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A new strategy of tandem transetherification–intramolecular hetero Diels–Alder reaction with (*E*,*Z*)-mixture of ethyl 2-nitro-3-ethoxyacrylate and δ,ε-unsaturated alcohols leading to functionalized *trans*-fused bicyclic nitronates

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Abstract—Tandem reaction of (*E*,*Z*)-ethyl 2-nitro-3-ethoxyacrylate (*E*:*Z* = 25:75) with δ,ε-unsaturated alcohols leading to functionalized *trans*-fused bicyclic nitronates as single stereoisomers in high yields has been developed under thermal condition and in the presence of a catalytic amount of a Lewis acid catalyst such as $Yb(OTf)_3$. This process involves the configurational control of transetherified intermediates under a rapid, reversible transetherification reaction pathway for affording stereoselective *trans*-fused cyclic nitronates as single stereoisomers in intramolecular hetero Diels–Alder reaction.

Tandem reactions have emerged as a powerful method for efficient and stereoselective construction of polyheterocyclic and polycarbocyclic skeletons.[1] One most remarkable example is the tandem Knoevenagel–intramolecular hetero Diels–Alder (HDA) reaction, which is useful for the construction of polyheterocycles. Recently, we have developed a new type of tandem reaction by the use of β-alkoxy-substituted α,β-unsaturated carbonyl compounds and δ,ε-unsaturated alcohols as electrophilic heterodienes and nucleophilic dienophiles, respectively. These tandem transetherification–intramolecular HDA reactions proceed stereoselectively to afford functionalized *trans*-fused hydropyranopyran derivatives.[2]

As part of our long-standing research program aimed at the development of an effective synthetic route in stereoselective preparation of polyheterocycles based on tandem transetherification–intramolecular HDA reactions, our attention has been directed to the investigation of the applicability of β-alkoxy-substituted nitroalkenes as heterodiene components in tandem reaction with unsaturated alcohols as mentioned above. Recently, it was found that the tandem reaction of (*E*)-1-ethoxy-2-nitroethene with terminal dimethyl-substituted δ,ε-unsaturated alcohols successfully proceeds to afford bicyclic γ-lactones via the formation of stereoselective bicyclic nitronates in one flask.[3a]

In this communication, we present the more potential utility of the tandem reactions by using an (*E*,*Z*)-mixture of ethyl 2-nitro-3-ethoxyacrylate (*E*,*Z*)-**1** as the activated electrophilic hetero 1,3-diene component with additional electron-withdrawing of the ethoxycarbonyl group (Fig. 1),[4] thus enabling use of a variety of δ,ε-unsaturated alcohols as nucleophilic dienophiles in this tandem process.[5] This process involves the conjugated addition of unsaturated alcohols **2**–**10** to (*E*,*Z*)-**1** and the reversible elimination of the alcohols, followed in tandem by the participation of the only transetheri-

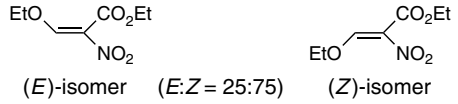

Figure 1. Configuration of nitro olefin **1**.

Keywords: Nitroalkene; Intramolecular hetero Diels–Alder reaction; Lewis acid; Tandem reaction; Transetherification; δ,ε-Unsaturated alcohols.
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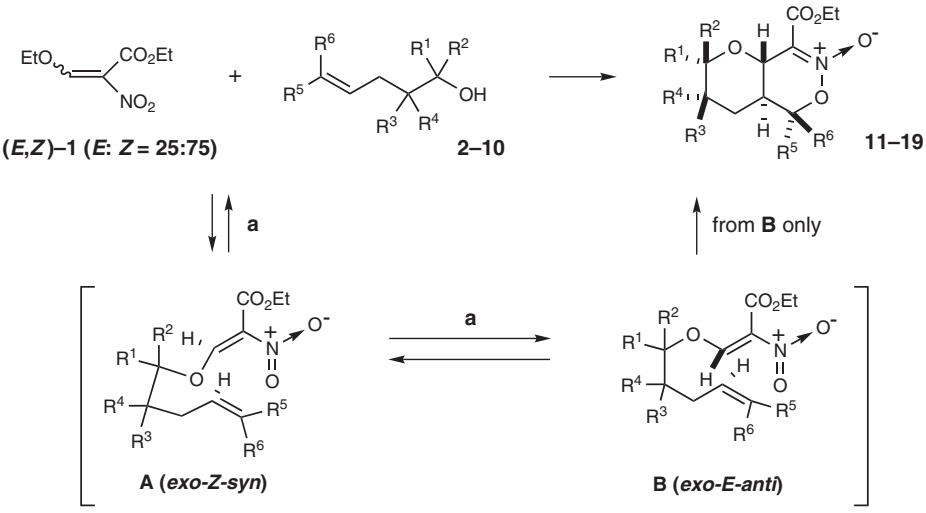
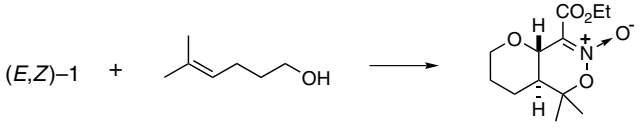


Scheme 1. Reaction pathways of tandem reaction of nitro olefin (*E*,*Z*)-**1** with alcohols **2**–**10** leading to *trans*-fused cyclic nitronates **11**–**19** under reversible transetherification reaction (a).

fied (*E*)-intermediate **B** (*exo-E-anti*), having the most favorable configuration with *exo-anti*-conformation of the tether in intramolecular cycloaddition, to afford *trans*-fused bicyclic nitronates **11**–**19**. A sufficient amount of (*E*)-intermediate **B** could be formed from the less favorable (*Z*)-intermediates **A** (*exo-Z-syn*), affording *cis*-fused cycloadducts in the intramolecular cycloaddition, under the rapid, reversible transetherification reaction pathway (Scheme 1). Thus, this tandem reaction is expected to afford *trans*-fused functionalized cyclic nitronates predominantly in good yields regardless of the configuration of the starting nitro olefin (*E*,*Z*)-**1**.

The tandem reaction of (*E*,*Z*)-**1** (*E*:*Z* = 25:75, 1.5 equiv) with 5-methyl-hex-4-en-1-ol **2** was investigated under thermal and Lewis acid-promoted conditions as a model reaction. The results are summarized in Table 1. Thermal tandem reaction was carried out at 90 °C (40 h), 110 °C (20 h), to 140 °C (8 h) to afford *trans*-fused cyclic nitronate **11** as a single stereoisomer in good to high yields of 80%, 85%, and 75% beyond the existence ratio of (*E*)-configuration (25%) in the starting nitro olefin, respectively (entries 1–3).[6] The stereochemistry at the junction of **11** was estimated to be *trans* based on the large vicinal coupling constant for J_{8a-4a} (10.2 Hz) by ^{1}H NMR spectrum analysis. The *trans*-structure arises from only the *exo-E-anti* transition state of similar substrates to intermediate **B**, which is well documented.[1c,7] These results indicate that the reversible transetherification is a key reaction pathway for supplying a sufficient amount of (*E*)-intermediate **B** (R^1–R^4 = H, R^5 = R^6 = Me), which was cyclized with *exo-E-anti* conformation to afford *trans*-fused cycloadduct **11**.[8] Furthermore, Lewis acids (10 mol %) such as $Yb(OTf)_3$, $Ni(ClO_4)_2{\cdot}6H_2O$, $Cu(SbF_6)_2$, and $Zn(ClO_4)_2{\cdot}6H_2O$, which were effective catalysts in tandem transetherification–intramolecular HDA reaction with (*E*)-2-ethoxy-1-nitroethene as the electrophilic hetero diene component,[3a] were examined at room temperature in CH_2Cl_2 (entries 4–8) and $Yb(OTf)_3$ was found to be the most effective promotor affording **11** stereoselectively in 1 h in 93% yield (entry

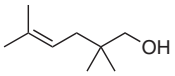
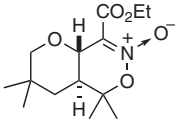
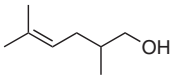
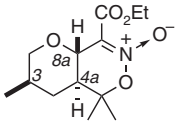
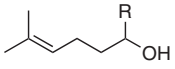
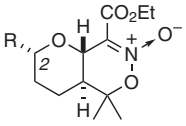
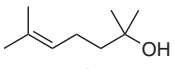
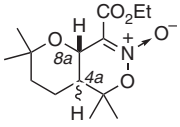
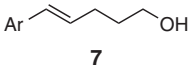
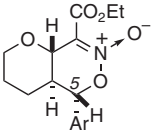
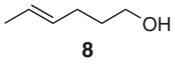
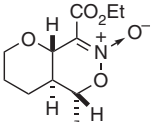
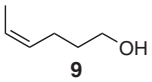
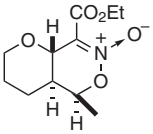
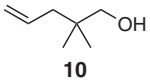
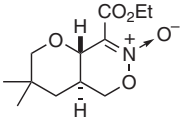
Table 1. Tandem reaction of (*E*,*Z*)-**1** with alcohol **2** leading to cyclic nitronate **11**[a]



Entry	Catalyst/10 mol %	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	—	$ClCH_2CH_2Cl$	90	40	80
2	—	Toluene	110	20	83
3	—	Xylene	140	8	75
4	$Yb(OTf)_3$	CH_2Cl_2	rt	1	93
5[c]	$Yb(OTf)_3$	CH_2Cl_2	rt	15	84
6	$Ni(ClO_4){\cdot}6H_2O$	CH_2Cl_2	rt	15	38
7	$Cu(SbF_6)_2$	CH_2Cl_2	rt	15	60
8	$Zn(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	rt	20	61

[a] 1.5 equiv of nitro olefin [*E*,*Z*-**1** (*E*:*Z* = 25:75) was used].
[b] Isolated yields.
[c] 1 mol % of catalyst was used.

Table 2. Tandem reaction of (*E*,*Z*)-**1** with alcohols **3**–**10** leading to cyclic nitronates **12**–**19** in the presence of $Yb(OTf)_3$[a]

Entry	Alcohols	$Yb(OTf)_3$ (mol%)	Time (h)	Products	Yield (%)[b]
1	 **3**	10	1	 **12**	98
2	 **4**	10	1	 **13**	90
3	 **5**	10	2	 **14**	**14a** (94)
4		10	5		**14b** (86)
5	**5a** (R = Me), **5b** (R = *i-Pr*), **5c** (R = Ph)	10	5	**14a** (R = Me), **14b** (R = *i-Pr*), **14c** (R = Ph)	**14c** (88)
6	 **6**	10	30	 **15**	**15a** (64)
				15a (4a,8a-*trans*), **15b** (4a,8a-*cis*)	**15b** (8)
7	 **7** Ar = *p*-$MeOC_6H_4$	10	2	 **16**	87
8	 **8**	10	30	 **17**	78
9		20	15		81
10		100	0.5		84
11	 **9**	10	30	 **18**	76
12	 **10**	20	72	 **19**	6
13		100	3		15

[a] All reactions were carried out at rt in CH_2Cl_2 by using 1.5 equiv of nitro olefin (*E*,*Z*)-**1** in the presence of $Yb(OTf)_3$ (10–100 mol%).
[b] Isolated yields.

4). It was also found that cycloadduct **11** was obtained stereoselectively in 84% yield by using only 1 mol% of $Yb(OTf)_3$ catalyst at rt for 15 h (entry 5).

Encouraged by these results, the generality of the present tandem reaction leading to stereochemically defined functionalized cyclic nitronates was investigated by using a variety of δ,ε-unsaturated alcohols **3**–**10** as nucleophilic dienophile components at rt in the presence of $Yb(OTf)_3$ (10 mol%) and the results are summarized in Table 2. The relative stereochemistry of products **12**–**19** was estimated on the basis of ^{1}H NMR spectral data.

The reaction with primary alcohol **3** having additional dimethyl substituents at the 2-position of the tether proceeded smoothly in 1 h to afford the corresponding *trans*-fused cycloadduct **12** ($J_{4a-8a} = 10.4$ Hz) as a single stereoisomer in the best yield of 98% (entry 1). With primary alcohol **4** monomethylated at the 2-position of the tether, the corresponding cycloadduct **13** [3,4a-*cis* and 4a,8a-*trans*: $J_{8a-4a} = 10.4$ Hz and notable NOEs (H-2ax → H-8a, 6.32%; H-2ax → 3-Me eq, 1.19%)] was obtained in high yield of 90% (entry 2). The reactions with *sec*-alcohols **5a**–**c** (**5a**, R = Me; **5b**, R = *i*-Pr; **5c**, R = Ph) also took place in 2–5 h to afford the corresponding **14a**–**c** [each 2,8a-*cis* and 4a,8a-*trans*; **14a**: $J_{8a-4a} = 10.2$ Hz and NOEs (H-8a → H-2ax, 7.70%)·**14b**: $J_{8a-4a} = 10.4$ Hz and NOEs (H-8a → H-2ax, 6.81%); **14c**: $J_{8a-4a} = 9.9$ Hz and NOEs (H-8a → H-2ax, 7.41%)] each as single stereoisomers in high yield of 94%, 86%, and 88%, respectively (entries 3–5). When bulky tertiary alcohol **6** was used, the reaction took a long time (30 h) and the corresponding both *trans*- and *cis*-cycloadducts **15** at the junction were obtained in good combined yields of 72% as a mixture of separable diastereomers by silica gel column chromatography [*trans*-adduct **15a** (64%, $J_{8a-4a} = 10.4$ Hz) and *cis*-adduct **15b** [8%, $J_{8a-4a} = 5.6$ Hz and NOEs (H-8a → H-4a, 4.82%)] (entry 6).

To evaluate the reactivity and stereospecificity in this tandem reaction, (*E*,*Z*)-**1** was allowed to react with primary alcohols **7**–**9** having terminal (*E*)-aryl, (*E*)-methyl, and (*Z*)-methyl substituents. The tandem reaction with (*E*)-5-(4-methoxyphenyl)pent-4-en-1-ol **7** also proceeded smoothly in 2 h to afford the cycloadduct **16** [4a,8a-*trans* ($J_{8a-4a} = 9.7$ Hz) and 4a,5-*trans* ($J_{5-4a} = 10.9$ Hz)] as a single stereoisomer in high yield of 87% (entry 7). When (*E*)- and (*Z*)-hex-4-en-1-ol **8**, **9** were used, it took a long time (30 h) to afford the cycloadduct **17** [78%, 4a,8a-*trans* ($J_{8a-4a} = 9.9$ Hz) and 4a,5-*trans* (NOEs: H-4a →···· 4.52%; H-8a →·H-5ax··1.92%)] and **18** [76%, 4a,8a-*trans* ($J_{8a-4a} = 10.4$ Hz) and 4a,5-*cis* ($J_{5-4a} = 4.6$ Hz)] each as a single stereoisomer in good yields, respectively (entries 8 and 11). When the amount of catalyst was increased to 100 mol%, this tandem reaction successfully proceeded within 30 min to afford stereoselective cycloadduct **18** in high yield of 84% (entry 10). As mentioned above, the relative stereochemistry between H-4a and H-5 of cycloadducts **16**–**18** was found to be retention of the configuration of starting alcohols **7**–**9** completely. These results indicate that this tandem reaction proceeds in a stereospecific manner. The tandem reaction with terminal unsubstituted δ,ε-alcohol **10** also proceeds stereoselectively to afford **19** ($J_{8a-4a} = 10.2$ Hz), but in low yield (15%) even by the use of 100 mol% of $Yb(OTf)_3$ as a catalyst (entries 12 and13).

In summary, we have developed an efficient new strategy of tandem transetherification–intramolecular HDA with an (*E*,*Z*)-mixture of ethyl 2-nitro-3-ethoxyacrylate (*E*,*Z*)-**1** and a variety of δ,ε-unsaturated alcohols **2**–**10** leading to the corresponding functionalized bicyclic nitronates **11**–**19** stereoselectively in high yields under thermal condition and with a catalytic amount of Lewis acids. We believe that the success of this tandem reaction depends upon the configurational control of more favorable transetherified (*E*)-intermediates in intramolecular cycloaddition under a rapid, reversible transetherification reaction pathway. Currently, efforts are under way to investigate the transformation of functional groups and further applicability to a catalytic asymmetric version.

References and notes

1. (a) Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992; (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131–163; (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136; (d) Denmark, S. K. *Chem. Rev.* **1996**, *96*, 137–165.
2. (a) Wada, E.; Kumaran, G.; Kanemasa, S. *Tetrahedron Lett.* **2000**, *41*, 73–76; (b) See also asymmetric version Wada, E.; Koga, H.; Kumaran, G. *Tetrahedron Lett.* **2002**, *43*, 9397–9400; (c) Koga, H.; Wada, E. *Tetrahedron Lett.* **2003**, *44*, 715–719.
3. (a) Wada, E.; Yoshinaga, M. *Tetrahedron Lett.* **2003**, *44*, 7953–7956; (b) see also Ono, N. *The Nitro Group in Organic Synthesis*; Wiley: New York, 2001; (c) Denmark, S. E.; Dappen, M. S.; Cramer, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 1306–1307; (d) Denmark, S. E.; Gomez, L. *Org. Lett.* **2001**, *3*, 2907–2910; (e) Denmark, S. E.; Juhl, M. *Helv. Chim. Acta* **2002**, *85*, 3712–3736, and references cited therein.
4. Knippel, E.; Knippel, M.; Michalik, M.; Kelling, H.; Kristen, H. *Tetrahedron* **1977**, *33*, 231–234, Chemical shifts of olefinic protons of (*E*,*Z*)-**1** by ^{1}H NMR ($CDCl_3$) spectrum analysis: (*E*)-**1** [δ = 8.22 (0.25H, s), lit. 8.19 ppm], (*Z*)-**1** [δ = 7.53 (0.75H, s), lit. 7.50 ppm].
5. Unsaturated alcohols **2**–**10** were prepared from the corresponding unsaturated carbonyls: (a) Cresson, P. *Bull. Soc. Chim. Fr.* **1964**, 2618–2628; (b) Saucy, G.; Marbet, R. *Helv. Chim. Acta* **1967**, *218*, 2091–2095; (c) Marbet, R.; Saucy, G. *Helv. Chim. Acta* **1967**, *218*, 2095–2100.
6. Characterization of the new compounds discussed in this work was based on the spectral and analytical data. Some typical spectral data are shown as follows: (a) *trans*-fused bicyclic nitonate **11** [(4a*R**,8a*S**)-ethyl 5,5- dimethyl-7-oxido-2,3,4,4a,5,8a-hexahydropyrano[2,3-*d*][1,2]oxazine-8-carboxylate]: viscous oil; IR (CH_3Cl):1735, 1598, 1440, 1377, 1290, and 952 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.31–1.37 (1H, m), 1.34 and 1.37 (each 3H, each s, 2×5-Me), 1.35 (3H, t, $J = 7.3$ Hz, ester Me), 1.74–1.78 (2H, m), 1.92–1.98 (2H, m), 3.55 (1H, dt, $J_{gem} = J_{2ax-3ax} = 11.6$ and $J_{2ax-3eq} = 4.1$ Hz, H-2ax), 4.07 (1H, dd, $J_{gem} = 11.6$ and $J_{2eq-3eq} = 3.9$ Hz, H-2eq), 4.13 (1H, d, $J_{8a-4a} = 10.2$ Hz, H-8a), and 4.31–4.39 (2H, m, OCH_2Me). ^{13}C NMR ($CDCl_3$)

$\delta = 14.00$, 19.05, 24.34, 25.12, 25.66, 43.35, 62.17, 68.74, 73.09, 86.36, 115.69, and 160.37. FAB-MS m/z 258 $(M+1)^+$ (calcd 257.1). FAB-HRMS calcd for $C_{13}H_{22}NO_2$ $(M+1)^+$ 258.1341, found 258.1334.

7. (a) Tietze, L. F.; Geissler, H.; Fennen, J.; Brumby, T.; Brand, S.; Schulz, G. *J. Org. Chem.* **1994**, *59*, 182–191; (b) Tietze, L. F.; Fennen, J.; Anders, E. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1371–1372.
8. Intramolecular cycloaddition reaction by using transetherified intermediates **A** and/or **B** themselves could not be examined because of their decomposition during the separation by silica gel column chromatography.