Acid-Catalyzed Nazarov Reaction Controlled by β-Alkoxy Groups

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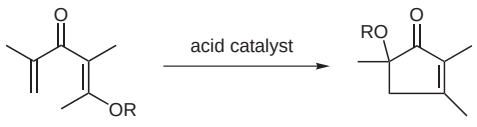
Abstract: Acid-catalyzed Nazarov reaction of β-alkoxy divinyl ketones providing 5-oxycyclopent-2-enones has been developed. The effects of the β-alkoxy group on the catalyst efficiency and the regioselectivity are based on the stabilization of the intermediates and the spontaneous elimination of the group followed by trapping. The substrates are easily accessible using the torquoselective olefination of esters with ynolates.

Key words: electrocyclic reactions, catalysis, cyclizations, Lewis acids, ynolates

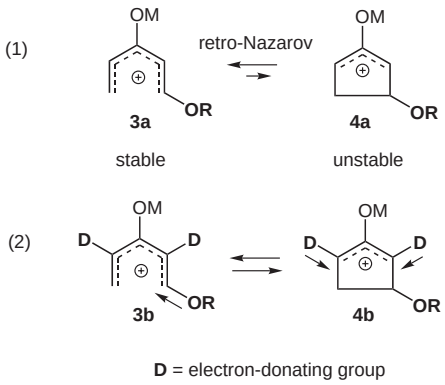
The Nazarov reaction is a 4π electrocyclic reaction providing cyclopentenones mediated by protic or Lewis acids.[1] Although it was developed some 60 years ago, certain limitation have kept the reaction from enjoying a wider use in synthetic organic chemistry, among which the harsh conditions often required due to use of a more than stoichiometric amount of acid and the poor regiochemistry of the alkene in the cyclopentenone product. In recent years, improved Nazarov reactions, such as the Lewis acid catalyzed reaction[2] and a substituent-controlled regioselective reaction, have been reported. Studies on these reactions are still in progress.[2,3] In this communication, we describe the highly efficient Brønsted acid catalyzed, as well as Lewis acid catalyzed, Nazarov reaction using the β-alkoxy divinyl ketones **1** to afford 5-alkoxycyclopent-2-enones **2**, in which the alkoxy group controls the reaction by its electronic properties, its facile elimination, and its ability to interrupt the key cation during the reaction (Scheme 1).



1 **2**

Scheme 1 Acid-catalyzed Nazarov reaction of β-alkoxy divinyl ketones

Since a β-alkoxy group in divinyl ketones would stabilize the pentadienyl cation **3a**, it was thought that the electrocyclic reaction to give the oxyallyl cation **4a** might not proceed. Actually, this type of substrates induced the retro-Nazarov reaction [Scheme 2 (1)].[4] We reasoned that if the oxyallyl cation **4b** also was properly stabilized by the α-substituents, the pentadienyl cation **3b** and the oxyallyl cation **4b** would be in equilibrium thus leading to the Nazarov products [Scheme 2 (2)].[5]



Scheme 2 Equilibrium between pentadienyl cation and oxyallyl cation

The starting *E*-β-alkoxy divinyl ketones were easily prepared according to our torquoselective olefination methodology with ynolates.[6] Ethyl 3-phenylpropionate was olefinated by the ynolate **5**[7] to afford the β-alkoxy-α,β-unsaturated acid **6** with high *E*-selectivity.[8] The acid **6** was converted into the Weinreb amide,[9] which was subjected to alkenylation to provide the β-alkoxy divinyl ketone **7** in satisfactory overall yield (Scheme 3).

We first tried the Nazarov reaction of the β-alkoxy divinyl ketone **7** with 10 mol% of $FeCl_3$ as a catalyst,[2a] and successfully obtained the 5-ethoxycyclopent-2-enone **8** in excellent yield as a single regioisomer (Table 1, entry 1); however, 1 mol% of the Lewis acid did not work. Encouraged by these results, we screened several Lewis acids, and found $Sc(OTf)_3$ to be a much better catalyst (entries 2–4).[10] Even only 1 mol% of $Sc(OTf)_3$ worked well as a catalyst (entry 2). When it was used, 5–20% of 5-hydroxylcyclopentenone **9** was generated, probably due to contamination with water and/or generation of the triflate **10**, which would be hydrolyzed during workup. In the presence of 10 equivalents of MeOH (entry 3), 5-methoxycyclopent-2-enone **11** was produced in good yield, and in the presence of 1 equivalent of H_2O (entry 4), **9** was obtained exclusively, suggesting the intermolecular interruption of

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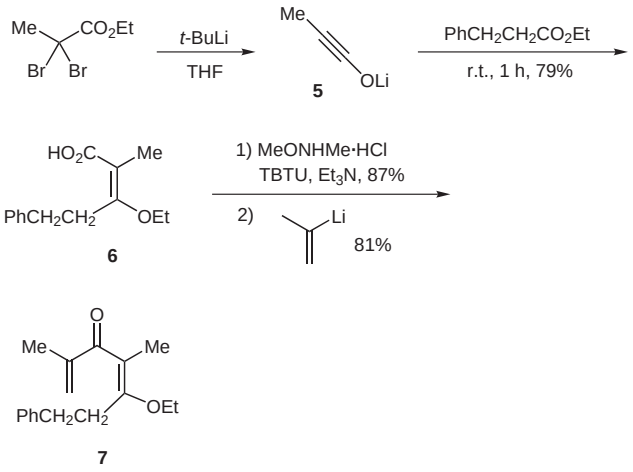


Scheme 3 Preparation of β-alkoxy divinyl ketone

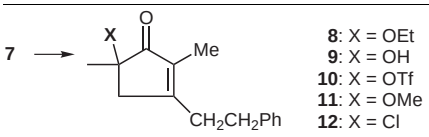
some cation species by the external nucleophiles. A stoichiometric amount of titanium(IV) chloride was needed for the activation to afford the α-chlorocyclopent-2-enone **12** (entry 5).

We next examined Brønsted acids as catalysts and found that the super acids, TfOH[11] and Tf_2NH, were excellent catalysts for the Nazarov reaction (entries 6–9). When 0.1 mol% of TfOH was used, the reaction was complete within 3 minutes to provide **8** in 74% yield (entry 6). The anhydrous TfOH, prepared by the pretreatment with Tf_2O (5 mol% to TfOH), considerably improved the yield up to 91%. When only even 0.001 mol% of Tf_2O was solely used, the product **8** was obtained in good yield (entry 8), probably due to the generation of TfOH by in situ hydrolysis of Tf_2O in the presence of a trace amount of water. An excess amount of HCl provided **12** in good yield (entry 10), and TsOH and TFA were less effective (entries 11, 12). The divinyl ketones were inert to acetic acid (entry 13).

The crossover experiment using the divinyl ketones **13** and **14** afforded a mixture of **15a**–**d** (Scheme 4). When the products (e.g. **8**) were exposed to methanol in the presence of acids, nothing happened. These results support that the products are stable enough to the acid and the intermolecular interruption of the oxyallyl cations by ethanol is irreversible.

Several β-alkoxy divinyl ketones were examined under catalytic conditions using TfOH and/or Tf_2O (0.1 mol%) or $Sc(OTf)_3$ (10 mol%, Table 2). Substrates equipped with the α,α′-dialkyl group (Me or *i*-Pr) provided the 5-alkoxycyclopent-2-enones in good to excellent yields (entries 1–8, 12). An isopropoxy group can also be introduced at the

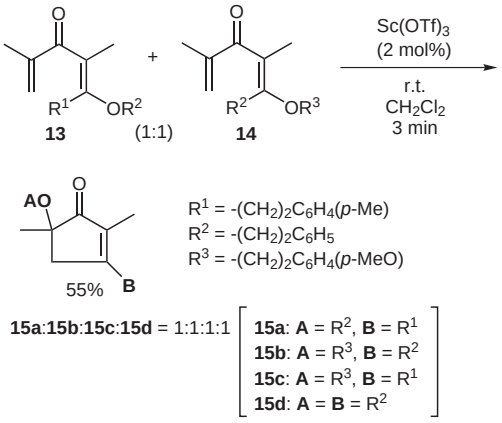
Table 1 Acid-Catalyzed Nazarov Reaction



8: X = OEt
9: X = OH
10: X = OTf
11: X = OMe
12: X = Cl

Entry	Acid	mol%	Conditions[a]	Product	Yield (%)
1	$FeCl_3$	10	r.t., 3 min	**8**	62
2	$Sc(OTf)_3$	1	r.t., 10 min	**8**	76
3	$Sc(OTf)_3$	10	r.t., 3 min[b]	**11**	72
4	$Sc(OTf)_3$	10	0 °C, 20 min[c]	**9**	94
5	$TiCl_4$	100	r.t., 1 h	**12**	73
6	TfOH	0.1	r.t., 3 min[d]	**8**	74
7	TfOH/Tf_2O	0.1/0.005	r.t., 3 min[d]	**8**	91
8	Tf_2O	0.001	r.t., 3 min[d]	**8**	80
9	Tf_2NH	0.1	r.t., 3 min[d]	**8**	76
10	HCl	300	r.t., 3 min	**12**	83
11	TsOH	10	r.t., 10 min	**8**	40
12	CF_3CO_2H	200	r.t., 4 h	**9**	39
13	AcOH	100	r.t.		n.r.

[a] 0.025 M in CH_2Cl_2, unless otherwise noted.
[b] In the presence of MeOH (10 equiv).
[c] In the presence of H_2O (1 equiv) in MeCN.
[d] 0.25 M.



Scheme 4 Crossover experiment

α-position (entry 3–5). The divinyl ketone **22** bearing cyclohexene mainly provided the dienone **23** (entries 9, 10), and in the presence of 10 equivalents of ethanol, the α-ethoxy product **24** was obtained (entry 11). Owing to the steric hindrance of the cyclohexene, the β-elimination might compete with the addition of ethanol to the cation. From these results, the α,α′-dialkyl-β-alkoxy divinyl ketones were found to be excellent substrates for the Nazarov reaction.

Since the reactions with the α,α′-monoalkyl substrates **27** and **28** gave a complex mixture, we reasoned that the α,α′-alkyl group is essential. Furthermore, the fact that the reaction of nonoxygenated divinylketone **29** (Figure 1) did not provide the cyclized product under the catalytic conditions (A, A′, and B) indicated the importance of the β-alkoxy group. The β-alkoxy and the α,α′-dialkyl groups stabilize **3b** and **4b** (Scheme 2), respectively, resulting in their equilibrium. Nucleophilic attack by a nucleophile such as alkoxide or triflate, followed by the irreversible elimination of β-alkoxide, would lead to the product along with the regeneration of the acid catalyst. If the nucleophilic attack is prevented for steric reasons, β-elimination would proceed to give a dienone like **23**.[14] An investigation into a detailed mechanism is now in progress.

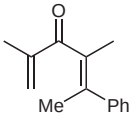


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Figure 1

In conclusion, we have developed a highly efficient acid-catalyzed Nazarov reaction of β-alkoxy divinyl ketones providing 5-oxycyclopent-2-enones. The remarkable effects of the β-alkoxy group on the high catalyst turnover and the regioselective formation of products are based on the stabilization of the intermediates and the spontaneous elimination of the group followed by interruption.

Table 2 TfOH- and $Sc(OTf)_3$-Catalyzed Nazarov Reaction

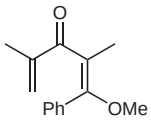
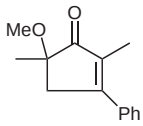
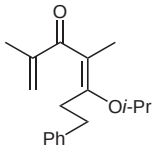
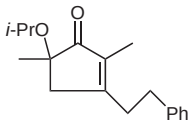
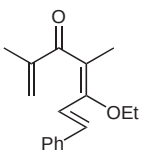
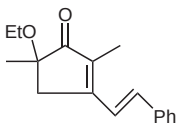
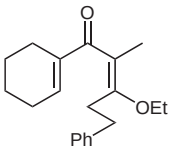
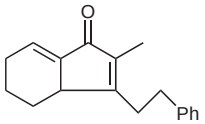
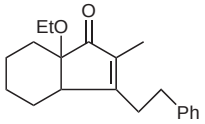
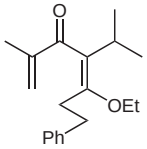
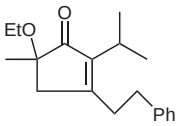
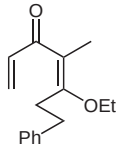
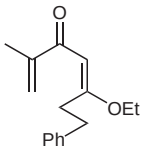
Entry	Substrate	Product	Conditions[a]	Yield (%)
1	 **16**	 **17**	A	96
2	**16**	**17**	B[b]	89
3	 **18**	 **19**	A	69
4	**18**	**19**	A′	73
5	**18**	**19**	B[c]	70
6	 **20**	 **21**	A	87
7	**20**	**21**	A′	92

Table 2 TfOH- and $Sc(OTf)_3$-Catalyzed Nazarov Reaction (continued)

Entry	Substrate	Product	Conditions[a]	Yield (%)
8	**20**	**21**	B	85
9	 **22**	 **23**	A	64 (**23**) 27 (**24**)
10	**22**	**23**	B	56 (**23**)
11	**22**	 **24**	B[d]	64 (**24**)
12	 **25**	 **26**	A	82
13	 **27**		A, B	0
14	 **28**		A, B	0

[a] Conditions A:[12] TfOH (0.1 mol%) and Tf_2O (0.005 mol%) at r.t. for 3 min in CH_2Cl_2. Conditions A′:[13] Tf_2O (0.1 mol%) at r.t. for 3 min in CH_2Cl_2. Conditions B: $Sc(OTf)_3$ (10 mol%) at r.t. for 3 min in CH_2Cl_2.
[b] In the presence of MeOH (10 equiv).
[c] In the presence of *i*-PrOH (10 equiv).
[d] In the presence of EtOH (10 equiv).

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(5) (a) In contrast, Denmark's β-silyl alkenes stabilize oxyallyl cations by the β-effect. See: Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, *104*, 2642. (b) In Frontier's polarized substrate, both of the pentadienyl and oxyallyl cations are stabilized. See ref. 2c.

(6) For reviews on ynolates, see: (a) Shindo, M. *Tetrahedron* **2007**, *63*, 10. (b) Shindo, M. *Synthesis* **2003**, 2275. (c) Shindo, M. *Synth. Org. Chem. Jpn.* **2000**, *58*, 1155. (d) Shindo, M. *Chem. Soc. Rev.* **1998**, *27*, 367.

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(9) Mannekens, E.; Tourwé, D.; Lubell, W. D. *Synthesis* **2000**, 1214.

(10) **General Procedure for the Sc(OTf)$_3$-Catalyzed Nazarov Reaction**
A solution of the (*E*)-β-alkoxy divinyl ketone (0.125 mmol) in CH_2Cl_2 (2 mL) was added to a solution of $Sc(OTf)_3$ (10 mol%) in CH_2Cl_2 (3 mL) in one portion at r.t. and the solution was stirred. After 3 min, a sat. aq $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The organic extracts were washed with a sat. aq $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residual oil was purified through silica gel column chromatography (hexane–EtOAc, 90:10) to give the α-ethoxy cyclopentenone.
Compound **8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (t, *J* = 7.2 Hz, 3 H), 1.27 (s, 3 H), 1.58 (s, 3 H), 2.38 (d, *J* = 18.4 Hz, 1 H), 2.67–2.80 (m, 3 H), 2.86 (t, *J* = 7.2 Hz, 2 H), 3.21–3.33 (m, 2 H), 7.15–7.30 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.98, 15.8, 23.2, 32.8, 33.1, 42.4, 59.4, 78.9, 126.4, 128.1, 128.5, 134.9, 140.2, 169.3, 208.3. IR (neat): 1705, 1643, 1088 cm^{-1}. MS (EI): *m/z* = 214 [M$^+$ – OEt]. Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.81; H, 8.73.

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(12) **General Procedure for the TfOH/Tf$_2$O-Catalyzed Nazarov Reaction**
Preparation of the TfOH/Tf_2O stock solution: 2.0 μL of a mixture, prepared from TfOH (1.0 mL, 11.3 mmol) and Tf_2O (50 μL), was dissolved in CH_2Cl_2 (50 mL). To the divinylketone (0.210 mmol) was added the stock solution (0.5 mL), containing TfOH (0.2 μmol) and Tf_2O (0.01 μmol), at r.t. under argon and stirred. After 3 min, a sat. aq $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The organic extracts were washed with a sat. aq $NaHCO_3$, and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residual oil was purified through silica gel column chromatography (hexane–EtOAc) to give the cyclopentenone.

(13) **General Procedure for the Tf$_2$O-Catalyzed Nazarov Reaction**
To a solution of the substrate (0.15 mmol) in anhyd CH_2Cl_2 (0.6 mL), under argon, was added TfOH (0.1 mol%) at r.t. and stirred. After 3 min, a sat. aq $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2. The organic extracts were washed with a sat. aq $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford a crude cyclopentenones. The residual oil was purified through silica gel column chromatography (hexane–EtOAc, 90:10) to give the desired α-ethoxy cyclopentenone as colorless oil.

(14) Interruption of oxyallyl cations: (a) Shoppee, C. W.; Cooke, B. J. A. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2271. Other examples, see: (b) Magnus, P.; Quagliato, D. *J. Org. Chem.* **1985**, *50*, 1621. (c) Asokan, C. V.; Bhattacharji, S.; Ila, H.; Junjappa, H. *Synthesis* **1988**, 281. (d) Hara, S.; Okamoto, S.; Narahara, M.; Fukuhara, T.; Yoneda, N. *Synlett* **1999**, 411. (e) Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 876. (f) Dhoro, F.; Tius, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 12472.