

Cascade Olefin Isomerization/Intramolecular Diels–Alder Reaction Catalyzed by N-Heterocyclic Carbenes**

Marcin Kowalczyk and David W. Lupton*

Abstract: The addition of an N-heterocyclic carbene to the carbonyl group of an $\alpha,\beta,\gamma,\delta$ -unsaturated enol ester affords a hemiacetal azolium intermediate that enables a cascade olefin isomerization/Diels–Alder reaction, for which mechanistic studies implicate Lewis base catalysis. Preliminary studies into the utility of the products have been undertaken with reductive and oxidative cleavage, giving materials for potential use in complex-target synthesis.

The capacity of N-heterocyclic carbenes (NHCs)^[1] to engage with non-aldehyde-containing substrates introduces exciting opportunities in reaction discovery.^[1h] In 2009, we reported an early example of nucleophilic NHC catalysis with ester substrates.^[2,3] Since then, NHC-catalysis with esters, and starting materials in the ester oxidation state, has received increased attention.^[4] In most instances, these substrates (i.e. **1**) provide acyl azolium intermediates (i.e. **2**),^[5] which then engage in a remarkable array of reaction cascades.^[6,7] However, in certain cases hemiacetal azolium species **3**,^[8] a direct precursor to the acyl azolium intermediate, can be applied in reaction discovery. For example hemiacetal azolium species **3a** undergoes sigmatropic rearrangement in the transformation of enol ester **4** to dihydropyranone **5** [Eq. (1)].^[2,6c] This mechanism is supported by the work of Bode and co-workers, who exploited hemiacetal azolium intermediates derived from kojic acid in a related reaction.^[9a] Despite these observations and the intense research activity on NHC catalysis, the hemiacetal azolium intermediate is yet to be exploited in any other NHC-catalyzed transformations.

Recently we became intrigued by the potential of the hemiacetal azolium intermediate to enable olefin isomerization reactions (Figure 1). Olefin-containing materials are ubiquitous and their isomerization, particularly to unstable isomers, can be challenging.^[10,11] We postulated that the NHC-mediated formation of hemiacetal azolium species **3b** would eliminate the intrinsic stabilizing effect of conjugation within dienyl ester **6**, thereby lowering the barrier for olefin isomerization, and enabling reaction discovery [Eq. (2)]. Herein, we describe the realization of this strategy with the

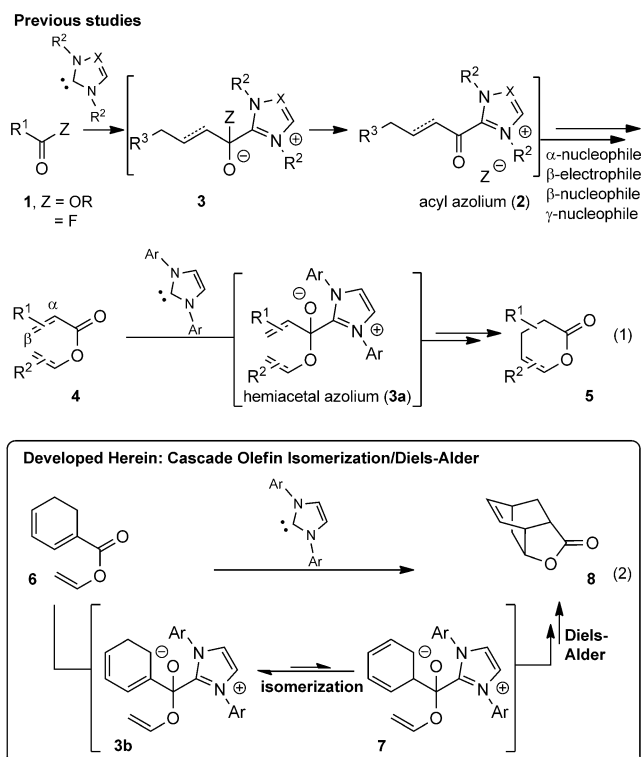


Figure 1. NHC-mediated reactions via hemiacetal azolium intermediates.

NHC-catalyzed cascade olefin isomerization/Diels–Alder reaction. In addition to demonstrating a novel application of the hemiacetal azolium intermediate, this study defines a concise entry to functionalized bicyclo[2.2.2]octanes (i.e. **8**), motifs found in a range of natural products.

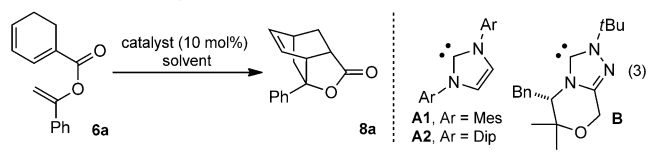
Our investigation commenced with dienyl ester **6a**.^[12] Previous studies with α,β -unsaturated enol esters annulated across the α - and β -positions (see **4**) have shown that they are resistant to Coates–Claisen rearrangement [Eq. (1)],^[6b] hence **6a** should not undergo this undesired reaction. In addition, the activation energy for olefin isomerization of 1,3-hexadiene through [1,5] shift is 41 kcal mol⁻¹,^[13] with conjugation to the ester moiety likely to increase this value, thus uncatalyzed olefin isomerization is unlikely. To confirm this hypothesis, diene **6a** was heated at reflux in a range of solvents, including the high-boiling *ortho*-dichlorobenzene. In all cases, bicyclooctane **8a** was not observed (Table 1, entry 1). In contrast, 10 mol % of IMes (**A1**) in 1,4-dioxane at 101 °C (Table 1, entry 2) rearranged dienyl ester **6a** to the bicyclo[2.2.2]octane **8a**, albeit after an extended reaction time

[*] M. Kowalczyk, Dr. D. W. Lupton
School of Chemistry, Monash University
Clayton 3800, Victoria (Australia)
E-mail: david.lupton@monash.edu

[**] The authors thank Dr. Andreas Stasch (Monash University) for crystallography, and the Australian Research Council through the Discovery (DP120101315) and Future Fellowship (FT110100319) programs for financial support.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201402067>.

Table 1: Selected optimizations.



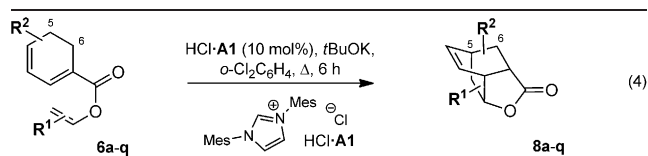
Entry	Catalyst ^[a]	Solvent	T [°C]	t [h]	Yield [%] ^[b]
1	—	<i>o</i> -Cl ₂ C ₆ H ₄	181	6	—
2	A1	1,4-dioxane	101	48	trace
3	A1	THF	100 ^[c]	48	3
4	A1	xylene	138	72	22
5	A1	toluene	150 ^[c]	72	20
6	A1	<i>o</i>-Cl₂C₆H₄	181	6	64
7	A2	<i>o</i> -Cl ₂ C ₆ H ₄	181	6	57
8	A1 ^[d]	<i>o</i> -Cl ₂ C ₆ H ₄	181	6	32
9	A1 ^[e]	<i>o</i> -Cl ₂ C ₆ H ₄	181	6	51
10	A1	<i>o</i> -Cl ₂ C ₆ H ₄	181 ^[f]	6	41
11	B ^[g]	<i>o</i> -Cl ₂ C ₆ H ₄	181	6	—

[a] NHCs were generated using equimolar *t*BuOK except as noted.

[b] Yields of isolated products following flash column chromatography on silica gel. [c] Sealed tube. [d] **A1** generated and isolated from salt by-products. [e] **A1** generated with LiHMDS (10 mol%). [f] Heated using microwave irradiation. [g] **B** generated with KHMDS (10 mol%). Entry in bold marks optimized reaction conditions. Bn = benzyl, Dip = 2,6-diisopropylphenyl, Mes = 2,4,6-trimethylphenyl.

and in low yield. Similar results were obtained in THF heated within a sealed tube (Table 1, entry 3), while xylene at reflux or toluene in a sealed tube provided **8a** in 22 and 20% yield respectively (Table 1, entries 4 and 5). When the reaction was heated at reflux in *ortho*-dichlorobenzene, bicyclooctane **8a** was isolated in an acceptable yield of 64% after 6 hours (Table 1, entry 6). Changing the catalyst to the more hindered IPr (**A2**; Table 1, entry 7) decreased the yield, as did the use of IMes (**A1**) in the absence of salt by-products,^[14] or generated using LiHMDS, or with microwave heating (Table 1, entries 8–10). Finally, using the electron-rich triazolylidene **B**, designed for substrates in the ester oxidation state,^[6i] only decomposition of the starting materials was observed (Table 1, entry 11).

The generality of the reaction was examined with $\alpha,\beta,\gamma,\delta$ -unsaturated enol esters **6a–q** (Table 2). Using *para*-substituted acetophenone derivatives, the sensitivity of the reaction to electronic effects was investigated. When either electron-rich (**6b** and **d**) or electron-poor substrates (**6c**) were subjected to the standard reaction conditions, bicyclo[2.2.2]octanes **8b–d** were isolated in comparable yields. Bicyclic aromatic moieties could be incorporated (i.e. **8e**), while the furan-containing product **8f** could only be accessed in modest yield. Unfortunately, the use of alkyl-substituted enol esters failed to provide the expected product (i.e. **8g**). Regarding the modest yield of furan **8f**, we postulated that olefin isomerization should be favored by non-hydrogen substituents at C5 ($R^2 = \text{CH}_3$), and hence the modest yield of bicyclo[2.2.2]octanes should improve. This proved to be the case with product **8h**, which was prepared in 44% yield (compare with **8f**, 34% yield). Similarly, naphthyl-containing substrate **6i** and acetophenone derivatives **6j–m** provided the

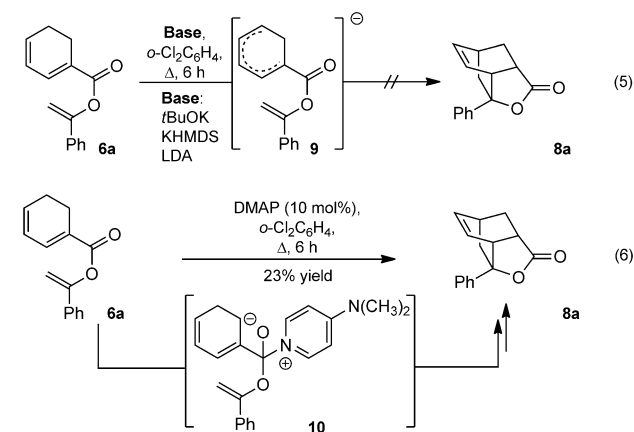
Table 2: Scope of the cascade olefin isomerization/intramolecular Diels–Alder reaction.^[a]


Entry	Substrate	Product	Yield [%]
8a	R = H	8a	69%
8b	R = OCH ₃	8b	42%
8c	R = Br	8c	57%
8d	R = CH ₃	8d	72%
8e	R = 2-naphthyl	8e	59%
8f	R = furan	8f	34%
8g	R = H	8g	0%
8h	Ar = 2-furyl	8h	44%
8i	Ar = 2-naphthyl	8i	69%
8j	R = H	8j	97%
8k	R = OCH ₃	8k	56%
8l	R = Br	8l	63%
8m	R = CH ₃	8m	80%
8n	R = H	8n	11%
8o	R = H	8o	32%
8p	R = CH ₃	8p	25%
8q	R = H	8q	47% (3:2 d.r.)

[a] Yields of isolated products following flash column chromatography on silica gel. [b] Diastereoselectivity determined by ¹H NMR analysis.

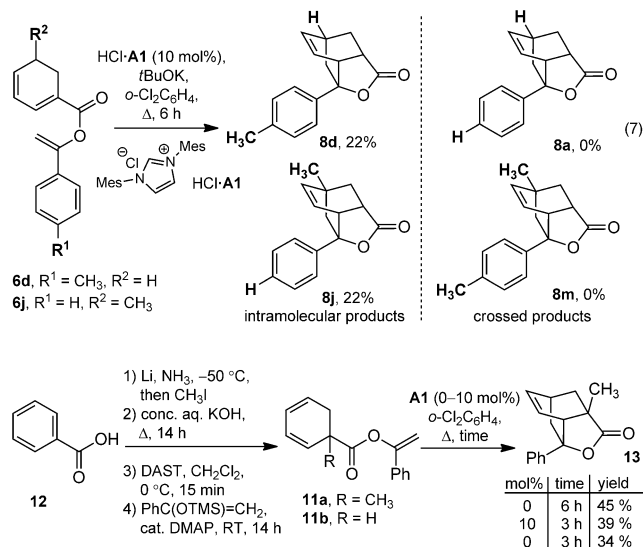
expected bicyclo[2.2.2]octanes **8i–m** with yields that were increased by around 10%. Changing R^2 to ethyl (i.e. **6n**) unfortunately hampered the reaction, with **8n** isolated in 11% yield. Next, aldehyde-derived enols were examined using phenylacetaldehyde-derived substrate **6o**, which was converted to **8o** in a low yield. Unfortunately, the introduction of a methyl substituent at C5 with this type of enol decreased the yield (**8o** versus **8p**), presumably as a consequence of steric crowding effects. Finally, the diastereoselectivity of the reaction was examined with **6q**, a substrate that bears a stereogenic methyl group at C6 ($R^2 = \text{CH}_3$). While this reaction was successful, bicyclo[2.2.2]octane **8q** was formed with little diastereoselectivity.

While nucleophilic catalysis of the olefin isomerization provides a reasonable mechanistic explanation for this transformation (Figure 1), an alternate mechanism might involve the deprotonation of **6a** by the NHC to generate enolate **9**, which is protonated to give an unconjugated diene en route to **8a** (Scheme 1). To test this scenario, the reaction was attempted using a range of non-nucleophilic Brønsted bases. In all cases, unreacted starting materials were isolated [Eq. (5)].^[15] While this result is consistent with a process mediated by a Lewis base, more compelling support was obtained using DMAP as the catalyst. While DMAP is a good Lewis base, it has low Brønsted basicity, and would be unable to generate enolate **9**.^[16] In the event, the use of DMAP provided the expected lactone **8a** in 23% yield of isolated product, presumably via hemiacetal pyridinium intermediate **10** [Eq. (6)].



Scheme 1. Comparison between Brønsted base mediated and nucleophilic catalysis. DMAP = 4-dimethylaminopyridine, HMDs = hexamethyldisilazane, LDA = lithium diisopropylamide.

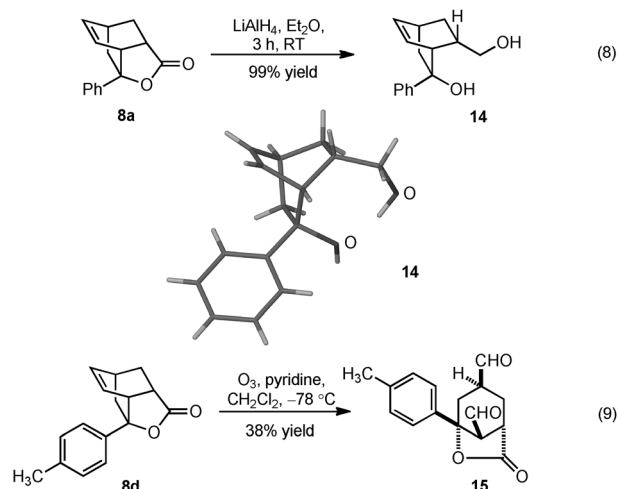
Reversible fragmentation of the hemiacetal azolium intermediate to form the acyl azolium species could occur under the reaction conditions. To establish whether this occurs, cross-over studies using **6d** and **j** were performed [Eq. (7)]. In this case, none of the crossed products (i.e. **8a** or **8m**) were observed, thus indicating that the formation of the acyl azolium intermediate is unlikely. Finally, the involvement of the NHC in the Diels–Alder process was examined. Enol ester **11a** was prepared by Birch reduction of benzoic acid **12**^[17] followed by standard conversions (Scheme 2).^[12] This substrate proved to be viable in a thermal Diels–Alder reaction, providing lactone **13** in good yield after 6 hours.^[18] When this reaction was repeated with 10 mol % **A1**, and taken to partial conversion, the yield of bicycle **13** was comparable to that without the catalyst. These results indicate that the NHC is unlikely to be accelerating the cycloaddition, however the impact of the quaternary methyl group cannot be



Scheme 2. Cross-over studies and thermal intramolecular Diels–Alder reaction. DAST = (diethylamino)sulfur trifluoride, TMS = trimethylsilyl.

dismissed. Attempts to prepare the desmethyl variant (**11b**, R = H) by allylic oxidation and elimination strategies have not been successful because of a rapid olefin isomerization during substrate synthesis.^[19] Further mechanistic studies are currently being conducted to clarify the impact of the NHC on the Diels–Alder step, and other aspects of the reaction mechanism.

Finally, derivatization of the bicyclo[2.2.2]octanes was examined through oxidative and reductive ring-openings. When lactone **8a** was exposed to one equivalent of LiAlH_4 , conversion to diol **14** was achieved in 99 % yield of isolated product, with X-ray analysis of a single crystal confirming the structure (Scheme 3).^[20] Next, the oxidative cleavage of the double bond within **8d** was examined. In this case, ozonolysis provided access to diastereomerically pure and heavily functionalized bicyclo[3.2.1]heptane **15**.



Scheme 3. Derivatization studies.

In conclusion, ester-containing materials served as novel substrates for reaction discovery using NHCs. In this study, we were able to achieve a cascade olefin isomerization/Diels–Alder reaction. This sequence defines a novel entry to bicyclo[2.2.2]octanes materials bearing an array of substituents. These can be elaborated oxidatively or reductively to provide heavily functionalized products.

Received: February 4, 2014

Revised: February 27, 2014

Published online: April 6, 2014

Keywords: Diels–Alder reaction · hemiacetal azolium intermediates · N-heterocyclic carbenes · olefin isomerization · organocatalysis

- [1] For a selection of recent reviews on NHC catalysis, see: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; for homoenolate chemistry, see: b) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose, V. Sreekumar, *Chem. Soc. Rev.* **2011**, *40*, 5336; for acyl azolium enolates, see: c) H. U. Vora, P. Wheeler, T. Rovis, *Adv. Synth. Catal.* **2012**, *354*, 1617; d) J.

- Douglas, G. Churchill, A. D. Smith, *Synthesis* **2012**, *44*, 2295; for cascade catalysis, see: e) A. Grossmann, D. Enders, *Angew. Chem.* **2012**, *124*, 320; *Angew. Chem. Int. Ed.* **2012**, *51*, 314; for acyl anion chemistry, see: f) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511; for applications in total synthesis, see: g) J. Izquierdo, G. E. Hutson, D. T. Cohen, K. A. Scheidt, *Angew. Chem.* **2012**, *124*, 11854; *Angew. Chem. Int. Ed.* **2012**, *51*, 11686; for acyl anion free catalysis, see: h) S. J. Ryan, L. Candish, D. W. Lupton, *Chem. Soc. Rev.* **2013**, *42*, 4906; and for acyl azolium and enol azolium species, see: i) J. Mahatthananchai, J. W. Bode, *Acc. Chem. Res.* **2014**, *47*, 696.
- [2] S. J. Ryan, L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2009**, *131*, 14176.
- [3] NHC transesterification with esters was reported in 2002, however it is considered to involve Brønsted base catalysis. For selected examples, see: a) G. A. Grasa, R. M. Kissling, S. P. Nolan, *Org. Lett.* **2002**, *4*, 3583; b) G. W. Nyce, J. A. Lamboy, E. F. Connor, R. M. Waymouth, J. L. Hedrick, *Org. Lett.* **2002**, *4*, 3587; c) G. W. Nyce, T. Glauser, E. F. Connor, A. Möck, R. M. Waymouth, J. L. Hedrick, *J. Am. Chem. Soc.* **2003**, *125*, 3046; d) G. A. Grasa, R. Singh, S. P. Nolan, *Synthesis* **2004**, 971. For the conjugate addition of alcohols to α,β -unsaturated esters, see: e) E. M. Phillips, M. Riedrich, K. A. Scheidt, *J. Am. Chem. Soc.* **2010**, *132*, 13179.
- [4] For a recent highlight on NHC catalysis with substrates in the ester oxidation state, see: P. Chauhan, D. Enders, *Angew. Chem. Int. Ed.* **2014**, *53*, 1485.
- [5] Access to acyl azolium species from acyl anions is far more developed, with a range of approaches enabling such chemistry, see reference [1].
- [6] For work from our group with ester substrates, see: a) reference [2]; b) L. Candish, D. W. Lupton, *Org. Lett.* **2010**, *12*, 4836; c) L. Candish, D. W. Lupton, *Org. Biomol. Chem.* **2011**, *9*, 8182; d) L. Candish, D. W. Lupton, *Chem. Sci.* **2012**, *3*, 380. For work using acyl fluorides, see: e) reference [2]; f) S. J. Ryan, L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2011**, *133*, 4694; g) S. J. Ryan, A. Stasch, M. N. Paddon-Row, D. W. Lupton, *J. Org. Chem.* **2012**, *77*, 1113; h) L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2013**, *135*, 58; i) L. Candish, C. M. Forsyth, D. W. Lupton, *Angew. Chem.* **2013**, *125*, 9319; *Angew. Chem. Int. Ed.* **2013**, *52*, 9149.
- [7] For selected examples from the elegant work of Chi and co-workers, see: a) L. Hao, Y. Du, H. Lv, X. Chen, H. Jiang, Y. Shao, Y. R. Chi, *Org. Lett.* **2012**, *14*, 2154; b) L. Hao, S. Chen, J. Xu, B. Tiwari, Z. Fu, T. Li, J. Lim, Y. R. Chi, *Org. Lett.* **2013**, *15*, 4956; c) S. Chen, L. Hao, Y. Zhang, B. Tiwari, Y. R. Chi, *Org. Lett.* **2013**, *15*, 5822; d) Z. Fu, J. Xu, T. Zhu, W. W. Y. Leong, Y. R. Chi, *Nat. Chem.* **2013**, *5*, 835; e) J. Xu, Z. Jin, Y. R. Chi, *Org. Lett.* **2013**, *15*, 5028.
- [8] For the behavior of acyl thiazolium ions and its hemiacetal in aqueous systems, see: G. E. Lienhard, *J. Am. Chem. Soc.* **1966**, *88*, 5642.
- [9] In this work the acyl azolium intermediate is formed through internal redox isomerization from the Breslow intermediate: a) J. Kaeobamrung, J. Mahatthananchai, P. Zheng, J. W. Bode, *J. Am. Chem. Soc.* **2010**, *132*, 8810; for related reactions, see: b) B. Wanner, J. Mahatthananchai, J. W. Bode, *Org. Lett.* **2011**, *13*, 5378; c) A. G. Kravina, J. Mahatthananchai, J. W. Bode, *Angew. Chem.* **2012**, *124*, 9568; *Angew. Chem. Int. Ed.* **2012**, *51*, 9433; for mechanistic studies by Schoenebeck and co-workers, see: d) E. Lyngvi, J. W. Bode, F. Schoenebeck, *Chem. Sci.* **2012**, *3*, 2346.
- [10] For comprehensive reviews, see: a) A. J. Hubert, H. Reimlinger, *Synthesis* **1969**, 97; b) A. J. Hubert, H. Reimlinger, *Synthesis* **1970**, 405.
- [11] For recent studies predominantly dealing with Z-selective olefin isomerization, see: C. Chen, T. R. Dugan, W. W. Brennessel, D. J. Weix, P. L. Holland, *J. Am. Chem. Soc.* **2014**, *136*, 945 and references therein.
- [12] The synthesis of all dienes was achieved in three steps using reported methods: a) H. Gradén, J. Hallberg, N. Kann, *J. Comb. Chem.* **2004**, *6*, 783 and references therein; b) A. R. Tunoori, J. M. White, G. I. Georg, *Org. Lett.* **2000**, *2*, 4091; c) T. Poisson, V. Dalla, C. Papamicaël, G. Dupas, F. Marsais, V. Levacher, *Synlett* **2007**, *3*, 381.
- [13] B. A. Hess, Jr., J. E. Baldwin, *J. Org. Chem.* **2002**, *67*, 6025 and references therein.
- [14] The role of salt by-products can be significant with NHC organocatalysis. For the application of these effects in cooperative catalysis, see: D. T. Cohen, K. A. Scheidt, *Chem. Sci.* **2012**, *3*, 53 and references therein.
- [15] These controls have also been performed with *t*BuOK in both dioxane and DMSO. In the former case, no reaction was observed, and in the latter case, decomposition was observed.
- [16] DMAP has a similar nucleophilicity to the Enders triazolyldiene NHCs and is less nucleophilic than imidazoylidene NHCs such as **A1**, see: a) B. Maji, M. Breugst, H. Mayr, *Angew. Chem.* **2011**, *123*, 7047; *Angew. Chem. Int. Ed.* **2011**, *50*, 6915 and references therein. For a recent review on the physical properties of DMAP, see: b) N. De Rycke, F. Couty, O. R. P. David, *Chem. Eur. J.* **2011**, *17*, 12852. For the pK_a of DMAP in THF, see: c) T. Rodima, I. Kaljurand, A. Pihl, V. Mäemets, I. Leito, I. A. Koppel, *J. Org. Chem.* **2002**, *67*, 1873.
- [17] D. Kuck, J. Schneider, H.-F. Grützmacher, *J. Chem. Soc. Perkin Trans. 2* **1985**, 689.
- [18] Related Diels–Alder sequences have been developed: a) A. Krantz, C. Y. Lin, *J. Am. Chem. Soc.* **1973**, *95*, 5662; b) K. Harano, T. Aoki, M. Eto, T. Hisano, *Chem. Pharm. Bull.* **1990**, *38*, 1182.
- [19] Allylic acetoxylation of methyl cyclohex-3-ene-1-carboxylate was achieved following: a) S. Hansson, A. Heumann, T. Rein, B. Åkermarck, *J. Org. Chem.* **1990**, *55*, 975. While the Pd^0 -mediated elimination reported in b) B. M. Trost, T. R. Verhoeven, J. M. Fortunak, *Tetrahedron Lett.* **1979**, *20*, 2301 affords the precursor to **11b**, rapid olefin isomerization to the undesired conjugated species occurs upon ester cleavage.
- [20] CCDC 983932 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.