NHC-Catalyzed Annulation of Enals to 2,4-Dien-1-ones: Efficient Diastereoselective Synthesis of 1,3-Diaryl-4-styrenyl Cyclopentenes

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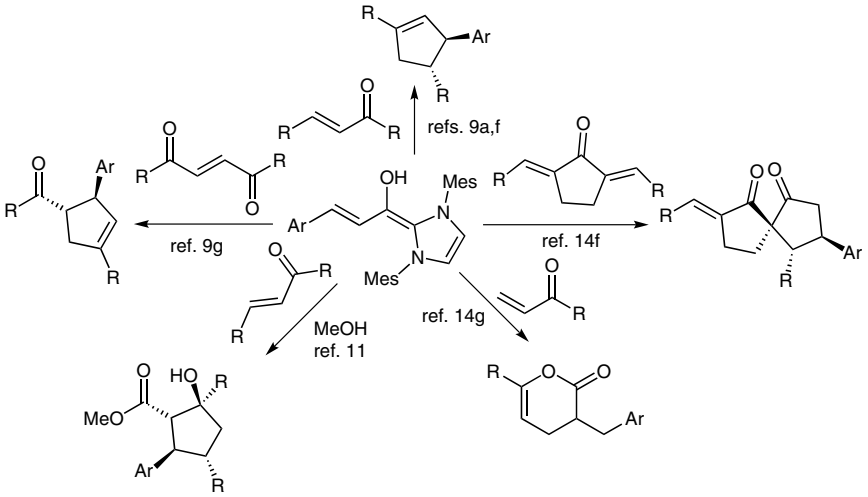
Abstract: Nucleophilic heterocyclic carbene (NHC)-catalyzed annulation strategy has been utilized for the efficient synthesis of styrenyl-substituted cyclopentenes from 2,4-dienones.

Key words: NHC, catalysis, homoenolate, annulation, cyclopentene

In the context of organocatalysis,[1] defined as catalysis of organic reactions by small organic molecules, nucleophilic heterocyclic carbenes (NHCs) have emerged as powerful tools with uniquely inherent ability to impose polarity reversal (umpolung) on aldehydes. Historically, definitive experiments by Breslow[2] in 1958 revealing the catalysis of benzoin condensation by the ylide (currently called NHC) liberated from a thiazolium salt laid the foundation of NHC catalysis. However, just as it happens with many original discoveries, the Breslow protocol remained dormant for more than four decades except for its application in Stetter reaction.[3] With the renaissance of organocatalysis, the situation changed dramatically, and in recent years a number of synthetic procedures availing NHC catalysis have been reported.[4] The signal change in this area may be attributed to the NHC-catalyzed formation of homoenolate and the addition of the latter to aldehydes culminating in the synthesis of γ-lactones reported by Glorius and Bode.[5,6] In short order, work in this area by different groups, including our own, has uncovered the application of homoenolates in the synthesis of a variety of compounds such as γ-spirolactones,[7] lactams,[8] cyclopentenes,[9] pyrazolidinones[10] and cyclopentanols.[11] Efficient homoenolate additions to nitrostyrenes,[12] sulfonimines[8a,13] and assorted electrophiles[14] have also been reported. Other homoenolate reactions of note include co-operative Lewis acid/N-heterocyclic carbene catalysis[15] and intramolecular reactions.[16]

The happenstance of an NHC-catalyzed annulation of homoenolate to chalcones, constituting an unprecedented synthesis of trisubstituted cyclopentenes may be singled out for its mechanistic intrigue and potential applications in synthesis. In the course of our exploration of this reaction, we were impressed by the versatility of homoenolate in delivering a range of products by engaging a variety of carbonyl compounds (Scheme 1).

In view of the results outlined in the above scheme, it was of great interest to examine the reactivity of homoenolate towards 2,4-dien-1-ones. Our studies commenced by exposing homoenolate derived from 4-methoxycinnamaldehyde (**1a**) to 1,5-diphenylpenta-2,4-dien-1-one (**2a**) in dichloromethane. The reaction afforded a product in 87% yield, and it was characterized as the styryl-substituted cyclopentene **3a** (Scheme 2).



Scheme 1 Homoenolate reaction towards enone

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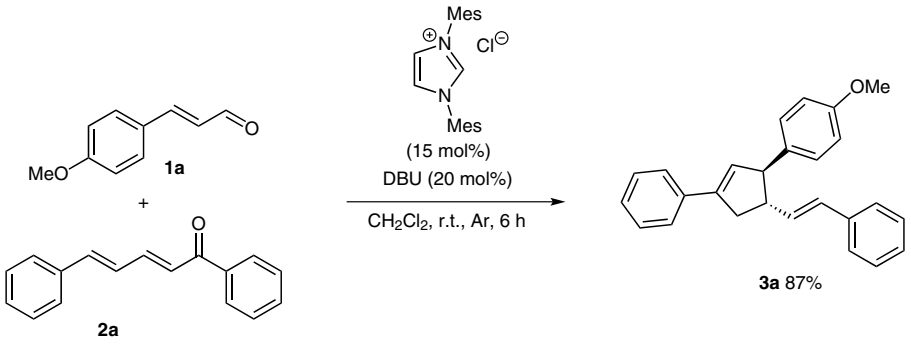
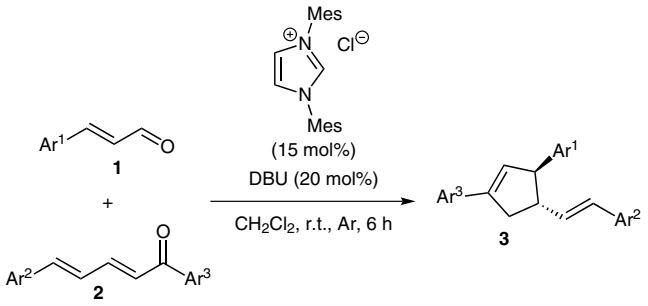


Scheme 2 Homoenolate reaction of enal and dienone

The structure of product was established by spectroscopic analysis. In ^{1}H NMR spectrum, the methoxy protons resonated as singlet at δ = 3.79 ppm, and a peak corresponding to the olefinic proton was assigned the singlet at δ = 6.19 ppm. The presence of styryl moiety was confirmed by a doublet of doublet at δ = 6.40 (J_1 = 15.8 Hz and J_2 = 8.2 Hz) and a doublet at δ = 6.28 (J = 15.8 Hz). The ^{13}C NMR spectrum, showed a peak at δ = 158.3 ppm attributable to the aromatic carbon bearing OMe group. It also displayed a peak at δ = 57.8 ppm corresponding to the methoxy carbon and one at δ = 39.7 ppm due to the methine carbon. All other signals were in good agreement with the assigned structure.

With a view to examine the scope of the reaction, a series of experiments were performed by varying the enals and the dienones. The results are summarized in Table 1.

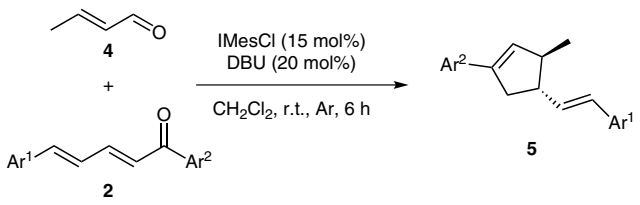
Table 1 Scope of the Reaction



Entry	Ar^1	Ar^2	Ar^3	Product	Yield (%)
1	4-methoxyphenyl	Ph	Ph	**3a**	87
2	4-methoxyphenyl	4-methoxyphenyl	4-methylphenyl	**3b**	86
3	4-methoxyphenyl	4-methoxyphenyl	pyridinyl	**3c**	86
4	4-methoxyphenyl	4-methoxyphenyl	Ph	**3d**	71
5	2-methoxyphenyl	Ph	Ph	**3e**	74
6	2-methoxyphenyl	4-methoxyphenyl	pyridinyl	**3f**	80
7	Ph	Ph	Ph	**3g**	43
8	Ph	4-methoxyphenyl	pyridinyl	**3h**	61
9	2-methoxyphenyl	Ph	4-bromophenyl	**3i**	66
10	4-methoxyphenyl	Ph	4-bromophenyl	**3j**	91
11	Ph	Ph	4-bromophenyl	**3k**	90
12	4-methoxyphenyl	Ph	furyl	**3l**	66
13	4-methoxyphenyl	Ph	thienyl	**3m**	61

In view of the promising results obtained, we extended the reaction to an aliphatic enal, namely crotonaldehyde, and the results are shown in Table 2.

Table 2 Reaction of Crotonaldehyde with Dienones



Entry	Ar^1	Ar^2	Product	Yield (%)
1	4-methoxyphenyl	pyridinyl	**5a**	81
2	4-methoxyphenyl	Ph	**5b**	75
3	4-methoxyphenyl	4-methylphenyl	**5c**	78
4	Ph	Ph	**5d**	69
5	Ph	4-bromophenyl	**5e**	67
6	Ph	furyl	**5f**	87
7	Ph	thienyl	**5g**	61

In order to probe the reactivity of dienal towards dienone, hexa-2,4-dienal (**6**) was subjected to the above homoenolate reaction condition with 5-(4-methoxyphenyl)-1-(4-tolyl)penta-2,4-dien-1-one (**2b**). The reaction proceeded via the same pathway of enals and afforded the product **7** (Scheme 3).

A mechanistic rationale for the reaction, analogous to the one established[9a,17] for the original cyclopentene synthesis, may be advanced (Scheme 4). The homoenolate **I** formed by the reaction of IMes with enal undergoes conjugate addition to the dienone and the subsequent proton transfer generates the enolate **II** which endures intramolecular aldol reaction to deliver the cyclopentane carbinolate **III**. The latter undergoes β-lactonization to eject IMes, allowing the catalytic cycle to continue. The β-lactone **V** thus formed is unstable and undergoes retro [2+2]-process to yield the cyclopentene **A** with the loss of carbon dioxide.

In conclusion, a homoenolate annulation strategy has been utilized for the synthesis of styryl-substituted cyclopentenes.[18]

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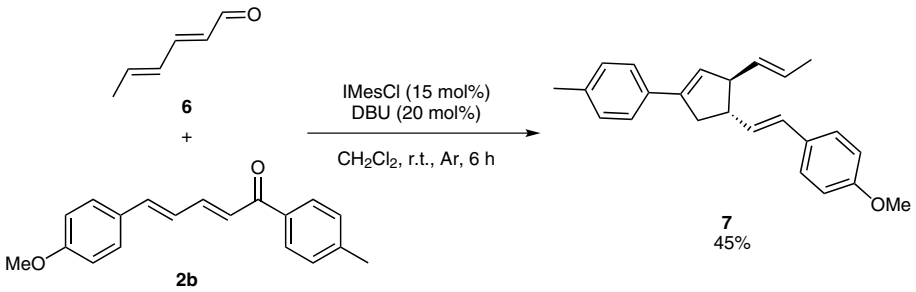
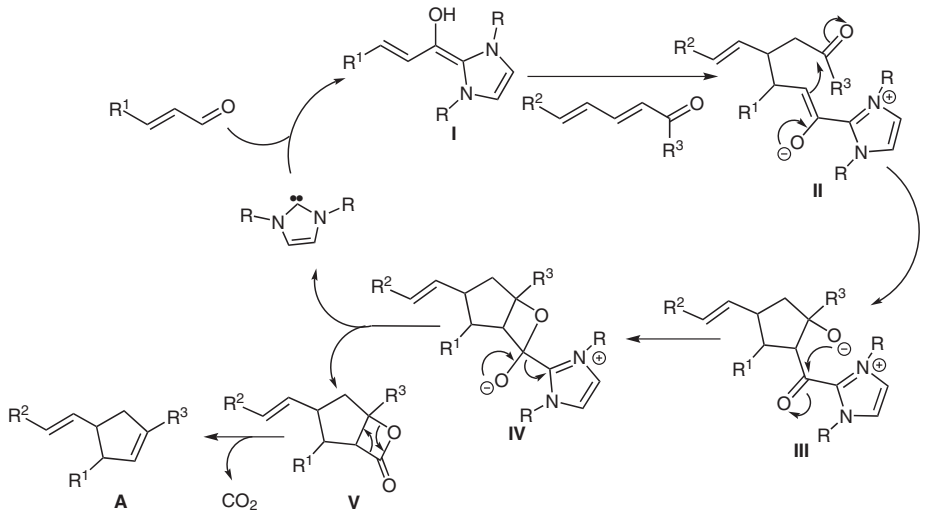


Scheme 3 Homoenolate reaction of dienal to dienone



Scheme 4 Proposed mechanism

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(18) **Synthesis of (*E*)-1-Methoxy-4-(3-phenyl-5-styrylcyclopent-2-enyl)benzene (3a)**: 1,5-Diphenylpenta-2,4-dien-1-one (117 mg, 0.5 mmol), 4-methoxycinnamaldehyde (162 mg, 1 mmol) and IMesCl (15 mol%) were taken in a 25-mL round-bottom flask. Into this was added anhyd CH_2Cl_2 (5 mL) followed by DBU (20 mol%) and the reaction mixture was stirred under an inert atmosphere of argon. The completion of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was subjected to column chromatography on 100–200 mesh silica gel using EtOAc–hexane (2:98) mixture, affording the styryl cyclopentene **3a** (85%) as a colorless liquid. Chemical formula: $C_{26}H_{24}O$. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 7.9 Hz, 2 H), 7.34 (t, *J* = 7.7 Hz, 4 H), 7.27 (dd, *J* = 13.0, 5.8 Hz, 3 H), 7.18 (t, *J* = 6.0 Hz, 1 H), 7.15 (d, *J* = 8.1 Hz, 2 H), 6.83 (d, *J* = 7.9 Hz, 2 H), 6.40 (dd, *J* = 15.8, 8.2 Hz, 1 H), 6.28 (d, *J* = 15.8 Hz, 1 H), 6.19 (s, 1 H), 3.85 (d, *J* = 7.8 Hz, 1 H), 3.79 (s, 3 H), 3.12 (dd, *J* = 15.2, 8.2 Hz, 1 H), 2.99 (p, *J* = 8.0 Hz, 1 H), 2.79 (dd, *J* = 15.2, 7.8 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.3, 142.1, 137.5, 136.5, 136.1, 133.0, 129.8, 128.6, 128.5, 128.5, 128.4, 127.4, 127.0, 126.1, 125.7, 113.9, 57.8, 55.1, 53.2, 39.8.

