Stereoselective synthesis of spirocyclopentanones *via N*-heterocyclic carbene-catalyzed reactions of enals and dienones†

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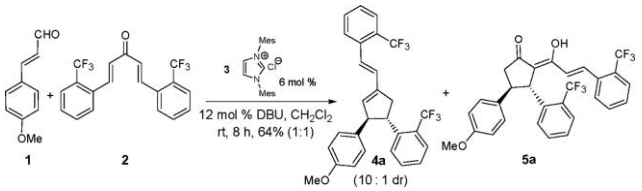
Homoenolates generated from enals by nucleophilic heterocyclic carbene (NHC) catalysis undergo a conjugate addition/cyclization sequence with cyclic dienones, culminating in the efficient synthesis of spirocyclopentanones.

In the context of designing efficient carbon–carbon bond forming reactions, the discovery of new catalytic protocols for the conjugate addition of carbon nucleophiles to enones assumes importance.[1] Ever since the first demonstration of their existence, homoenolates,[2] species containing an anionic carbon β to a carbonyl group, have been recognized as a unique class of synthons for catalytic conjugate additions. Although the application of homoenolates in organic synthesis[3,4] has been limited, since no direct method for their generation exists, it is noteworthy that a number of elegant protocols for the generation of homoenolate-equivalents have been developed.[5,6] The renewed interest in these species can be attributed to the concept of "conjugate umpolung", introduced by Bode *et al.*[7] and Glorius *et al.*[8], involving the reaction of *N*-heterocyclic carbenes (NHCs) and enals, allowing the direct generation of homoenolates for the first time. These homoenolates undergo annulation with aldehydes, leading to the efficient synthesis of γ-butyrolactones. The trapping of such catalytically-generated homoenolates with other electrophiles, such as *N*-sulfonyl imines,[9] 1,2-diones,[10] tropone[11] and azomethine imines[12] has been accomplished. In addition, their application to novel carbon–carbon bond forming processes *via* the intermediacy of enols/enolates have been reported.[13]

In the course of our work on the reactions of homoenolates, we discovered an NHC-catalyzed[14,15] homoenolate annulation of enals with chalcones, leading to an efficient synthesis of 1,3,4-trisubstituted cyclopentenes.[16,17] This unexpected cyclopentene formation was attributed to the isomerization of the initially formed enolate to a more stable imidazolium-bound enolate, which participates in aldol lactonization and the loss of CO_2 by a retro [2 + 2] process from the resulting β-lactone. Naturally, it was of interest to explore the reactivity of homoenolates towards other Michael acceptors, especially cross-conjugated dienones. Thus, an experiment was performed using dienone **2** as the electrophile and



Scheme 1 Reaction of 4-methoxycinnamaldehyde with a dienone.

4-methoxycinnamaldehyde as the homoenolate precursor in presence of a catalytic amount of 1,3-dimesityl imidazol-2-ylidene (IMes) [generated *in situ* from IMesCl (6 mol%) using DBU (12 mol%)]. Gratifyingly, the reaction afforded a separable mixture of 1,3,4-trisubstituted cyclopentene **4a**[18] and 2,3,4-trisubstituted cyclopentanone **5a**; this is in contrast to the experiments involving chalcones, which yielded only cyclopentene derivatives (Scheme 1).

The structure of the products were established by spectroscopic analysis, and a final confirmation of the structure and stereochemistry of compound **5a** was obtained from a single crystal X-ray determination (Fig. 1).‡

A range of enones bearing the styryl activating group participate in this interesting reaction sequence (Table 1). It is noteworthy that only one diastereomer was formed in each case.

The following mechanistic interpretation is proposed to account for the formation of cyclopentanones (Scheme 2). The first step of the reaction is a conjugate addition of an NHC-bound homoenolate to the dienone to generate enolate **V**. Conceivably, the latter undergoes an intramolecular aldol reaction to afford **VII**, with the ejection of IMes. The cyclopentanone thus formed is stabilized as its enol tautomer, presumably by the various hydrogen bonding interactions present in this compound.[19]

As already reported,[16] the formation of cyclopentenes can be rationalized by invoking the formation of isomeric enolate **VI** by intramolecular proton transfer, which participates in aldol lactonization and the loss of CO_2 by a retro [2 + 2] process from the resulting β-lactone.

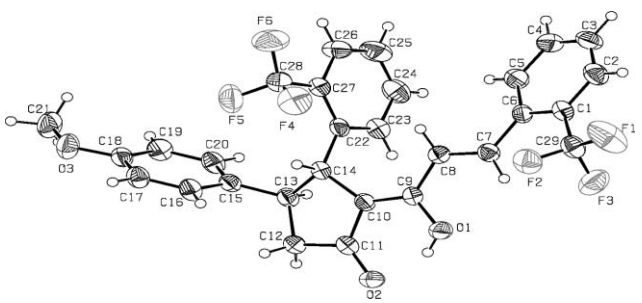


Fig. 1 ORTEP diagram for **5a** (40% probability thermal ellipsoids).

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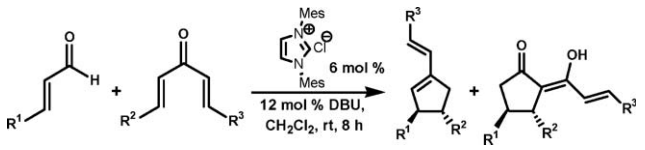
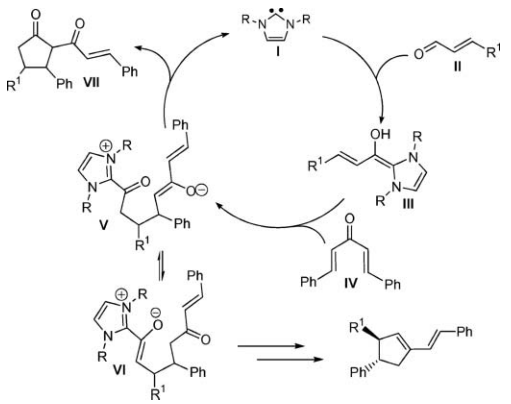
† Electronic supplementary information (ESI) available: General experimental procedure and spectroscopic characterization data. See DOI: 10.1039/b715733a

Table 1 NHC-catalyzed reaction of enals with dienones



Entry	R^1	$R^2 = R^3$	Products	Ratio	Yield (%)[a]
1	4-MP[b]	Phenyl	**4b** & **5b**	1.5 : 1	79
2	4-MP[b]	4-Methylphenyl	**4c** & **5c**	2 : 1	65
3	4-MP[b]	4-Fluorophenyl	**4d** & **5d**	1 : 1	67
4	4-MP[b]	2-Thienyl	**4e** & **5e**	2 : 1	60
5	Phenyl	4-MP[b]	**4f** & **5f**	1 : 1	61
6	Phenyl	Phenyl	**4g** & **5g**	1.2 : 1	80
7	Phenyl	4-Methylphenyl	**4h** & **5h**	1.1 : 1	79

[a] Isolated yield. [b] MP = methoxyphenyl.

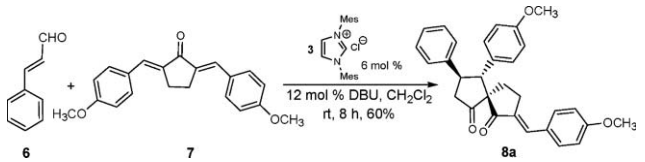


Scheme 2 Postulated catalytic cycle involving NHC.

With a view to achieving selectivity in this annulation, we considered the possibility of engaging cyclic enolates, formed by the addition of a homoenolate to dibenzylidene cyclopentanone. In general, the cyclopentanone-derived enolates are expected to be more reactive than their acyclic counterparts.[20] In the event, when a solution of dibenzylidene cyclopentanone (**7**) and cinnamaldehyde (**6**) in dry CH_2Cl_2 (3 mL) was treated with IMes (6 mol%) at room temperature for 8 h, we observed the exclusive formation of spiro annulated cyclopentanone derivative **8a** in 60% yield as a single isomer (Scheme 3).[21,22]

Spirocyclopentanone **8a** was characterized by spectroscopic analysis, and confirmation of the structure and the stereochemistry of the compound was obtained by a single crystal X-ray analysis (Fig. 2).§

The efficient conversion of a number of dibenzylidene cyclopentanones to their corresponding spirocyclopentanone derivatives[23,24] (Table 2) and the complete stereoselectivity of the reactions are especially noteworthy.



Scheme 3 Reaction of cinnamaldehyde with dibenzylidene cyclopentanone.

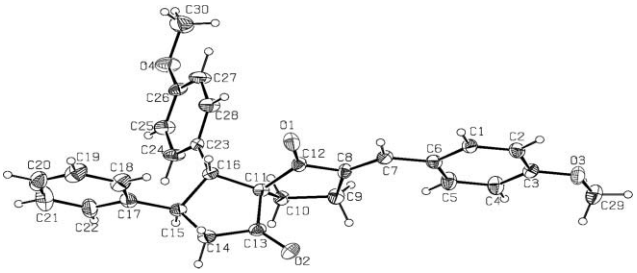
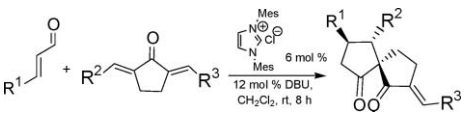


Fig. 2 ORTEP diagram for **8a** (40% probability thermal ellipsoids).

Table 2 Synthesis of spirocyclopentanones

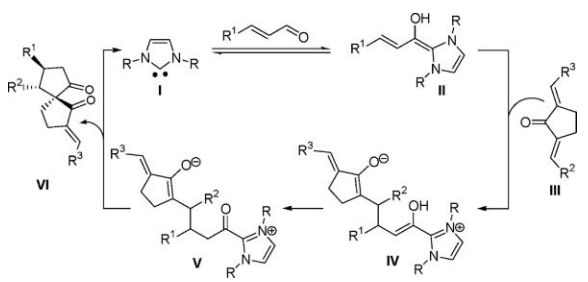


Entry	R^1	$R^2 = R^3$	Product	Yield (%)[a]
1	2-MP[b]	Phenyl	**8b**	71
2	2-MP[b]	4-Methylphenyl	**8c**	72
3	4-MP[b]	4-Methylphenyl	**8d**	58
4	2-MP[b]	4-MP[b]	**8e**	73
5	4-MP[b]	Phenyl	**8f**	53
6	Phenyl	4-Methylphenyl	**8g**	57
7	Phenyl	Phenyl	**8h**	55
8	4-MP[b]	4-MP[b]	**8i**	64
9	2-MP[b]	2-Thienyl	**8j**	57
10	4-MP[b]	2-Thienyl	**8k**	54

[a] Isolated yield. [b] MP = methoxyphenyl.

The formation of spirocyclopentanones at the exclusion of bicyclic cyclopentenes may be rationalized as follows (Scheme 4). The two steps proposed in the mechanism, the conjugate addition of **II** and the aldol cyclization of **V**, have opposite electronic requirements. The conjugate addition requires an electrophilic π-system, while the cyclization step calls for a highly reactive enolate. Evidently, the addition of homoenolates to **III** would produce cross-conjugated cyclic dienolates **V**.[25] Due to the inherently marked nucleophilicity of cyclic enolates **V**, they undergo rapid aldol cyclization with the activated carboxyl surrogate, producing spirocyclopentanones **VI**.

A different reactivity pattern was observed with dibenzylidene cyclohexanone (Scheme 5). The latter, on reaction with cinnamaldehyde under standard conditions, afforded exclusively bicyclic *trans*-cyclopentene.[26] This may be attributed to the relatively strain free transition state for proton transfer involving cyclohexyl enolate *vis a vis* the cyclopentyl system.



Scheme 4 Plausible mechanism of NHC-catalyzed spirocyclopentanone formation.

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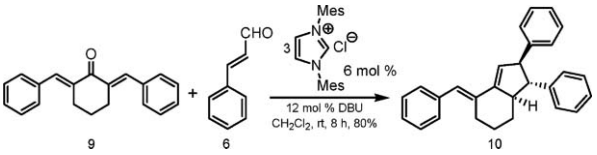

Scheme 5 Reaction of cinnamaldehyde with dibenzylidene cyclohexanone.

In conclusion, we have devised a new cyclopentanone annulation by a conjugate addition/cyclization sequence. This method provides easy access to a highly stabilized cyclopentanone enol and synthetically challenging functionalized spirocyclopentanone. The stereoselective construction of a quaternary carbon center is noteworthy.

Notes and references

‡ Crystal data for compound **5a**: $C_{29}H_{22}F_6O_3$, M_r = 532.47, triclinic, space group *P*-1, a = 8.360(3), b = 10.923(3), c = 14.100(4) Å, α = 75.738(5), β = 78.758(5), γ = 81.972(5)°, V = 1218.2(6) Å^3, Z = 2, ρ_{calc} = 1.452 g cm^{-3}, μ = 0.124 mm^{-1}, T = 296(2) K; reflections collected = 7210, independent reflections = 5322, R_{int} = 0.0181; $R1$ = 0.0622, w$R2$ = 0.1550, GOF = 1.067 [$I > 2\sigma(I)$]. CCDC 638979. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b715733a

§ Crystal data for compound **8a**: $C_{30}H_{28}O_4$, M_r = 452.52, monoclinic, space group *C*2/*c*, a = 43.220(18), b = 6.205(3), c = 17.784(7) Å, α = 90, β = 96.239(10), γ = 90°, V = 4741(4) Å^3, Z = 8, ρ_{calc} = 1.268 g cm^{-3}, μ = 0.083 mm^{-1}, T = 293(2) K; reflections collected = 11325, independent reflections = 4166, R_{int} = 0.1007; $R1$ = 0.0966, w$R2$ = 0.1833, GOF = 1.097 [$I > 2\sigma(I)$]. CCDC 653444. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b715733a.

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18 Only *ortho*-substituted dienones are found to yield a diastereomeric mixture of cyclopentenes; the *para*-substituted examples afforded only one diastereomer.

19 See the ESI for details†.

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