ORGANIC LETTERS

2009
Vol. 11, No. 14
3060−3063

Hetero-Diels−Alder Reactions of Cyclic Ketone Derived Enamide. A New and Efficient Concept for the Asymmetric Robinson Annulation

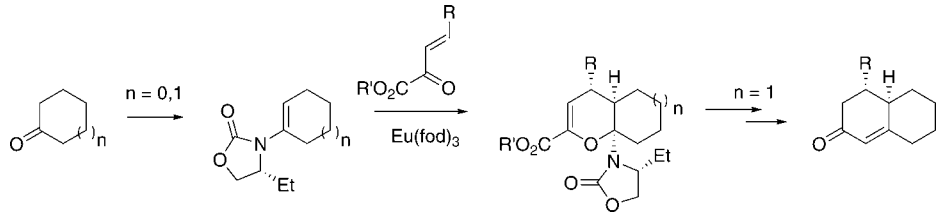
Florian Gallier,[†,‡] Hidayat Hussain,[†] Arnaud Martel,[†] Andreas Kirschning,[‡] and Gilles Dujardin*[,†]

UCO2M UMR 6011 & FR 2575 CNRS, Université du Maine, 72085, Le Mans, France, and Institut für Organische Chemie der Leibniz Universität Hannover, Schneiderberg 1B, 30167 Hannover, Germany

gilles.dujardin@univ-lemans.fr

Received May 14, 2009

ABSTRACT



Chiral enamides, easily prepared in one step from a cyclic ketone and an oxazolidinone, are successfully employed in high-yielding, endo, and facially selective Hetero-Diels−Alder reactions involving activated oxadienes and Siever's reagent as catalyst. From the resulting bicyclic heteroadducts, a novel and efficient asymmetric modification for the Robinson annulation of cyclic monoketones is described.

Inverse electron demand Hetero-Diels−Alder reactions[1] (IED HDA) between π-electron-deficient oxadienes and electron-rich dienophiles has been thoroughly studied in the last 40 years. Most of these reactions are based on aldehyde-derived enol ethers as dienophiles, and impressive asymmetric extensions have been reported in this area, culminating in enantioselective catalytic processes using chiral Lewis acid complexes.[2,3] One of the major breakthroughs was the use of BOX-Cu^{II} complexes developed by the Evans and Jørgensen groups.[3b,c] These catalysts are also efficient for the IED HDA reaction of acetophenone silyl enol ethers.[3b] However, when other ketone-derived enol ethers are employed, the results are consistently poor in terms of stereoselectivity and/or enantioselectivity. More recently, the first organocatalytic enantioselective IED HDA reaction between an enolizable aldehyde and an activated oxadiene in the presence of a chiral pyrrolidine has been published by Jørgensen's group.[4] Heteroadduct derivatives were obtained in good yields and ee's. However, Tang et al. showed that under similar conditions cyclic ketones afford bicyclic [3.3.1] products which are generated by a formal [3 + 3] annulation process.[5] So far no asymmetric version (either catalytic or stoichiometric) of IED HDA reactions between an oxadiene

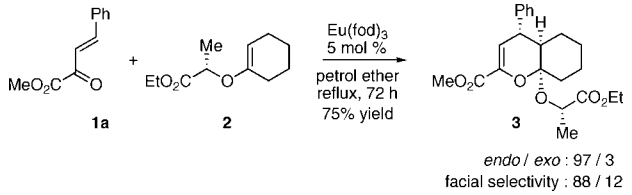
[†] UCO2M, UMR CNRS 6011, Université du Maine.
[‡] Institut für Organische Chemie, Leibniz University Hannover.

(1) (a) Boger, D. L. *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, chap. 4.1, pp 451−512.
(2) Reviews: (a) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (b) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289. (c) Pelissier, H. *Tetrahedron* **2009**, *65*, 2839.
(3) (a) Wada, E.; Yasuoka, H.; Kanemasa, S. *Chem. Lett.* **1994**, 1637. (b) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635. (c) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (e) Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3059.
(4) Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498.
(5) Cao, C.-L.; Sun, X.-L.; Kang, Y.-B.; Tang, Y. *Org. Lett.* **2007**, *9*, 4151.

10.1021/ol901065e CCC: $40.75
Published on Web 06/19/2009

and a cyclic ketone-derived dienophile has been successfully reported.[6,2c] Use of a chiral cyclic ketone-derived dienophile was investigated in our group. Our previous work on the $Eu(fod)_3$-catalyzed heterocycloaddition of chiral enol ether **2** and methyl benzylidene-pyruvate **1a** showed a very high endo selectivity but only a moderate facial selectivity[7] (Scheme 1), when compared to those obtained under similar

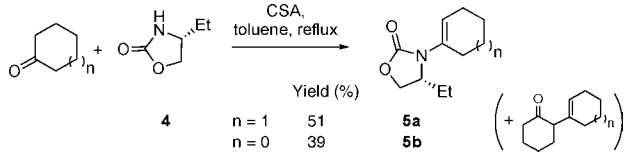
Scheme 1. HDA Reaction of Chiral Enol Ether **2**



conditions with *O*-vinyl mandelates[8] or with the *t*-butyl mandelate enol ether derived from 3-pentanone.[9]

In the late 1980s, Eiden et al. reported that the pyrrolidine enamine of cyclohexanone undergoes a thermal [4 + 2] cycloaddition yielding bicyclic [4.4.0] adducts.[10] An asymmetric extension of this method was envisioned, but the lack of stability of the bicyclic adduct led us to explore other chiral dienophiles, namely, new *N*-alkenyloxazolidin-2-ones **5** derived from cyclic ketones (Scheme 2). In this report,

Scheme 2. Preparation of *N*-Cycloalkenyloxazolidin-2-ones **5**

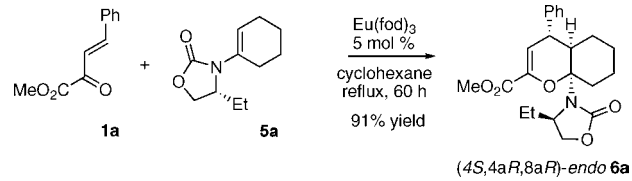


we wish to highlight a novel one-step procedure to prepare these new dienophiles and to report their unprecedented use in asymmetric [4 + 2] heterocycloadditions. We also describe that the bicyclic heteroadducts thus obtained can be efficiently involved as key intermediates in the asymmetric synthesis of octalones.

The most convenient way to access the desired enecarbamates **5** involves the copper(I)-catalyzed amination between oxazolidin-2-one and a (cyclo)alkenyl halide.[11] The latter can be prepared in two steps from the corresponding cyclic ketone. We observed that acid-catalyzed azeotropic distillation of a mixture of cyclohexanone and oxazolidin-2-one yields the desired product in only one step. These conditions allow us to synthesize a wide variety of enecarbamates more readily. The moderate yield is the result of the self-condensation of cyclic ketones (Scheme 2), and the residual oxazolidinone **4** is easily recovered.

Relevant chiral enamides have widely been utilized for asymmetric transformations in the past few years.[12] We demonstrated the high potential of vinyl oxazolidinones as new chiral dienophiles in IED HDA reactions.[13] More recently, our group demonstrated that β-substituted *N*-vinyloxazolidin-2-ones allow the high-yielding formation of endo adducts with a remarkable facial stereodivergency depending on the Lewis acid used ($Eu(fod)_3$ vs $SnCl_4$).[13b] However, $SnCl_4$-catalyzed heterocycloaddition of dienophile **5a** with oxabutadiene **1a** only resulted in the cleavage of the enamide bond, and no adduct was isolated. In contrast, the $Eu(fod)_3$-catalyzed reaction afforded the desired heteroadduct with excellent endo and facial selectivity (Scheme 3): one

Scheme 3. Hetero-Diels−Alder (HDA) Reaction of Enamide **5a**



(4*S*,4a*R*,8a*R*)-*endo* **6a**

diastereomer[14] was essentially obtained and isolated by chromatography in high yield (91%).

The endo stereochemistry of adduct **6a** was deduced from ^1H NMR data, and its absolute configuration was established by X-ray diffraction (Figure 1).

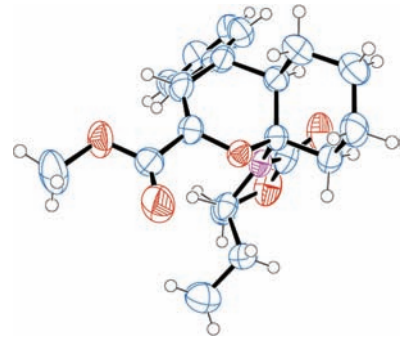
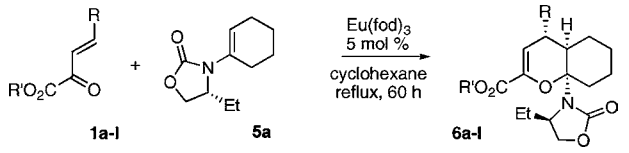


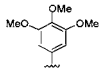
Figure 1. X-ray structure of adduct *endo*-**6a**.

The heterocycloaddition of dienophile **5a** was then extended to a range of activated heterodienes **1b**−**l** (Table 1). Under the same conditions, heteroadducts **6a**−**i** (R = Ar) were produced in homogeneous yields (85−91%) with high

(6) Jørgensen, K. A. *Eur. J. Org. Chem.* **2004**, 2093.
(7) Martel, A. *PhD Thesis*, Le Mans University, 2001.
(8) (a) Dujardin, G.; Rossignol, S.; Molato, S.; Brown, E. *Tetrahedron* **1994**, *50*, 9037. (b) Dujardin, G.; Rossignol, S.; Brown, E. *Synthesis* **1998**, *50*, 763.
(9) Gong, J.; Bonfand, E.; Brown, E.; Dujardin, G.; Michelet, V.; Genêt, J.-P. *Tetrahedon Lett.* **2003**, *44*, 2141.
(10) (a) Eiden, F.; Winkler, W.; Wanner, K. T.; Markhauser, A. *Arch. Pharm.* **1985**, *318*, 648. (b) Eiden, F.; Wünsch, B.; Schünemann, J. *Arch. Pharm.* **1990**, *323*, 481.
(11) (a) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (b) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667. (c) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809.

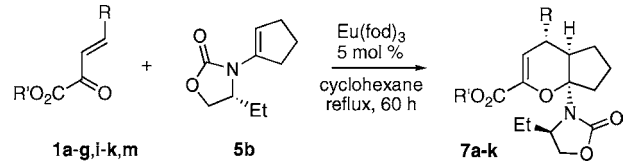
Table 1. HDA Reactions of Dienophile **5a** with Dienes **1a−l**

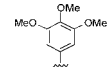


entry	1	R	R'	adduct	yield (%)[a]	diastereopurity[b] *endo / exo*[c]	diastereopurity[b] *facial*
1	**1a**	Ph	Me	**6a**	91	95:5	>98:2[e]
2	**1b**	Ph	Et	**6b**	89	97:3	98:2
3	**1c**	Ph	*n*-Pr	**6c**	88	>98:2	>98:2
4	**1d**	Ph	*n*-Bu	**6d**	87	>98:2	>98:2
5	**1e**		Et	**6e**	88	>98:2	>98:2[e]
6	**1f**		Me	**6f**	88	97:3	>98:2[e]
7	**1g**		Me	**6g**	89	>98:2[d]	>98:2[e]
8	**1h**		Me	**6h**	85	>98:2[d]	>98:2[e]
9	**1i**		Me	**6i**	89	84:16	>98:2
10	**1j**	Me	Me	**6j**	72	95:5	>98:2[e]
11	**1k**	Et	Me	**6k**	75	93:7	>98:2
12	**1l**	OEt	Et	**6l**	77	77:23	>98:2[e]

[a] Isolated product. [b] Diastereoselectivities were determined from the ^{1}H NMR spectrum of the purified adduct (vinylic proton). [c] One minor exo adduct. [d] exo adduct not detected. [e] Minor endo adduct not detected.

Table 2. HDA Reactions of Dienophile **5b** with Dienes **1a−k,m**



entry	1	R	R'	adduct	yield (%)[a]	diastereopurity[b] *endo / exo*[c]	diastereopurity[b] *facial*
1	**1a**	Ph	Me	**7a**	88	84:16[d]	>98:2[e]
2	**1b**	Ph	Et	**7b**	84	73:27	>98:2[e]
3	**1c**	Ph	*n*-Pr	**7c**	85	95:5	>98:2[e]
4	**1d**	Ph	*n*-Bu	**7d**	82	96:4	>98:2[e]
5	**1m**		Me	**7e**	87	89:11	>98:2[e]
6	**1e**		Et	**7f**	86	>98:2	98:2
7	**1f**		Me	**7g**	84	92:8	>98:2[e]
8	**1g**		Me	**7h**	83	89:11	>98:2[e]
9	**1i**		Me	**7i**	83	88:12	>98:2[e]
10	**1j**	Me	Me	**7j**	70	95:5	>98:2[e]
11	**1k**	Et	Me	**7k**	73	98:2	>98:2[e]

[a] Isolated product. [b] Diastereoselectivities were determined from the ^{1}H NMR spectra of the purified adduct (vinylic proton). [c] One minor exo adduct. [d] Two minor exo adducts. [e] Minor endo adduct not detected.

diastereoselectivities, except for trimethoxy-phenyl-substituted adduct **6i** (Table 1, entry 9). In each case, one endo diastereomer was essentially obtained over the four possible, and the facial control appeared as complete. The nature of the ester function (R′) has no effect on the efficiency and a slight effect on the endo stereoselectivity (Table 1, entries 1−4). Alkyl-substituted heterodienes **1j**,**k** afforded adducts in moderate yield but with a good endo selectivity and a complete facial control (Table 1, entries 10 and 11). Switching from an aryl to an alkoxy substituent (R = OEt) led to a dramatic decrease of the endo selectivity, but still the facial differentiation was very high (Table 1, entry 12). The common endo geometry and absolute configuration of the major (or sole) adducts **6b**−**l** was determined from the strong analogies between their ^{1}H NMR data and those of adduct (4*S*,4*aR*,8*aR*)-*endo*-**6a**.

We then extended this study to the cyclopentanone-derived dienophile **5b** (Table 2). Again, aryl-substituted heteroadducts **7a**−**i**,**m** were produced in good yields (82−88%) under standard conditions with high facial control. In contrast to the cyclohexenyl series, the endo selectivity proved to be not total in most cases and notably dependent on the nature of the ester function beared by the heterodiene (entries 1−6). Unexpectedly, a high double diastereocontrol was obtained in the case of **7f** (entry 6). Only little fluctuations of the endo selectivity were observed when the aryl substituent was varied (entries 5 and 7−9). Finally, alkyl-substituted heterodienes **1j**,**k** afforded adducts in moderate yields but with a high endo selectivity and complete facial control (entries 10 and 11).

Adduct **6i** was then subjected to functional group modification. After ester reduction with Dibal-H in the presence of BF_3•Et_2O,[15] the corresponding allylic alcohol was easily isolated in a pure diastereomeric form and converted into the iodide **8** in good overall yield. Samarium(III)-induced reduction of the iodide afforded **9**. Hydrolysis of the *N*,*O*-ketal under acidic conditions yielded the 1,5-diketone **11**, in a 2.6:1 diastereomeric ratio (35% yield), in a separable mixture with the diastereomerically pure octalone **10** (53%

(12) (a) Aciro, C.; Davies, S. G.; Garner, A. C.; Ishii, Y.; Key, M.-S.; Ling, K. B.; Prasad, R. S.; Roberts, P. M.; Rodriguez-Solla, H.; O'Leary-Steele, C.; Russel, A. G.; Sanganee, H. J.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron* **2008**, *64*, 9320. (b) Lu, T.; Song, Z.; Hsung, R. P. *Org. Lett.* **2008**, *10*, 541, and references cited.

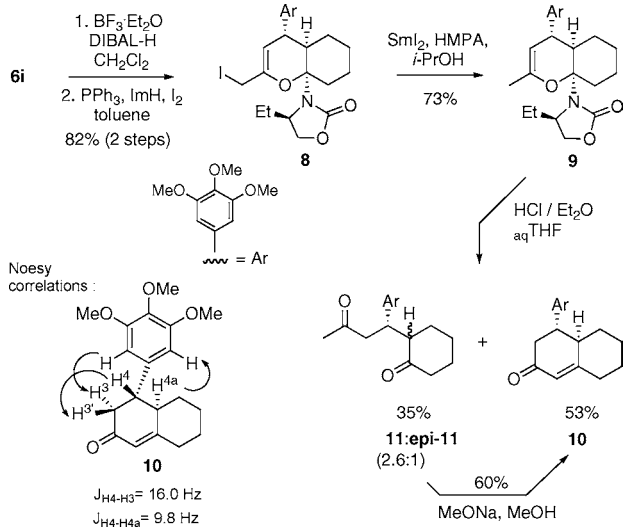
(13) (a) Gaulon, C.; Dhal, R.; Chapin, T.; Maisonneuve, V.; Dujardin, G. *J. Org. Chem.* **2004**, *69*, 4192. (b) Gohier, F.; Bouhadjera, K.; Faye, D.; Gaulon, C.; Maisonneuve, V.; Dujardin, G.; Dhal, R. *Org. Lett.* **2007**, *9*, 211.

(14) 95:5:0:0 Ratio of the four possible diastereomers assuming a concerted mechanism.

(15) Gonda, J.; Helland, A. C.; Ernst, B.; Belluš, D. *Synthesis* **1993**, *7*, 729.

yield), the latter presumably resulting from the spontaneous Robinson-type annulation of the former. The (4*S*,4a*R*)-configuration of the octalone **10** was established by ^{1}H NMR data (Scheme 4).[16] The presence of minor amounts of 1,5-

Scheme 4. Enantioselective Octalone Synthesis (I)



diketone *epi*-**11** (∼10% yield) appears as a consequence of an unavoidable acid-mediated epimerization of **11**. Fortunately, only the octalone **10** resulting from the aldolisation−crotonization of the major (*S*,*R*)-diketone **11** was observed. Interestingly, treatment of the residual diastereomeric mixture of diketone **11** with MeONa in methanol led mainly to the diastereomerically pure octalone **10**,[17] thus increasing the global yield in octalone **10** from dihydropyran **9** up to 74%.[18]

In summary, we have shown that ene-carbamates derived from cyclanones and oxazolidinone **4** can act as powerful chiral dienophiles to yield heteroadducts with a range of activated heterodienes. HDA reactions proceeded in high yield and endo selectivity as well as facial selectivity under mild conditions using Siever's reagent as catalyst. The new bicyclic heteroadducts served as a starting point for unprecedented asymmetric access to a 4-aryl-substituted octalone.

In the important field of Robinson annulation products derived from cyclic monoketones, this novel enantioselective [4 + 2] route offers new synthetic opportunities due to its complementarity with the well-established Pfau-d'Angelo's method. Indeed, although highly efficient for a range of α-substituted cyclic monoketones toward alkyl vinyl ketones, this method based on the Michael addition of a chiral imine-tautomer is known to suffer from a dramatic decrease of reactivity when the Michael acceptor is β-substituted.[19] Studies on the scope and limitations of the title HDA reaction and of the new and promising enantioselective annulation procedure are currently underway.

Acknowledgment. Dr. K. Adil (LdOF-UMR 6010 CNRS) is gratefully acknowledged for X-ray structure determination. F.G. thanks the DAAD for a sandwich scholarship (A/04/20592). H.H. thanks the Région Pays de la Loire for a postdoctoral grant.

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

OL901065E

(16) NMR data of close octalone (Ar = Ph, racemic mixture of isomers) was previously described, but the relative configuration was not assigned: (a) Wada, E.; Funakoshi, J.; Kanemasa, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2456. (b) Aurell, M. J.; Gavina, P.; Mestres, R. *Tetrahedron* **1994**, *50*, 2571.

(17) This reaction afforded as a separable byproduct a ketol (∼25% yield) that could be the OH-epimer of the precursor aldol of **10**.

(18) Enantiopure oxazolidinone **4** was recovered in high global yield by easy chromatographic separation from the annulation product.

(19) D'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459.