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Authors: Lydia Scott, Yuji Nakano, Changhe Zhang, and David W Lupton

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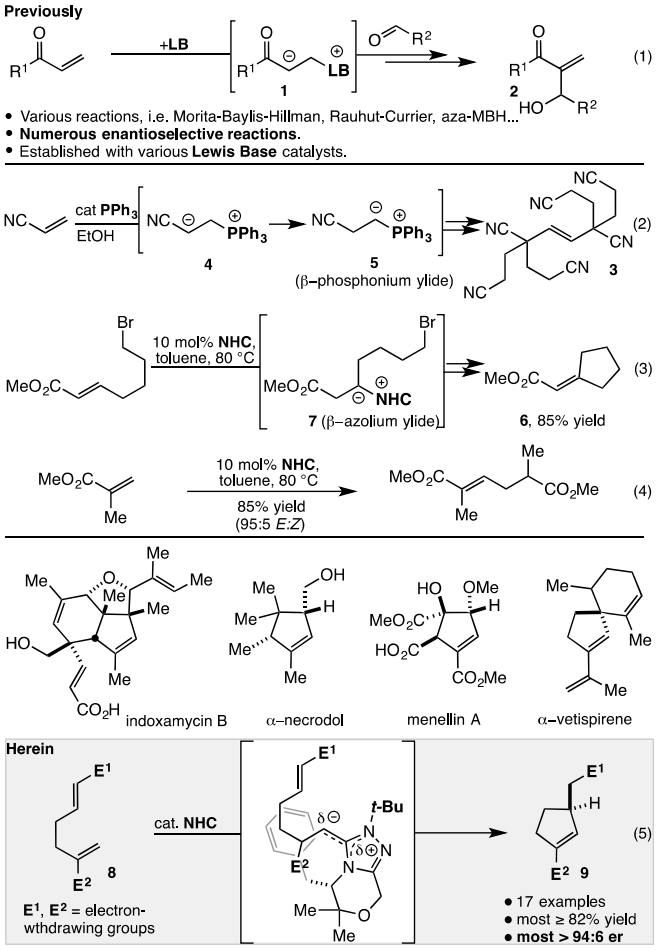
Enantioselective N-heterocyclic carbene catalyzed cyclopentene synthesis via the β–azolium ylide**

*Lydia Scott, Yuji Nakano, Changhe Zhang and David W. Lupton**

***Abstract**: Herein we report the cycloisomerization of electron-poor 1,5-dienes via the β–azolium ylide to give enantioenriched cyclopentenes. The reaction exploits readily available substrates, has good generality (17-examples), and displays excellent enantioselectivity (most > 94:6). Studies demonstrating the viability of a related dynamic kinetic resolution are reported, as are those with alternate tethers and derivatizations.*

More than 45 years ago, work from Morita[1a] and Baylis/Hillman[1b,c] led to the discovery that simple conjugate acceptors can couple with aldehydes using catalytic phosphine or amine Lewis bases (eq. 1). Key mechanistic features of these, and the related Rauhut-Currier reaction, [1o,p] involve 1,4-addition of the Lewis base to give enolate **1**, which is alkylated, and following elimination of the catalyst, provides α–substituted products (i.e. **2**). Finer mechanistic detail, enantioselective variants, and more sophisticated reaction designs, have since allowed these reactions to enter the lexicon of synthesis.[1]

In 1962, Takashina and Price observed that acrylonitrile gives hexamer **3** in the presence of triphenyl phosphine and ethanol (eq. 2).[2a] It was proposed that following 1,4-addition of the Ph_3P, alcohol mediated tautomerization gives the novel β–phosphonium ylide (i.e **4**→**5**), which goes on to provide **3**.[2] More recently, Fu reported the N-heterocyclic carbene (NHC) catalyzed formation of cyclopentane **6**, via the related β–azolium ylide **7** (eq. 3).[3] This species, a type of deoxy-Breslow intermediate,[4] is analogous to adducts discovered by Enders in stoichiometric reactions of the triphenyltriazolium carbene with conjugate acceptors.[4a] While reactions of the Breslow intermediate, the archetypal acyl anion equivalent formed under NHC catalysis, continue to attract significant attention,[5a,c] β–azolium ylides (i.e. **7**) have remained largely overlooked. Specifically, Matsuoka,[6] Glorius,[7] and Berkessel[8] have studied the dimerization (and oligomerization) of electron-poor olefins (i.e. eq. 4), Chen has exploited the β–azolium ylide in polymerization catalysis,[9] and we have developed a moderately enantioselective (most <79:21 er) synthesis of aryl propionates.[10]



Scheme 1. Background and reaction design.

The unusual reactivity of the β–azolium ylide, combined with the proximity of the chiral azolium to the site of bond formation, *a priori*, make it well-suited to new enantioselective reaction designs. To demonstrate this, we envisaged a synthesis of cyclopentenes, exploiting the cycloisomerization of electron-poor 1,5-dienes (i.e. **8**) (eq. 5). While cyclopentenes are found extensively in bioactive and natural products (Scheme 1),[11] their enantioselective synthesis is often more challenging than that of analogous cyclohexenes. Herein we report studies that have led to the discovery of a highly enantioselective (most > 94:6 er) route to cyclopentenes **9**. The reaction exhibits good generality (17-examples), while exploiting readily accessible substrates and catalysts.

Reaction discovery commenced with the preparation of 1,5-diene **8a**. This was achieved by alkylation of the enamine of

[*] Ms. Lydia Scott, Dr. Yuji Nakano, Dr. Changhe Zhang
Professor David W. Lupton*
School of Chemistry, Monash University
Clayton 3800, Victoria, AUSTRALIA
Fax: (+) 61 3 9905 4597
E-mail: david.lupton@monash.edu

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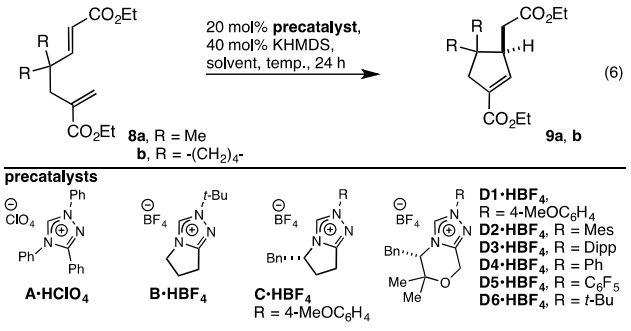
isobutyraldehyde with bromomethylethylacrylate and Wittig homologation of the resultant unpurified aldehyde.[12] With facile access to the required substrate, the cycloisomerization was examined with the Enders TPT catalyst **A**[4a,13] and triazolylidene **B**. While both were viable, the latter gave cyclopentene **9a** in 99% yield (Table 1, entries 1 and 2). Oligomerization can plague reactions of the β–azolium ylide and was not observed in either case. Studies into the enantioselective variant commenced with NHCs **C** and **D1** bearing the N-4-MeOC$_6$H$_4$ substituent, as exploited in other β–azolium ylide reactions.[3a,10] Pleasingly, cyclopentene **9a** formed with moderate enantioenrichment in both cases (Table 1, entries 3 and 4). Further catalyst screening, with six NHCs bearing various N-substituents (**D1-6**),[14] in refluxing THF, using 1,5-diene **8b**, demonstrated that the least nucleophilic[14a] catalyst **D6** gave cyclopentene **9b** in 73% yield and an 85:15 enantiomeric ratio (Table 1, entry 10). This selectivity was enhanced at lower temperature, although the yield was compromised (Table 1, entry 11). However, at 40 °C in the absence of salt by-products,[15] cyclopentene **9b** formed in 93% isolated yield and in a 97:3 er (Table 1, entry 12).

Table 1. Selected optimization studies.

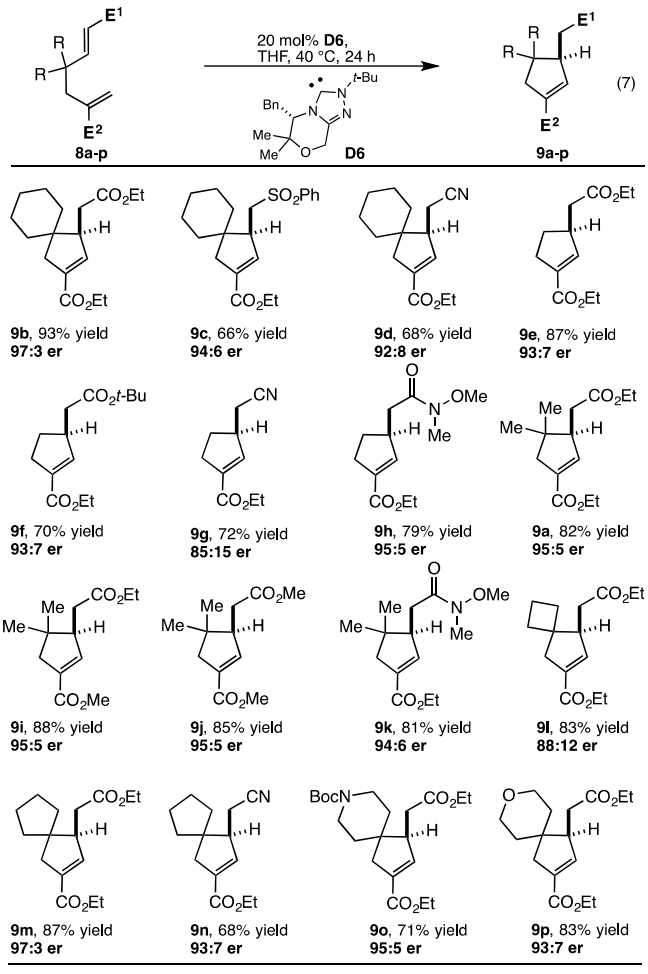


entry	8	cat	T (°C)	solvent	yield[a]	er[b]
1	**a**	**A**	Δ	toluene	53	-
2	"	**B**	Δ	"	99	-
3	"	**C**	Δ	"	60	~68:32
4	"	**D1**	Δ	"	95	72:28
5	**b**	**D1**	Δ	THF	28	80:20
6	"	**D2**	Δ	"	-	-
7	"	**D3**	Δ	"	-	-
8	"	**D4**	Δ	"	26	ND
9	"	**D5**	Δ	"	18	ND
10	"	**D6**	Δ	"	73	85:15
11	"	**D6**	rt	"	50	96:4
12	**"**	**D6**[c]	**40**	**"**	**93**	**97:3**

[a] Isolated yield [b] Enantiomeric ratio by HPLC over chiral stationary phases [c] NHC prepared with 40 mol% KHMDS and isolated from KBF$_4$ and HMDS, see experimental section.

Reaction generality was examined through variation of the two Michael acceptor groups (E^1 and E^2) and the R substituents (Table 2). Substrates were prepared, using the previously described procedure[11] or, in the case of **8e-h**, by Wittig reaction of a known aldehyde precursor.[16] The cycloisomerization proved robust, with 17 cyclopentenes **9a-q** prepared in good yield and with high enantiopurity. Specifically, studies commenced by examining variation in the E^1 group to give spirocyclic decanes **9b-d** containing ethyl ester, sulfonyl ketone, and nitrile functionality. In all cases high enantioselectivity (≥92:8 er) and acceptable yields were achieved. Deletion of the R group was subsequently examined to probe the role of Thorpe-Ingold rate enhancement. Gratifyingly, *bis*-ethyl ester **9e**, *t*-butyl/ethyl ester **9f**, cyano/ethyl ester **9g**, and Weinreb amide/ethyl ester **9h** all formed in 70-87% yield and in most cases ≥ 93:7 er. Dimethyl cyclopentenes, bearing various E^1 groups and both ethyl and methyl ester E^2 groups, were also readily prepared. Thus, products **9a** and **i-k** were formed in 81-88% yield and high enantiopurity (all ≥94:6 er). In addition, cyclobutane **9l**, and cyclopentanes **9m** and **n** were prepared in good yield and with high enantioselectivity (88:12, 97:3 and 93:7 er respectively). Finally, introduction of oxygen and nitrogen containing heterocycles was examined. Thus, piperidine **9o** and tetrahydropyran **9p** were prepared in good yields and high enantioselectivity (95:5 and 93:7 er).

Table 2. Scope of the enantioselective cyclopentene synthesis.[a-c]



[a] NHC **D6** generated with 40 mol% KHMDS and isolated from KBF$_4$ and HMDS [b] Isolated yield [c] Enantiomeric ratio determined by HPLC over chiral stationary phases.

Next we envisioned exploiting the Brønsted basicity of the NHC to allow the dynamic kinetic resolution of racemic 1,5-diene substrates.[17] When benzyl 1,5-diene **8q** was exposed to the reaction conditions, a 2:1 diastereomeric mixture of cyclopentene **9q** formed with 82% yield and high levels of enantiopurity (89:11 and 94:6 er) (eq. 8). Resubjection of this mixture to the reaction conditions had little impact on stereochemical purity, indicating that the diastereoselectivity likely arose from resolution prior to

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cycloisomerization. To increase the effectiveness of the resolution the reaction was repeated at elevated temperature. This gave the expected product **9q** in an increased 7:1 diastereomeric ratio, with moderate reduction in enantiopurity.

While the Brønsted basicity of the NHC was advantageous in the previous reaction this compromised enantioselectivity when aryl linkers were examined in the substrate (i.e. **10**). Specifically, diene **10** provided indene **11**[18] as a racemic mixture under the standard conditions. It was postulated that racemization occurred via the aromatic indenyl anion. Lowering the temperature allowed indene **11** to be prepared in 85:15 er; however conversion was compromised (eq. 9).

Next derivatizations were examined to probe the utility of the products and determine the absolute configuration of the cyclopentenes. Thus, diester **9e** was converted to the known diacid **13e**[19] by exhaustive alkylation, followed by ester hydrolysis. In addition, derivatization through complete reduction with DIBAL-H afforded diol **14m**, while reduction at sustained low temperatures provided aldehyde **15m** (eq. 10).

Preliminary mechanistic studies were undertaken to examine the nature of the turn-over limiting step. Thus, the synthesis of cyclopentene **9b** was performed with the pseudo-racemic catalyst mixture derived from ***ent*-D1** and **D6**. The reaction was terminated after around 30% conversion and the enantiopurity of **9b** determined to be 97:3 er (eq. 11); unchanged from the reaction with **D6** alone (Table 2). Since the **D6** catalyst is less nucleophilic than ***ent*-D6**,[14a] this result is inconsistent with either turn-over limiting 1,4-addition of the catalyst (**D6** + **8e**→**16**) or cyclization (i.e. **17**→**18**); steps that would be expected to be accelerated by a highly nucleophilic catalyst. Consistent with this result is turn-over limiting proton transfer (i.e. **16**→**17**) and reversible 1,4-addition of the NHC. Thus, a plausible mechanism for the cycloisomerization begins with the reversible 1,4-addition of NHC **D6** to 1,5-diene **8e** to give enolate **16**. To minimise steric interactions the enolate is likely oriented such that *Re* protonation is hindered by the benzyl group. Thus, *Si*-protonation followed by deprotonation gives β–azolium ylide **17**, with the enediamine oriented to minimise interactions with the *t*-butyl group, while the none conjugated ethyl ester is oriented to minimise interactions with the benzy group. Diastereoselective, and ultimately enantiodetermining, cyclization with the conjugate acceptor in a pseudo-equatorial position then provides cyclopentane **18**. Consistent with stereoselective cyclisation via this conformation is the reaction's sensitivity to the size of the E group, with the smaller nitrile group decreasing the enantioselectivity of the cyclopentene synthesis compares to the ethyl ester (Table 2: **9b** cf. **d**, **e** cf. **g**, and **m** cf. **n**). Finally, protonation and elimination of the catalyst gives cyclopentene **9e**.

The Breslow intermediate, derived from the 1,2-addition of carbenes to aldehydes, remains the most influential species in NHC organocatalysis.[5,20] Beyond enabling direct acyl anion equivalent reactions, its subsequent rearrangement underpins a host of alternative transformations.[5] In contrast, the β–azolium ylide is far less developed. Although studies into the fundamental reactivity of the β–azolium ylide have been reported in the last 12-years, further work is required to allow it to gain general utility. This study is the first to deliver a highly enantioselective reaction. In addition to providing a concise approach to diverse cyclopentenes, it should serve to support future studies in β–azolium ylide catalysis.

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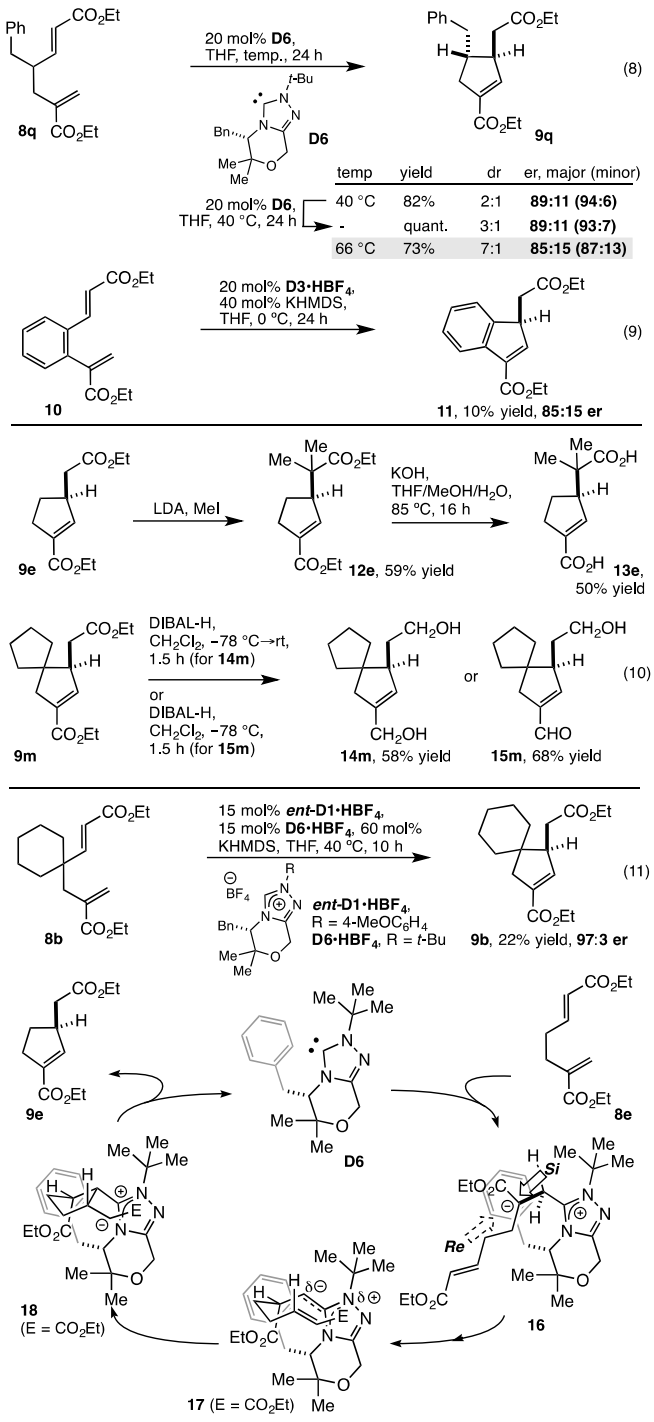

Scheme 2. Dynamic kinetic resolution, derivatizations, and mechanism.

Keywords: enantioselective catalysis • N-heterocyclic carbene • 1,4-addition • β-azolium ylide • cyclopentene •

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Lydia Scott, Yuji Nakano, Changhe Zhang and David W. Lupton*

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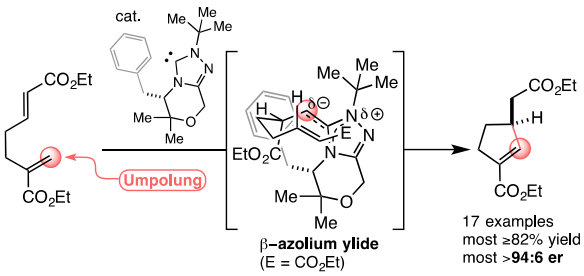
Enantioselective N-heterocyclic carbene catalyzed cyclopentene synthesis via the β–azolium ylide.



High five! A highly enantioselective synthesis of cyclopentenes has been developed by cycloisomerization of electron poor 1,5-dienes. The reaction is viable with chiral N-heterocyclic carbenes (NHCs), providing 16 cyclopentenes in good yields (most ≥ 82% yield) and with high enantiopurity (most > 94:6 er). The reaction proceeds via the β–azolium ylide, a relatively rare example of a conjugate acceptor umpolung. Derivatizations and a related kinetic resolution are presented.