DOI: 10.1002/adsc.200800174

Organocatalytic Asymmetric Formal [3+3] Cycloaddition Reactions of α,β-Unsaturated Aldehydes with Nazarov Reagents

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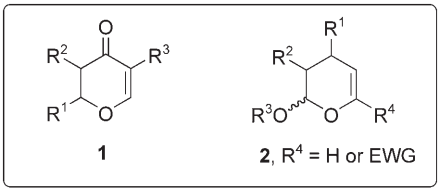
Received: March 5, 2008; Published online: May 19, 2008

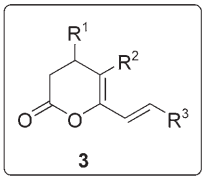
Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: An organocatalytic asymmetric formal [3+3] cycloaddition reaction of α,β-unsaturated aldehydes with Nazarov reagents promoted by prolinol derivatives afforded, after oxidation, 3,4-dihydropyranones in good yields with high enantioselectivities of up to 97% *ee*.

Keywords: asymmetric catalysis; formal [3+3] cycloaddition; Nazarov reagents; organocatalysis; prolinol derivatives; unsaturated aldehydes

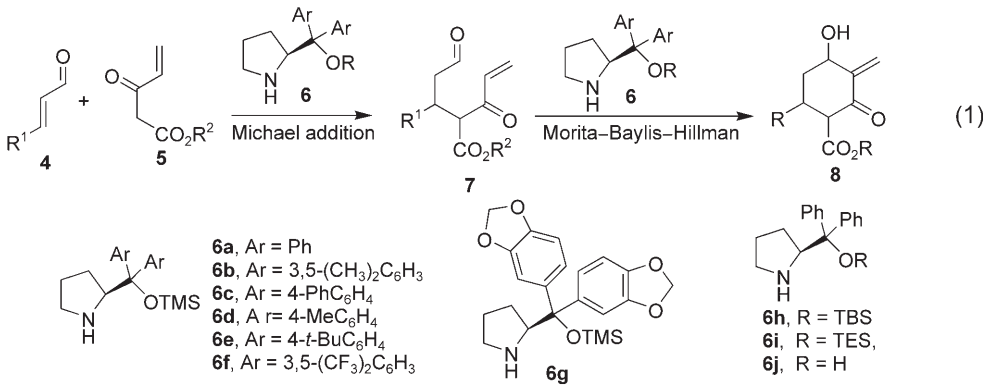
Tetrahydropyran and dihydropyran derivatives are structural subunits that commonly appear in numerous natural products and biologically active compounds;[1,2] they also serve as versatile and important building blocks that have widespread applications in organic synthesis.[2,3] Synthetic methods that yield chiral tetrahydropyran and dihydropyran derivatives have thus received much research interest. The focus of studies on this synthetic methodology has been the development of asymmetric hetero-Diels–Alder (HDA) reactions that provide an efficient pathway to access 2,3-dihydropyran derivatives.[4] A number of excellent asymmetric HDA procedures catalyzed either by chiral Lewis acids[5] or by organic molecules[6,7] have readily afforded 3,4-dihydropyran derivatives **1** and **2** in high optical purity. Compared with **1** and **2**, the presence of a C=C bond conjugated to an enol in **3** definitely increases the possibility for the structural modulation and thereby enhances the synthetic utility. However, no efficient synthetic method is yet available to access chiral vinyl-3,4-dihydropyran architectures like **3**. In this communication, we describe an organocatalytic asymmetric formal oxa-[3+3] cycloaddition reaction[8] of α,β-unsaturated aldehydes with Nazarov reagents[9] catalyzed by prolinol derivatives[10,11] which, after a subsequent oxidation, leads to the formation of 6-vinyl-3,4-dihydropyranones **3** with excellent enantioselectivities (97% *ee*).





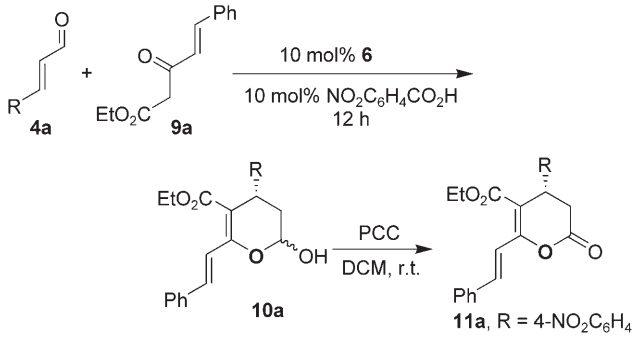
Very recently, an elegant study by Jørgensen and co-workers revealed that α,β-unsaturated aldehydes **4** underwent a tandem Michael/Morita–Baylis–Hillman reaction (MBH) with Nazarov reagent **5** in the presence of prolinol derivatives **6**, leading to the formation of cyclohexenone derivatives with high levels of stereoselectivity [Eq. (1)].[12]

However, we observed that Nazarov reagent **9a**, which differs from **5** by the presence of a phenyl substituent at C-5, did not undergo the tandem Michael/Morita–Baylis–Hillman reaction under the promotion of **6a** using *para*-nitrobenzoic acid as an additive, but underwent rather a formal [3+3] cycloaddition reaction which, after oxidation using PCC, furnished a chiral pyranone in 86% yield with 88% *ee* (Table 1, entry 1). This interesting result, together with the importance of pyranones in organic synthesis, triggered



(1)

Table 1. Catalyst screening and optimization of reaction conditions.[a]



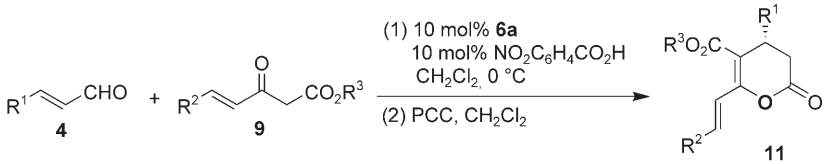
Entry	Catalyst	Solvent	Yield [%][b]	*ee* [%][c]
1	**6a**	CH_2Cl_2	86	88
2	**6b**	CH_2Cl_2	86	86
3	**6c**	CH_2Cl_2	73	82
4	**6d**	CH_2Cl_2	66	79
5	**6e**	CH_2Cl_2	54	68
6	**6f**	CH_2Cl_2	71	83
7	**6g**	CH_2Cl_2	70	68
8	**6h**	CH_2Cl_2	67	84
9	**6i**	CH_2Cl_2	65	70
10	**6j**	CH_2Cl_2	44	0
11[d]	**6a**	CH_2Cl_2	88	95
12[d]	**6b**	CH_2Cl_2	82	95
13	**6a**	$CHCl_3$	63	90
14	**6a**	THF	71	78
15	**6a**	$PhCH_3$	68	82
16	**6a**	CH_3CN	83	90
17	**6a**	EtOH	81	93

[a] The reaction of **4a** (0.24 mmol) with **9a** (0.20 mmol) in the presence of an organocatalyst **6** (0.02 mmol) and 4-nitrobenzoic acid (0.02 mmol) was performed in CH_2Cl_2 (1.0 mL) at 25 °C.
[b] Isolated yield of **10a**.
[c] Determined by HPLC.
[d] The reaction was performed at 0 °C.

us to optimize the reactions parameters. Various prolinol derivatives were then screened for the model reaction between **4a** and **9a**. As shown in Table 1, all the protected diarylprolinol derivatives showed good catalytic activity and some of them provided high yields when the reactions were conducted for 12 h. The enantioselectivity varied depending highly on the aryl substituent and **6a** was identified as the optimal catalyst (entry 1). Unprotected prolinol **6j** showed no stereoselectivity (entry 10). Lowering the reaction temperature from room temperature to 0 °C enabled the enantioselectivity to be improved to 95% *ee* when either **6a** or **6b** was used as the catalyst while not compromising the yields (entries 11 and 12). A survey of solvents revealed that THF and toluene are not suitable for the reaction, in which much lower enantioselectivities were obtained (entries 14 and 15). Other polar solvents such as chloroform, acetonitrile, and ethanol all provided lower enantioselectivity than dichloromethane (entries 13, 16, and 17). The best results were attained by conducting the reaction in dichloromethane (entry 11).

The optimized procedure was then extended to formal [3+3]cycloaddition reactions between various α,β-unsaturated aldehydes and Nazarov reagents (Table 2). The scope of α,β-unsaturated aldehydes was first investigated by their reaction with **9a**. Cinnamaldehydes with different substituents could be tolerated and underwent smooth cyclization reactions, after oxidation with PCC, furnishing **11a–j** in varying yields and enantioselectivities that both depended highly on the electronic features of the substituent in the aldehydes. Accordingly, the electron-withdrawing group facilitates the formation of the desired cyclic products with excellent enantioselectivities ranging from 91% to 96% *ee* (entries 1–6). However, cinnamaldehyde and its analogues substituted with either a methyl or a halogen provided comparably lower enantioselectivities although the products were attained in good yields (entries 7–11). Despite this, the enantiopurity of **11h–j** could be enhanced to over 99% *ee* by a single recrystallization to compensate the disadvantage associated with the unsatisfactory *ee* (entries 9–11). Alkyl-substituted α,β-unsaturated aldehydes show a poor reactivity. However, an acryl aldehyde with an ester substituent at the β-position pro-

Table 2. Scope and limitations of the unsaturated aldehydes and Nazarov reagents.[a]



Entry	R^1	R^2	R^3	**11**	Time [h]	Yield [%][b]	*ee* [%][c]
1	4-$NO_2C_6H_4$ (**4a**)	Ph	Et	**11a**	12	77	95
2	3-$NO_2C_6H_4$ (**4b**)	Ph	Et	**11b**	30	78	92
3[d]	3-$NO_2C_6H_4$ (**4b**)	Ph	Et	**11b**	36	71	94
4	2-$NO_2C_6H_4$ (**4c**)	Ph	Et	**11c**	36	58	91
5	4-$CF_3C_6H_4$ (**4d**)	Ph	Et	**11d**	18	41	96
6	4-CNC_6H_4 (**4e**)	Ph	Et	**11e**	24	47	95
7[d]	Ph (**4f**)	Ph	Et	**11f**	36	54	84
8	4-$CH_3C_6H_4$ (**4g**)	Ph	Et	**11g**	36	41	83
9	4-BrC_6H_4 (**4h**)	Ph	Et	**11h**	36	58	84 (>99[e])
10	4-ClC_6H_4 (**4i**)	Ph	Et	**11i**	36	44	90 (>99[e])
11[f]	2,3-$Cl_2C_6H_3$ (**4j**)	Ph	Et	**11j**	36	45	79 (>99[e])
12	COOEt (**4k**)	Ph	Et	**11k**	10	63	97
13	4-$NO_2C_6H_4$ (**4a**)	Ph	*t*-Bu	**11l**	36	43	96
14	COOEt (**4k**)	Ph	$CH_2CH{=}CH_2$	**11m**	6	57	96
15	4-$NO_2C_6H_4$ (**4a**)	Ph	$CH_2CH{=}CH_2$	**11n**	18	51	94
16	3-$NO_2C_6H_4$ (**4b**)	Ph	$CH_2CH{=}CH_2$	**11o**	18	56	94
17	4-$NO_2C_6H_4$ (**4a**)	Ph	Bn	**11p**	24	48	92
18	COOEt (**4k**)	Ph	Bn	**11q**	10	45	97
19	COOEt (**4k**)	4-BrC_6H_4	Et	**11r**	6	78	96
20	3-$NO_2C_6H_4$ (**4b**)	4-BrC_6H_4	Et	**11s**	18	58	91
21	4-$NO_2C_6H_4$ (**4a**)	4-BrC_6H_4	Et	**11t**	20	72	93
22	4-$NO_2C_6H_4$ (**4a**)	4-$NO_2C_6H_4$	Et	**11u**	24	57	92
23	4-$NO_2C_6H_4$ (**4a**)	4-$CH_3C_6H_4$	Et	**11v**	36	51	81
24[f]	3-$NO_2C_6H_4$ (**4b**)	4-$OCH_3C_6H_4$	Et	**11w**	20	56	93
25[f]	4-$NO_2C_6H_4$ (**4a**)	2-$OCH_3C_6H_4$	Et	**11x**	30	51	92

[a] The reaction mixture of **4** (0.24 mmol) with **9** (0.20 mmol), **6a** (0.02 mmol), and 4-nitrobenzoic acid (0.02 mmol) was stirred in CH_2Cl_2 (1.0 mL) at 0 °C.
[b] Isolated yield of **11**.
[c] Measured by chiral HPLC.
[d] The reaction was performed at −10 °C.
[e] After a single recystallization.
[f] Yield of the products of cyclization.

vided the desired product in 63% yield with 97% *ee* (entry 12). Evaluation of the effect of R^3 group in the Nazarov reagents on the reaction indicated that the stereoselectivity is quite independent on the size of R^3. However, the yield seemingly suffered with more bulky substituent (entries 13–18). The general tolerance of the substituent at C-5 of the Nazarov reagents was demonstrated by reactions with unsaturated aldehydes **4a**, **4b**, and **4k** (entries 19–25). Both the electron-rich and electron-poor aryl substitents at C-5 of the Nazarov reagent could be tolerated and high enantioselectivities of over 90% *ee* were realized, with the exception of the reaction with a Nazarov reagent bearing a *p*-tolyl group at C-5 (entry 23). The absolute configuration of the stereogenic center of **11j** was assigned to be *S* on the basis of the X-ray structure (Figure 1, for crystallographic data, see Supporting Information).

The 3,4-dihydropyranol **10a** has been readily reduced to tetrahydropyran **12a** in moderate yield with an almost maintained enantiopurity by exposure to triethylsilane and Amberlyst resin in dichloromethane under mild conditions [Eq. (2)].

According to these experimental results, we proposed a mechanism to account for the formal [3+3] cycloaddition (Scheme 1). The unsaturated aldehydes **4** first condensed with the chiral pyrrolidine **6** to generate iminium salts **I**.[11] Enantioselective Michael addition of Nazarov reagents **9** to the active iminium salts **I** afforded intermediates **II**.[12] Numerous reports on the Morita–Baylis–Hillman reaction have demonstrated that acyclic electron-deficient al-

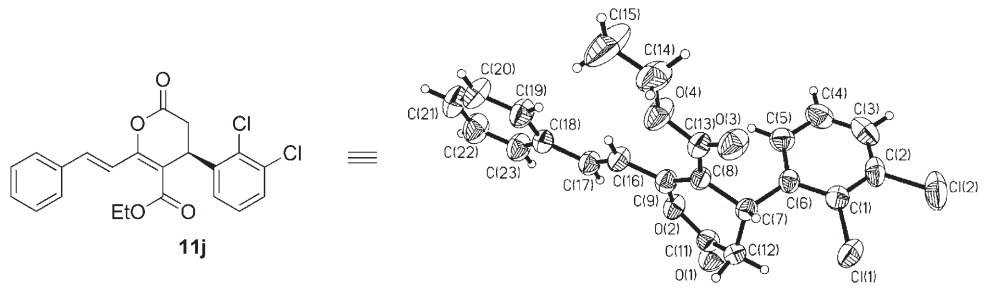
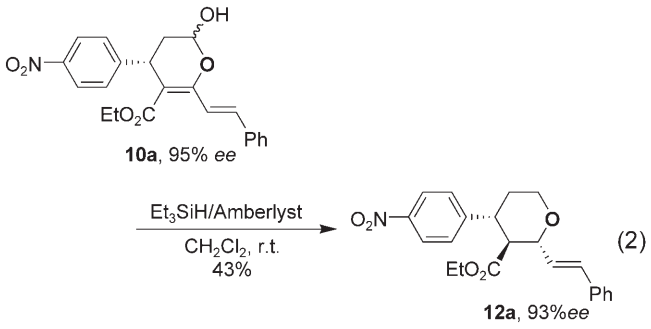


Figure 1. X-ray structure of **11j**; thermal ellipsoids at 50% probability.



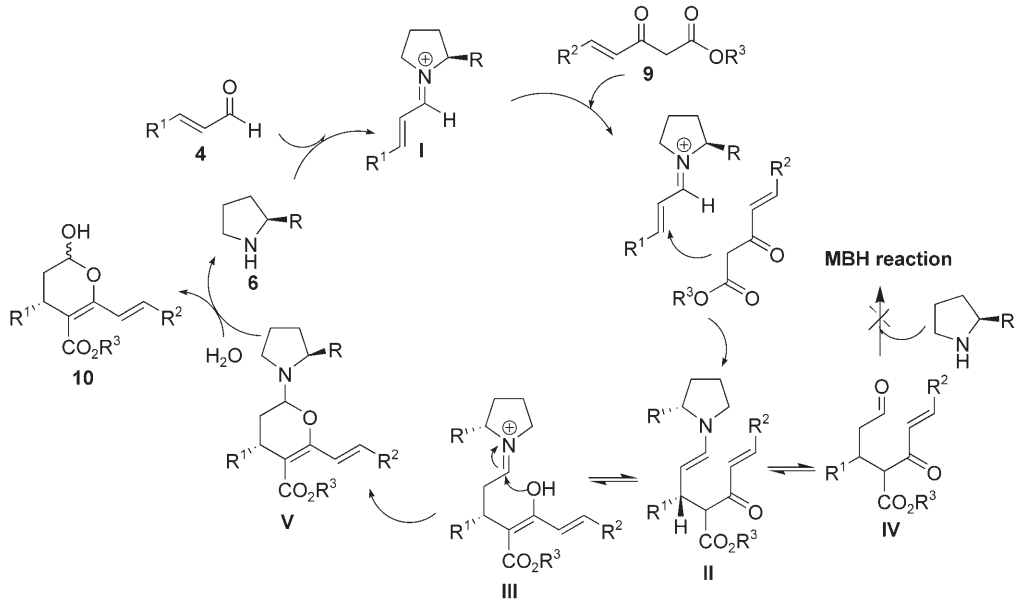
kenes with a substituent at the α-position are seemingly not reactive components of the Baylis–Hillman reaction.[13] Thus, the intermediates **II** have difficultly to undergo the Morita–Baylis–Hillman reaction after being isomerized to **IV** under the influence of pyrrolidine **6**. Alternatively, the intermediates **II** can be isomerized to **III** that occur from an intramolecular oxo-addition to form intermediates **V**. The hydrolysis of intermediates **V** with water generated from the condensation step releases the products **10** and the organocatalyst **6**.

In conclusion, we have disclosed a formal [3+3]cycloaddition reaction of α,β-unsaturated aldehydes with Nazarov reagents bearing an aryl group at C-5 which, after oxidation, affords 3,4-dihydropyranones in good yields with high enantioselectivities of up to 97% *ee*. In addition, chiral tetrahydropyrans could be accessed in high enantiopurity by diastereoselective reduction of the pyranols obtained directly from the [3+3]cycloaddition reaction.

Experimental Section

General Procedure for the Organocatalytic Asymmetric Formal [3+3]Cycloaddition of α,β-Unsaturated Aldehydes with Nazarov Reagents and Oxidation to the Corresponding 6-Vinyl-3,4-dihydropyranones

The catalyst **6** (0.02 mmol, 10 mol%), 4-nitrobenzoic acid (0.02 mmol, 10 mol%) and the α,β-unsaturated aldehydes **4**



Scheme 1. Proposed mechanism for the formal [3+3]cycloaddition of α,β-unsaturated aldehydes with Narzarov reagents.

(0.24 mmol, 1.2 equiv.) were stirred at ambient temperature in CH_2Cl_2 (1.0 mL) for 30 min, then stirred at 0 °C for 15 min before the addition of Nazarov reagents **9** (0.2 mmol). The reaction mixture was stirred for 6–36 h. The solvent was removed under reduced pressure and the residue was purified through column chromatography on silica gel. The products were stirred at ambient temperature in CH_2Cl_2 (3 mL) for 10 min, then oxidized using PCC (1.0 mmol, 5 equiv.) for 4 h. The solvent was removed under the reduced pressure and the residue was purified through column chromatography on silica gel.

Acknowledgements

We are grateful for financial support from National Science Foundation of China (20732006 and 20325211) and the Chinese Academy of Sciences.

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