ as alternative reactive intermediates has also been conceptualized and realized by the groups of Bode, Glorius, and Scheidt.^{5–7} Pioneering studies on enal enolate formations have led to self-redox reactions of enals,⁵ intermolecular azadiene Diels–Alder reactions using electron-deficient enals (such as *trans*-4-oxo-2-butenate),^{6a} and nicely designed intramolecular Michael and aldol reactions.^{6c,d} The use of simpler enals in the direct generation of enolate intermediates for *intermolecular* reactions remained as an unsolved problem until recently at which point the Bode group reported elegant Diels–Alder reactions between simple enals and ketoenones.⁸ In Bode’s work,⁸ they achieved the selective β -enal protonations by using triazolium-based chiral NHC catalysts and weak bases such as DMAP and NMM. The typical homoenolate pathways were largely suppressed for most substrates under the optimized conditions using weak bases. When more electron-deficient enone substrates or strong bases (e.g., DBU) were used, the homoenolate pathway products could still be formed to a large extent.

Our recent observation of the direct generation of NHC-bound enolates from simple enals for intermolecular reactions came as a somewhat unexpected result during our studies in employing enal homoenolate intermediates for cascade reactions.⁹ We examined chalcones with an electron-withdrawing group (EWG) at the α -position (alkylidene diketones) as the electrophiles and found the reactivity modes of the NHC-activated enals were alternated (eq 1). No typical homoenolate pathway products, as previously observed when chalcones were the electrophiles,^{3h,j} were formed in our reactions with the modified chalcone substrates. Instead, a Diels–Alder product

was formed presumably *via* an NHC-bound enolate intermediate generated from an enal.^{5–8}



Our reactions between cinnamaldehyde **1a** and alkylidene diketone **2a** in the presence of NHC catalysts are summarized in Table 1. We initially attempted to generate products that were proposed to result from a homoenolate equivalent intermediate through Michael-type addition of an enal β -carbon to **2a** to form the first C–C bond (e.g., **5a–c**). Somewhat to our surprise, no such products were observed. Instead, a Diels–Alder product **3a** was obtained in excellent yield using imidazolium **A** as the precatalyst and DBU as the base (entry 1, Table 1). The product was formed presumably through an inverse-electron-demand Diels–Alder pathway between an enal-derived NHC-bound enolate ester intermediate and the alkylidene diketone.¹⁰ It is worth noting that previously imidazolium-based NHC catalyst **A** has mainly been used for homoenolate generation.^{3,11}

Further catalyst screening and condition optimization showed that the electronic properties and steric bulkiness of carbene catalysts had profound effects on the reaction outcomes.¹² The use of the triazolium catalysts **B** and **C** led to neither Diels–Alder adducts nor any typical homoenolate pathway products; instead a Stetter product **4a** was obtained in low yield (Table 1, entries 2, 3).¹³ Fortunately we found that the triazolium-based chiral NHC catalyst **D** can mediate our Diels–Alder reaction with 83% yield and excellent diastereo- and enantioselectivities (Table 1, entry 4). Decreasing the catalyst loading did not affect the reaction yields and selectivities obviously (Table 1, entry 5). The Stetter product **4a** was also detected but with low yield (typically less than 5%). Solvent and base screenings indicated that dichloromethane and toluene were not suitable solvents and weaker bases such as DIPEA resulted in lower yields (Table 1, entries 6–8). We also conducted our reactions using conditions employed by Bode.⁸ It is interesting to note that weak bases (e.g., DMAP, NMM) cannot mediate our reactions efficiently (Table 1, entries 9–12),

(5) For protonation of the enal β -carbons leading to self-redox formations of esters/amides/acids, see: (a) Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873–3876. (b) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905–908. (c) Zeitler, K. *Org. Lett.* **2006**, *8*, 637–640. (d) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799. (e) Maki, B. E.; Patterson, E. V.; Cramer, C. J.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 3942–3945.

(6) For protonation of the enal β -carbons leading to enolate intermediates for C–N and C–O bond formations of the enal α -carbons, see: (a) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418–8420. (b) Burstein, C.; Tschan, S.; Xie, X. L.; Glorius, F. *Synthesis* **2006**, 2418–2439. (c) Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3107–3110. (d) Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098–10099.

(7) Enolates are believed to be involved as intermediates in the enal homoenolate reactions after the enal β -carbon forms the first new C–C or carbon–heteroatom bonds with the substrate electrophiles; see refs 3h, 3j, and 9.

(8) Kaeobamrung, J.; Kozłowski, M. C.; Bode, J. W. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20661–20665.

(9) Fang, X.; Jiang, K.; Xing, C.; Hao, L.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 1910–1913.

(10) Stepwise pathways *via* Michael reactions followed by intramolecular enol ester formations cannot be ruled out. Thus this reaction may be considered as a “formal” Diels–Alder reaction.

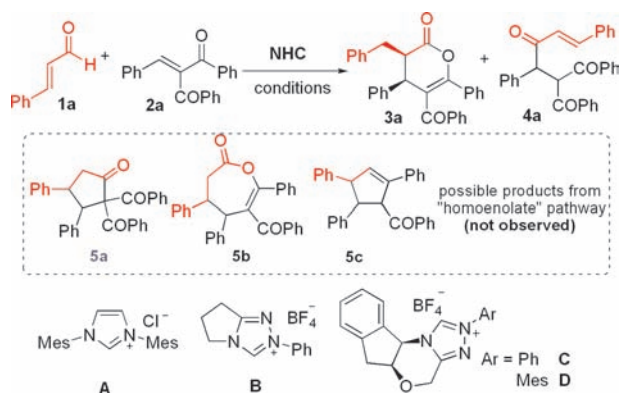
(11) For an example of imidazolium-based NHC-mediated enolate generations in competing with homoenolate generations, see ref 6b.

(12) For selected similar observations, see: (a) Ryan, S. J.; Lisa Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176–14177. (b) Hirano, K.; Piel, I.; Glorius, F. *Adv. Synth. Catal.* **2008**, *350*, 984–988. (c) Wang, L.; Thai, K.; Gravel, M. *Org. Lett.* **2009**, *11*, 891–893. Also see ref 3a, 5c, and 6a.

(13) For a very recent related report of enantioselective Stetter reactions of enals with nitroalkenes, see: DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 10402–10405.

which is in contrast to Bode's observations where weak bases such as DMAP were optimal and strong bases (e.g., DBU) led to significant competing (or even dominated) homoenolate pathway products. Bases stronger than DBU (e.g., TBD)¹⁴ worked effectively as well in our Diels–Alder reactions (Table 1, entry 13). In all conditions studied, regardless of the bases and solvents used, no homoenolate pathway products (e.g., **5a–c**) were detected. This absence of typical homoenolate pathway products is significantly different from literature reports that use chalcones as substrates in NHC catalysis.^{3h,j}

Table 1. NHC-Catalyzed Reaction of Enal **1a** and Alkylidene Diketones **2a**^a



entry	NHC	base	solvent	yield % ^b		dr ^c	ee % ^d
				3a	4a		
1	A	DBU	THF	92	0	5:1	-
2	B	DBU	THF	0	21	-	-
3	C	DBU	THF	0	33	-	-
4	D	DBU	THF	83	6	12:1	>99%
5^e	D	DBU	THF	82	<5	12:1	> 99%
6	D	DBU	CH ₂ Cl ₂	0	<5	-	-
7	D	DBU	toluene	44	9	10:1	>99%
8	D	DIPEA	THF	56	0	10:1	>99%
9	D	DMAP	THF	0	0	-	-
10 ^f	D	DMAP	CH ₂ Cl ₂	0	0	-	-
11 ^f	D	NMM	CH ₂ Cl ₂	0	0	-	-
12	D	NMM	THF	<5	0	-	-
13 ^e	D	TBD	THF	86	<5	11:1	>99%

^a **1a** (0.2 mmol), **2a** (0.1 mmol), NHC (30 mol %), base (30 mol %), 12 h. ^b Isolated yield. ^c Diastereoselectivity of **3a**, determined via ¹H NMR analysis of unpurified reaction mixtures; relative stereochemistry was determined via X-ray. ^d Enantiomeric excess of **3a**, determined via chiral-phase HPLC analysis; absolute configuration was determined via analogy (see SI). ^e Catalyst (20 mol %), base (20 mol %). ^f Reaction temperature was 40 °C. Mes = 2,4,6-trimethylphenyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, THF = tetrahydrofuran, DIPEA = *N,N*-diisopropylethylamine, DMAP = 4-(dimethylamino)pyridine, NMM = *N*-methylmorpholine, TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene.

(14) (a) Raup, D. E. A.; Cardinal-David, B.; Holte, D.; Scheidt, K. A. *Nat. Chem.* **2010**, *2*, 766–771. (b) Cohen, D. T.; Cardinal-David, B.; Roberts, J. M.; Sarjeant, A. A.; Scheidt, K. A. *Org. Lett.* **2011**, *13*, 1068–1071.

A variety of β -aryl enals were examined to react with alkylidene diketone **2a** under our standard Diels–Alder reaction condition (Table 2, products **3a–3i**). In all cases the reactions proceeded with exceptionally high diastereo- and enantioselectivities, and the products were isolated in good yields with essentially 100% optical purities. We then examined the β -substituents (R^2) on alkylidene diketones **2**. The electronic properties of R^2 aryl substituents showed little observable effects on the reaction outcomes with respect to both yields and stereoselectivities (Table 2, products **3j–3o**). Finally, we found that substrates **2** with different R^3 substituents could also react with enals to afford the corresponding Diels–Alder products with consistently high diastereo- and enantioselectivities (Table 2, products **3p–3t**). A notable observation was that substrate **2** with an electron-donating methyl group on the R^3 substituent reacted much slower and a longer reaction time (42 h) was necessary to achieve an acceptable yield (Table 2, product **3u**). More electron-deficient **2** usually behaves as a more effective substrate for the Diels–Alder reactions. This electronic effect appears to be different from Bode's reactions⁹ where more electron-deficient electrophiles tended to give more homoenolate pathway adducts. It should be noted that we also checked substrates **2** with EWGs other than $-\text{CO}_2\text{Ar}$, such as $-\text{CO}_2\text{Et}$, $-\text{CN}$, and a phenyl group. These substrates failed to give Diels–Alder or homoenolate pathway products. Substrate **2** with R^2 as alkyl groups showed low reactivities toward enals as well.

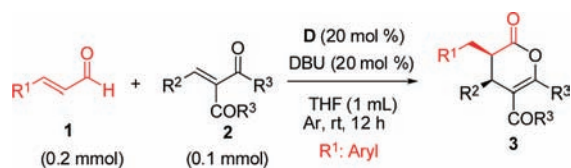
We next checked the tolerance of enals with β -alkyl substituents such as *trans*-2-pentenal under the standard conditions used above for the Diels–Alder reactions. To our surprise, with trizolium **D** as the catalyst, only a Stetter type reaction¹³ occurred without the detection of any Diels–Alder adducts or any products from the typical homoenolate pathways. We then went back to identify catalysts and conditions that could mediate Diels–Alder reactions using β -alkyl enal substrates as the enolate precursors. At last achiral imidazolium catalyst **A** (Table 3, entry 1) was found to mediate the reaction between β -alkyl enals with alkylidene diketones to exclusively give Diels–Alder products without the detection of Stetter products or possible homoenolate pathway products. The scope of the β -alkyl enal Diels–Alder reactions was then briefly explored, as summarized in Table 3. Additional attempts to get an enantioselective version of the reactions were unsuccessful.

Our postulated reaction pathways are summarized in Scheme 1.¹⁵ The reactions start with the formation of Breslow intermediate **I** between enal **1** and an *in situ* generated NHC. Protonation of the enal β -carbon of **I** results in an NHC-bounded enolate ester intermediate **II** that readily undergoes a Diels–Alder reaction with alkylidene diketone to eventually give the products.

In conclusion, we have found by introducing an EWG to the α -positions of chalcone substrates the typical reactivity modes of NHC-activated enals can be alternated. The

(15) For a recapitulative discussion of further transformations of Breslow intermediates, see: Struble, J. R.; Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 957–960.

Table 2. Substrate Scope of NHC Catalyzed Formal Diels–Alder Reaction with β -Aryl Enals

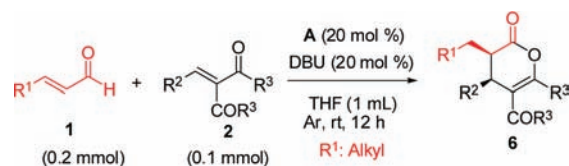


3	R ¹	R ² , R ³	yield, % ^a	ee % ^b (dr) ^c
3a	Ph	Ph, Ph	82	99 (12:1)
3b	4-Br-Ph	Ph, Ph	85	99 (16:1)
3c	4-F-Ph	Ph, Ph	84	99 (>20:1)
3d	3-F-Ph	Ph, Ph	83	99 (>20:1)
3e	4-Me-Ph	Ph, Ph	75	99 (>20:1)
3f	4- ⁱ Pr-Ph	Ph, Ph	61	99 (>20:1)
3g	2-thienyl	Ph, Ph	71	99 (>20:1)
3h	1-naphthyl	Ph, Ph	76	99 (>20:1)
3i	2-naphthyl	Ph, Ph	80	99 (>20:1)
3j	Ph	4-Br-Ph, Ph	80	99 (17:1)
3k	4-F-Ph	4-Br-Ph, Ph	63	99 (>20:1)
3l	Ph	4- ⁱ Pr-Ph, Ph	76	98 (>20:1)
3m^d	4-Me-Ph	4- ⁱ Pr-Ph, Ph	56	99 (20:1)
3n	Ph	3-OMe-Ph, Ph	88	99 (>20:1)
3o	3-F-Ph	3-OMe-Ph, Ph	79	99 (20:1)
3p^d	Ph	Ph, 4-Br-Ph	74	99 (12:1)
3q	4-F-Ph	Ph, 4-Br-Ph	65	99 (20:1)
3r	Ph	3-OMe-Ph, 4-Br-Ph	72	99 (17:1)
3s^d	Ph	Ph, 4-F-Ph	80	97 (>20:1)
3t	Ph	Ph, 4-Cl-Ph	84	99 (>20:1)
3u^e	Ph	Ph, 4-Me-Ph	50	99 (>20:1)
3v	Ph	Ph, Me	<10	N.D.

^a Isolated yield based on **2**. ^b Enantiomeric excess of **3**, determined *via* chiral phase HPLC, ee > 99% is reported as 99%. ^c Diastereoselectivity of **3**, determined *via* ¹H NMR analysis of unpurified reaction mixtures. ^d TBD (20 mol %) was used as the base to get better yields. ^e Reaction for 42 h.

selective generation of ester enolates from simple enals was realized to facilitate effective Diels–Alder reactions with alkyldiene diketones to give fully substituted cyclic enol esters. The ketone moieties from the EWGs offer additional possibilities for further transformations of the reaction products. With β -aryl enal substrates, the Diels–Alder products were obtained in essentially 100% optical purities with good yields. With β -alkyl substrates, the use of a bulky imidazolium-based NHC catalyst was necessary to obtain the Diels–Alder products. More electron-deficient alkyldiene diketones were found to favor this process. In all cases, no products that might have resulted from the typical homoenolate pathways were observed in our reactions. Further investigation of the new reactivities of modified chalcones in the presence of NHC catalysts is in progress.

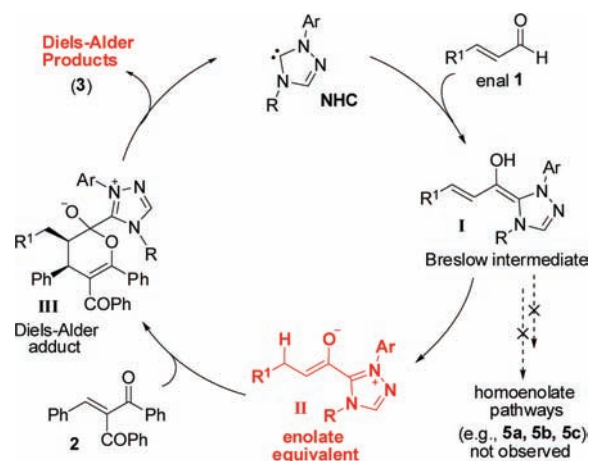
Table 3. Diels–Alder Reaction with β -Alkyl Enal Substrates



6	R ¹	R ² , R ³	yield % ^a	dr ^b
6a	Me	Ph, Ph	65	5:1
6b	Et	Ph, Ph	57	5:1
6c	<i>n</i> -C ₅ H ₁₁	Ph, Ph	79	3:1
6d	Et	4-Br-Ph, Ph	64	3:1
6e	Et	3-MeO-Ph, Ph	53	5:1

^a Isolated yields of both diastereomers based on **2**. ^b Determined *via* ¹H NMR analysis of unpurified reaction mixtures; relative stereochemistry was determined *via* ¹H NMR analysis.

Scheme 1. Postulated Reaction Pathways



Acknowledgment. We thank the Singapore National Research Foundation (NRF), Singapore Economic Development Board (EDB), GlaxoSmithKline (GSK), and Nanyang Technological University (NTU) for generous financial support as well as Dr. Y. Li and Dr. R. Ganguly (X-ray structure; NTU) and Ms. M.-J. Han (optical rotation measurements; a short-time visitor at NTU). We also appreciate the comments and suggestions from referees of this manuscript.

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