Organocatalysis

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A Highly Regio- and Stereoselective Cascade Annulation of Enals and Benzodi(enone)s Catalyzed by N-Heterocyclic Carbenes**

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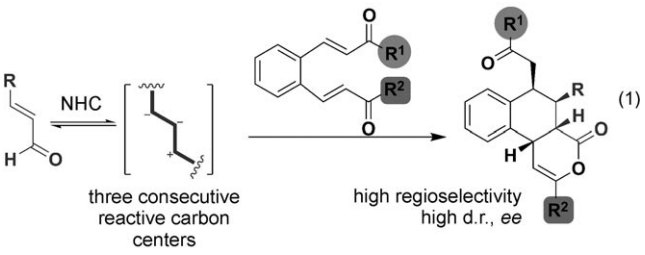
The rapid catalytic construction of relatively complex molecules in a highly selective manner is an attractive goal in organic synthesis.[1] In the area of N-heterocyclic carbene (NHC) catalysis, the unconventional NHC-mediated activation of enal compounds has led to a diverse set of new reactions,[2] such as lactone and lactam formations,[3] cycloaddition reactions,[4] Michael reactions,[5] and self-redox ester formations.[6,7] This diversity exists in the catalytic formation of multifarious intermediates that include activated carboxylates, enolates, and homoenolate equivalents.[8] Of particular interest to us is the generation of three consecutive reactive carbon centers [Eq. (1)], which opens an opportunity for the

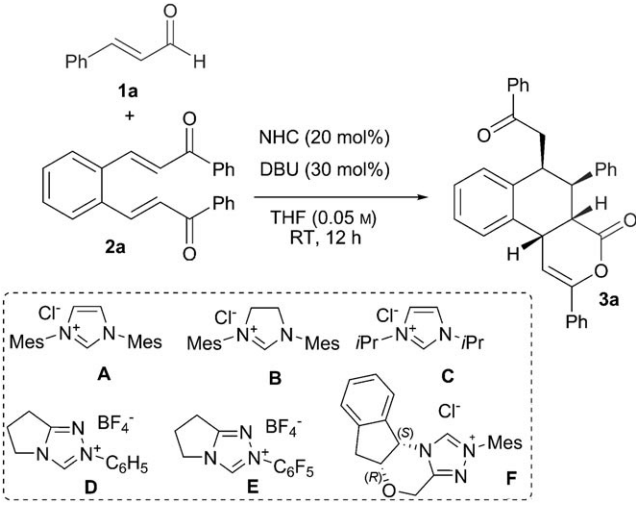


(1)

rapid assembly of relatively complex molecules containing rings and multiple chiral centers. Recently, the research groups of Nair,[9] Bode,[10] and Scheidt[11] reported enal/enone condensations to form cyclopentene derivatives using NHC or NHC/Lewis acid cooperative catalysts. Sanchez-Larios and Gravel reported a diastereoselective racemic indane synthesis via NHC-mediated activation of aldehydes for Stetter–Michael cascade reactions with benzodi(enone)s.[12a] Herein, we disclose a new annulation of enals and di(enone)s that generates benzotricyclic products with exceptionally high regio-, diastereo-, and enantioselectivities [Eq. (1)]. All of the three reactive carbon centers of the enals are involved in new C–C and C–O bond formations to generate the cascade products containing four stereogenic centers. Mechanistically, the reaction proceeds exclusively through Michael-type additions of the β- and α-carbon atoms of the enals to the two enone branches of the di(enone)s, and subsequent intramolecular enol ester formation to yield the products. Cyclopropene- or indane-based adducts, as might be postulated based on previous studies,[9–11,12] were not observed as products in our reactions.

We first studied the reaction between cinnamaldehyde (**1a**) and benzodi(enone) **2a** using imidazolium precatalysts (Table 1, entries 1–3). We initially expected a product that would result from a decarboxylation[9–11] as the last step. Surprisingly, no such cyclopentene-containing products were detected. Instead, benzotricyclic acylated enol **3a** was formed

Table 1: Annulation of enal **1a** and di(enone) **2a** mediated by NHCs.[a]



Entry	NHC	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**A**	76	12:1	–
2	**B**	40	20:1	–
3	**C**	0	–	–
4	**D**	95	20:1	–
5	**E**	0	–	–
6	**F**	51	10:1	99
7[e]	**F**	**84**	**13:1**	**99**

[a] Reaction conditions: **1a** (0.225 mmol), **2a** (0.15 mmol). [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of unpurified reaction mixtures. [d] Major diastereoisomer, determined by HPLC analysis on a chiral stationary phase. The configuration of **3a** was determined by X-ray crystallography of its derivative **3a′** (see [Eq. (2)] and the Supporting Information). [e] Two equivalents of **1a** was used and one equivalent of $MgSO_4$ was added. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Mes = 2,4,6-trimethylphenyl, THF = tetrahydrofuran.

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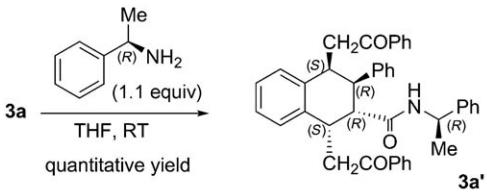
as the sole cascade product in good yield and diastereoselectivity using catalyst **A** (Table 1, entry 1). Screening of catalysts and reaction conditions revealed that triazolium-based NHCs were also effective catalysts (Table 1, entry 4). High enantioselectivity was achieved with the aminoindanol-derived triazolium catalyst **F**, which was first described by Bode and co-workers[4a] (Table 1, entry 6).[13] When two equivalents of enal **1a** was used and $MgSO_4$ was added as an additive,[14] product **3a** was obtained in 84% yield and >99% *ee* (Table 1, entry 7). The steric and electronic properties of both imidazolium- and triazolium-based NHCs significantly affected the reaction outcomes,[2] and no conversion was observed when using catalysts **C** or **E** (Table 1, entries 3 and 5). The relative and absolute configuration of the cascade product was determined by X-ray crystallography[20] after derivatization of **3a** into **3a′** [Eq. (2)].



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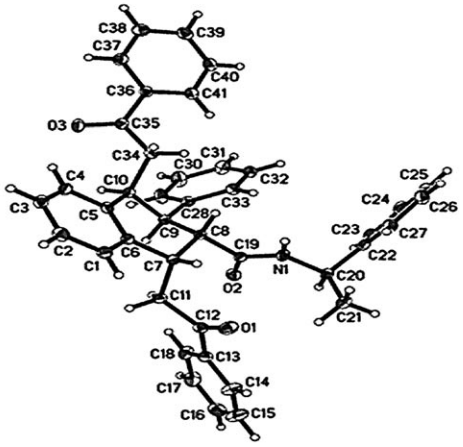
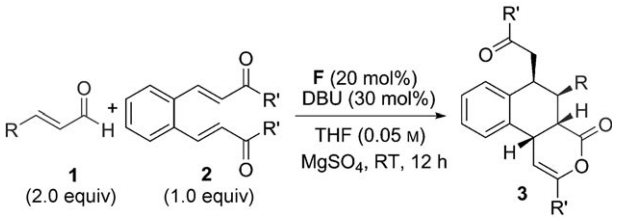


The scope of the enal and benzodi(enone) substrates was then examined. A variety of β-(hetero)aryl-substituted enals reacted smoothly with di(enone) **2a** and gave the products in good yield and excellent stereoselectivity (Table 2, entries 1–5). The use of β-alkyl-substituted enal **1f** afforded product **3f** with similar stereoselectivity, albeit in moderate yield (Table 2, entry 6). The derivatives of benzodi(enone) **2**, with either electron-donating or electron-withdrawing substitutes on the aryl rings next to the carbonyl groups, were all tolerated in the reactions and gave essentially optically pure products (Table 2, entries 7–16). Mechanistically, it is worth noting that enone compounds bearing electron-donating substitutes showed lower reactivities towards enal substrates. In such cases, a greater quantity of enal and prolonged reaction time were needed to achieve acceptable yields (Table 2, entries 7 and 12). The methyl-substituted benzodi(enone) did not react with enals under the conditions we tested (Table 2, entry 16). The reactivity differences present with enones possessing different electronic properties are consistent with those observed in conjugate addition reactions where electron-rich enones are generally poor Michael acceptors.

Enlightened by the reactivity difference between electron-rich and electron-poor di(enone)s (Table 2, entries 7–16), we examined unsymmetric benzodi(enone)s with two different substitutes to gain additional mechanistic insight (Table 3). For example, **4a** was treated with enals **1a**,**b** and gave cascade products with exceptionally high regioselectivity, excellent stereoselectivity, and good yield (Table 3, entries 1 and 2); the minor regioisomers were not detectable by ^{1}H NMR spectroscopy. The X-ray crystal structure[20] of **5a** (see the Supporting Information) confirmed that the reaction proceeded exclusively through an overall addition of the enal β-carbon atom to the electron-poor branch (R^1) of di(enone) **4** to form the first new C–C bond in the product. The high regioselectivity appears to be quite general for a wide range of unsymmetric di(enone)s **4b–e** (Table 3,

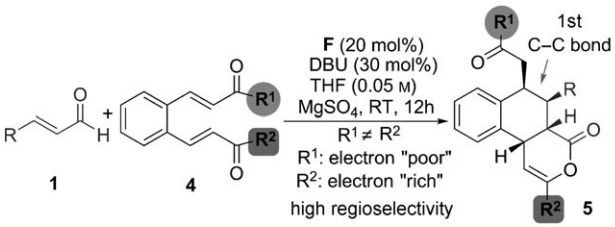
Table 2: Annulation reactions of enals **1** with benzodi(enone)s **2**.



Entry	**1**, R	**2**, R′	Product	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	**1a**, Ph	**2a**, Ph	**3a**	84	13:1	99
2	**1b**, 4-BrC_6H_4	**2a**	**3b**	80	18:1	99
3	**1c**, 4-$OMeC_6H_4$	**2a**	**3c**	80	14:1	99
4	**1d**, 2-naphthyl	**2a**	**3d**	70	11:1	99
5	**1e**, 2-thienyl	**2a**	**3e**	78	10:1	99
6	**1f**, *n*-C_7H_{15}	**2a**	**3f**	43	10:1	99
7[d]	**1a**	**2b**, 4-$OMeC_6H_4$	**3g**	53	14:1	96
8	**1a**	**2c**, 3,4-$Cl_2C_6H_3$	**3h**	75	20:1	97
9	**1g**, 4-FC_6H_4	**2c**	**3i**	70	11:1	99
10	**1a**	**2d**, 4-PhC_6H_4	**3j**	61	20:1	98
11	**1b**	**2e**, 4-MeC_6H_4	**3k**	58	20:1	98
12[d]	**1a**	**2e**	**3l**	70	12:1	99
13	**1b**	**2f**, 4-ClC_6H_4	**3m**	74	20:1	99
14	**1a**	**2g**, 4-BrC_6H_4	**3n**	82	17:1	99
15	**1a**	**2h**, 4-FC_6H_4	**3o**	77	20:1	98
16	**1a**	**2i**, Me	**3p**	0	–	–

[a] Yield of isolated product based on **2**. [b] Determined by ^{1}H NMR analysis of unpurified reaction mixtures. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Four equivalents of cinnamaldehyde, 24 h.

Table 3: Regioselective annulation of enals **1** with unsymmetric benzodi(enone)s **4**.

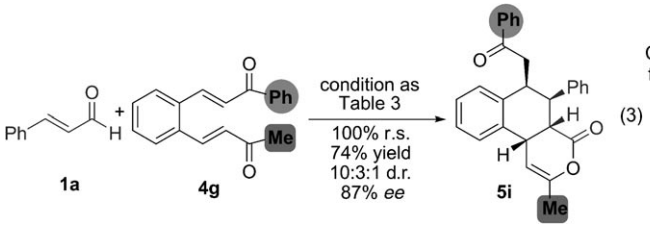


Entry	**1**, R	**4**, R^1, R^2	Product	Yield [%][a]	r.s.[b]	d.r.[c]	*ee* [%][d]
1	**1b**	**4a**, 4-BrC_6H_4, Ph	**5a**	73	100:0	20:1	97
2	**1a**	**4a**	**5b**	81	100:0	20:1	98
3	**1a**	**4b**, 4-BrC_6H_4, 4-MeC_6H_4	**5c**	82	100:0	19:1	99
4	**1h**, 4-*i*PrC_6H_4	**4b**	**5d**	74	100:0	11:1	99
5	**1a**	**4c**, 3,4-$Cl_2C_6H_3$, 4-MeC_6H_4	**5e**	84	100:0	20:1	99
6	**1b**	**4d**, 4-ClC_6H_4, 4-$OMeC_6H_4$	**5f**	69	100:0	14:1	94
7	**1a**	**4e**, Ph, 4-$OMeC_6H_4$	**5g**	67	15:1	20:1	90
8	**1a**	**4f**, Ph, 4-MeC_6H_4	**5h**	75	2:1	10:1	98

[a] Yield of isolated product based on **4**. [b] Regioselectivity was estimated by ^{1}H NMR analysis of unpurified reaction mixtures. For **5a–f** the minor regioisomer was not detectable. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis on a chiral stationary phase. r.s. = regioselectivity.

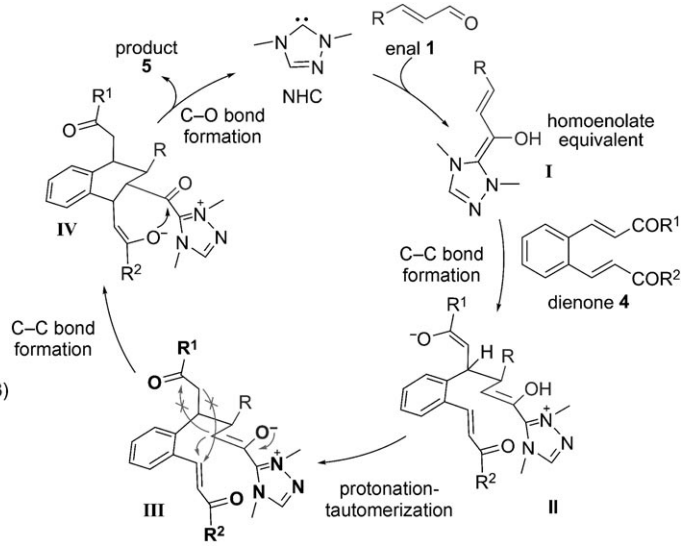
entries 3–7). Regioselectivity was low only when the two substitutes on the unsymmetric di(enone)s, such as the 4-MeC_6H_4/Ph pairs in di(enone) **4f**, have very similar electronic properties.

A reaction of special mechanistic interests in the unsymmetric di(enone) series is the reaction between Ph/Me-substituted benzodi(enone) **4g** and enal **1a** [Eq. (3)].



The observed preference in regioselectivity of Ph- over Me-substituted enone (in the first C–C bond formation) is consistent with a direct Michael addition pathway.[15] This study further confirms that electronic effects play a profound role in the regioselective addition of an enal β-carbon atom to enones. In contrast, steric effects determine the regioselectivities in NHC-mediated intramolecular benzoin addition of aldehydes to ketones, in which the sterically smaller methyl ketone reacts preferentially over the larger phenyl ketone, as observed by Lathrop and Rovis[16a] as well as Takikawa and Suzuki.[16b]

Our postulated reaction pathways are summarized in Scheme 1. The initial formation of Breslow intermediate **I** as a homoenolate equivalent[17] is followed by a Michael-type addition to one branch of di(enone) **4** to give intermediate **II**. The potential complication of this cascade reaction lies in the multiple feasible reaction pathways of intermediate **II**. According to the studies by Sanchez-Larios and Gravel[12a] the intermediate **II** might undergo an intramolecular Michael addition of the α-carbon atom of the ketone to the enone to form an indane compound. Based on previous work on enal/enone annulations in forming cyclopentenes,[9–11] this intermediate (**II**) might also undergo an aldol reaction followed by β-lactone formation and subsequent decarboxylation. Neither of the pathways described in the literature was observed in our reactions. Instead, protonation and tautomerization of intermediate **II** gives intermediate **III**, which exclusively undergoes intramolecular 1,4-addition of the enal α-carbon atom to the other branch of the di(enone) to afford intermediate **IV**. The last step of the catalytic cycle is the formation of an enol ester to generate the cascade product **5** with the release of the NHC catalyst.[18] Attempts to capture intermediate **II**/**III** with alcohol and amine nucleophiles were unsuccessful,[19] which suggests that the conversion of intermediate **II** into product **5** occurs spontaneously with excellent stereocontrol of the remaining two new stereogenic centers.



Scheme 1. Postulated catalytic pathways for NHC-mediated annulation of enals and di(enone)s.

In summary, we have developed a new annulation of di(enone) and enal substrates mediated by NHCs to generate substituted multicyclic compounds with high regio- and stereoselectivities. The observed regioselectivity is consistent with a Michael-type addition of the enal β-carbon atom to the enone to form the first new C–C bond of the cascade product. Our method provides a rapid entry to relatively complex structures from simple starting materials in a highly selective

manner. Further studies with respects to additional molecular complexity and mechanistic insights are in progress.

Experimental Section

General procedure for annulation reactions: Benzodi(enone) (0.15 mmol), enal (0.3 mmol, 2.0 equiv), triazolium salt **F** (0.011 g, 0.03 mmol), and anhydrous $MgSO_4$ (0.018 g, 0.15 mmol) were added to a 25 mL two-necked, oven-dried flask. The flask was then evacuated and refilled with dry N_2. Anhydrous THF (3 mL) was added followed by DBU (0.0069 g, 0.045 mmol). The reaction mixture was stirred at RT for 12 h. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography on silica gel with hexanes/ethyl acetate (4:1) as eluent to afford the annulation product.

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[1] For selected reviews and examples of organocatalytic cascade reactions (especially in the area of amine-based catalysis), see: a) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167–178; b) A. Alba, X. Companyo, M. Viviano, R. Rios, *Curr. Org. Chem.* **2009**, *13*, 1432–1474; c) B. Westermann, M. Ayaz, S. S. Van Berkel, *Angew. Chem.* **2010**, *122*, 858–861; *Angew. Chem. Int. Ed.* **2010**, *49*, 846–849; d) X. Yu, W. Wang, *Org. Biomol. Chem.* **2008**, *6*, 2037–2046; e) A. Michrowska, B. List, *Nat. Chem.* **2009**, *1*, 225–228; f) N. T. Jui, E. C. Y. Lee, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 10015–10017; g) G. Bencivenni, L. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M. Song, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7336–7339; *Angew. Chem. Int. Ed.* **2009**, *48*, 7200–7203; h) S. Brandau, E. Maerten, K. A. Jorgensen, *J. Am. Chem. Soc.* **2006**, *128*, 14986–14991; i) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Angew. Chem.* **2003**, *115*, 4365–4369; *Angew. Chem. Int. Ed.* **2003**, *42*, 4233–4237.

[2] Reviews: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606–5655; b) V. Nair, S. Vellalath, B. P. Babu, *Chem. Soc. Rev.* **2008**, *37*, 2691–2698; c) N. Marion, S. Silvia Díez-González, S. P. Nolan; *Angew. Chem.* **2007**, *119, 3046–3058; Angew. Chem. Int. Ed.* **2007**, 46, 2988–3000; *Angew. Chem.* **2007**, *119*, 3046–3058; *Angew. Chem. Int. Ed.* **2007**, *46*, 2988–3000.

[3] Early discoveries: a) C. Burstein, F. Glorius, *Angew. Chem.* **2004**, *116*, 6331–6334; *Angew. Chem. Int. Ed.* **2004**, *43*, 6205–6208; b) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370–14371; c) M. He, J. W. Bode, *Org. Lett.* **2005**, *7*, 3131–3134.

[4] a) M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418–8420; b) A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 5334–5335.

[5] a) E. M. Phillips, M. Wadamoto, A. Chan, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 3167–3170; *Angew. Chem. Int. Ed.* **2007**, *46*, 3107–3110; b) Y. Li, X. Q. Wang, C. Zheng, S. L. You, *Chem. Commun.* **2009**, 5823–5825.

[6] a) A. Chan, K. A. Scheidt, *Org. Lett.* **2005**, *7*, 905–908; functional aldehydes (e.g. α-haloaldehydes) can behave as enal equivalents, see: b) N. T. Reynolds, J. R. de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 9518–9519.

[7] For a NHC-mediated activation of α,β-unsaturated esters, see: C. Fischer, S. W. Smith, D. A. Powell, G. C. Fu, *J. Am. Chem. Soc.* **2006**, *128*, 1472–1473.

[8] For relevant discussions, see: a) S. S. Sohn, J. W. Bode, *Org. Lett.* **2005**, *7*, 3873–3876; b) J. R. Struble, J. Kaeobamrung, J. W. Bode, *Org. Lett.* **2008**, *10*, 957–960; c) B. E. Maki, E. V. Patterson, C. J. Cramer, K. A. Scheidt, *Org. Lett.* **2009**, *11*, 3942–3945.

[9] V. Nair, S. Vellalath, S. Poonoth, E. Suresh, *J. Am. Chem. Soc.* **2006**, *128*, 8736–8737.

[10] P.-C. Chiang, J. Kaeobamrung, J. W. Bode, *J. Am. Chem. Soc.* **2007**, *129*, 3520–3521.

[11] a) M. Wadamoto, E. M. Phillips, T. E. Reynolds, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 10098–10099; b) B. Cardinal-David, D. E. A. Raup, K. A. Scheidt, *J. Am. Chem. Soc.* **2010**, *132*, 5345–5347.

[12] a) E. Sanchez-Larios, E. Gravel, *J. Org. Chem.* **2009**, *74*, 7536–7539; for other selected reports of the reactions involving benzodi(enone)s, see: b) C. L. Oswald, J. A. Peterson, H. W. Lam, *Org. Lett.* **2009**, *11*, 4504–4507; c) C. Navarro, A. G. Csaky, *Org. Lett.* **2008**, *10*, 217–219; d) P. M. Brown, N. Käppel, P. J. Murphy, S. J. Coles, M. B. Hursthouse, *Tetrahedron* **2007**, *63*, 1100–1106.

[13] Rovis also initially used similar aminoindanol-derived triazoliums, see: a) M. S. Kerr, J. R. de Alaniz, T. Rovis, *J. Org. Chem.* **2005**, *70*, 5725–5728; b) H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797.

[14] For an example using $MgSO_4$ as an additive, see: J. R. de Alaniz, M. S. Kerr, J. L. Moore, T. Rovis, *J. Org. Chem.* **2008**, *73*, 2033–2040.

[15] A Benzoin–Cope rearrangement mechanism proposed by Bode and co-workers (Ref. [10]) is also possible if the Cope rearrangement step is slower than the reversible benzoin reaction step.

[16] a) S. P. Lathrop, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 13628–13630; b) H. Takikawa, K. Suzuki, *Org. Lett.* **2007**, *9*, 2713–2716.

[17] For reports involving homoenolate equivalent intermediates, see: a) V. Nair, S. Vellalath, M. Poonoth, R. Mohan, E. Suresh, *Org. Lett.* **2006**, *8*, 507–509; b) E. M. Phillips, T. E. Reynolds, K. A. Scheidt, *J. Am. Chem. Soc.* **2008**, *130*, 2416–2417; c) V. Nair, B. P. Babu, S. Vellalath, E. Suresh, *Chem. Commun.* **2008**, 747–749; also see Refs. [2b, 3a, and 3c]; for general reviews on homoenolate equivalents, see: d) N. H. Werstiuk, *Tetrahedron* **1983**, *39*, 205–268; e) D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376–2410; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282–2316.

[18] An inverse-electron-demand hetero-Diels–Alder process of intermediate **II/III** that leads to the cascade product cannot be ruled out.

[19] For examples of intermediate trapping, see: a) M. Movassaghi, M. A. Schmidt, *Org. Lett.* **2005**, *7*, 2453–2456; b) P. Chiang, Y. Kim, J. W. Bode, *Chem. Commun.* **2009**, 4566–4568; c) J. W. Bode, S. S. Sohn, *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799; d) S. D. Sarkar, A. Studer, *Org. Lett.* **2010**, *12*, 1992–1995; e) S. D. Sarkar, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2010**, *132*, 1190–1191; f) V. Nair, B. P. Babu, S. Vellalath, V. Varghese, A. E. Raveendran, E. Suresh, *Org. Lett.* **2009**, *11*, 2507–2510; also see Ref. [13b].

[20] CCDC 807125 (**3a′**) and 807126 (**5a**) contain 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.

