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Base-Catalyzed Stereoselective Isomerization of Electron-Deficient Propargylic Alcohols to *E*-Enones

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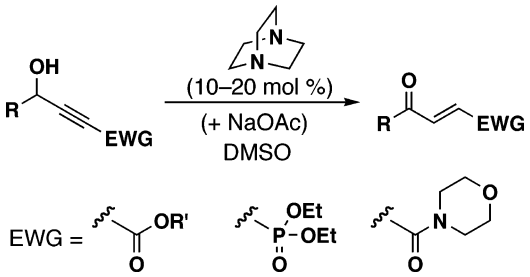
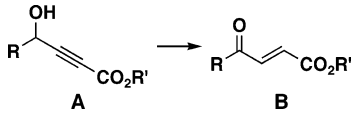


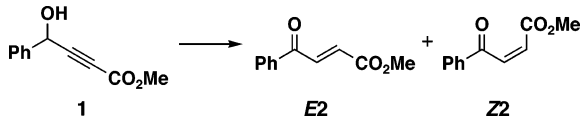
We have developed highly stereoselective methods to isomerize electron-deficient propargylic alcohols to *E*-enones under mild conditions (EWG = electron-withdrawing group). Among weak bases we screened, catalytic (10−20 mol %) 1,4-diazabicyclo[2.2.2]octane (DABCO) was found to be effective in most cases. When the substrate is conjugated with an amide, the addition of sodium acetate catalyzed the isomerization.

γ-Oxo-α,β-(*E*)-alkenyl esters (**B**, Scheme 1) are substrates for many types of organic reactions including Diels−Alder cycloadditions[1] and cyclopropanations.[2] These esters are also part of peptidomimetic[3] and natural products such as pyrenophorin[4] and macrosphelide B.[5] Compounds **B**, particularly those with R = aryl, are biologically and medicinally important small molecules.[6] While compounds **B** can be formed by means of Wittig-type condensations,[3] they can also be generated by the isomerization of readily accessible[7] γ-hydroxy-α,β-alkynyl esters **A**. In 1949, the first example of such an isomerization was reported by Nineham and Raphael (Scheme 2),[8] whereby **1** was subjected to excess Et_3N at 23 °C and the subsequent distillation afforded ***E*2**. The high *E*-selectivity is presumably due to the isomerization of ***Z*2** to ***E*2** at elevated temperature in the presence of Et_3N as indicated in more recent literature.[9] Although an alternative stereoselective isomerization of **A** to **B** is known, calling for 3 mol % of $Rh(PPh_3)_3Cl$ and air-sensitive[10] tri-*n*-butylphosphine at 110 °C,[11] currently the Nineham−Raphael method appears to be the method of choice.[9,12] Additional methods continue to emerge as isomerization of propargylic alcohols to enones is an important topic in organic synthesis.[13]

SCHEME 1. Isomerization of Propargylic Alcohol A to *E*-Enone B



SCHEME 2. Nineham-Raphael Reaction



The currently used, modified Nineham−Raphael method requires a high temperature (60 °C) and stoichiometric Et_3N in limited substrates, which prompted us to develop a more convenient method for the conversion of **A** to **B**. We found that treatment of **1** with 10 mol % of Et_3N in CH_2Cl_2 at 23 °C gave a mixture of ***E*2** and ***Z*2** in 70% yield with an *E*/*Z* ratio of 2:1. To optimize the reaction conditions, we screened organic bases (DBU, DMAP, DABCO, Et_3N, $^iPr_2NEt$) with **1** (initially at 0.25 M) in NMR tubes with various solvents at 23 °C, the result of which is summarized in Table 1. The conversion of **1** to ***E*2** and ***Z*2** was catalyzed by DBU with moderate *E*-selectivity in $CDCl_3$ (entry 1, *E*/*Z* = 5:1). Under these conditions, the *E*/*Z* ratio remained the same even after the starting material was consumed, excluding the isomerization of ***Z*2** to ***E*2**. Although the DBU-catalyzed redox isomerization was facile ($t_{1/2}$ < 0.3 h), less basic and more selective catalysts would be more desirable. Treatment of **1** with DMAP, a milder base, generated an intractable mixture (entry 2) that did not contain either ***E*2**

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TABLE 1. Redox Isomerization Optimization[a]

entry	base	solvent	$t_{1/2}$ (h)	***E*2/*Z*2**
1	DBU	$CDCl_3$	<0.3	5:1
2	DMAP	$CDCl_3$		not formed
3	Et_3N	$CDCl_3$	17	1.9:1
4	Et_3N	C_6D_6	16	1.3:1
5	Et_3N	DMSO-d_6	1.5	1.5:1
6	$^iPr_2NEt$	$CDCl_3$	60	1: 1.4
7	$^iPr_2NEt$	C_6D_6	126	1:1
8	$^iPr_2NEt$	DMSO-d_6	12	1:1.6
9	DABCO	$CDCl_3$		trace after 72 h
10	DABCO	C_6D_6		trace after 72 h
11	DABCO	DMSO-d_6	0.7	33:1
12	DABCO	CD_3CN		>10:1

[a] Conditions: initial [**1**] = 0.25 M, base (10 mol %), solvent (1.0 mL), 23 °C.

or ***Z*2**. Although Et_3N-catalyzed reactions were nearly quantitative in various solvents (entries 3−5), the *E*/*Z* ratios were low (∼1.7:1). It is noteworthy that despite the poor selectivity the reaction in DMSO (entry 5) was significantly faster than those in less polar solvents ($CDCl_3$, C_6D_6; entries 3 and 4). Interestingly, bulkier $^iPr_2NEt$ (entries 6−8) reversed the stereoselectivity, generating ***E*2** and ***Z*2** in 1:1−1.6 ratios. These reactions were again nearly quantitative; however, they were sluggish, requiring 12−126 h for 50% conversion. During these $^iPr_2NEt$-catalyzed reactions, the *E*/*Z* ratios remained the same for at least 96 h.

The isomerization did not proceed in the presence of DABCO in $CDCl_3$ and C_6D_6 (entries 9 and 10). However, a desirable isomerization protocol was finally found: treatment of **1** with 10 mol % of DABCO in DMSO-d_6 at 23 °C afforded ***E*2** and ***Z*2** in nearly quantitative combined yield with a 33:1 *E*/*Z* ratio (the yield and ratio were determined by NMR analysis). This operation is convenient because it requires only inexpensive DABCO and relatively nontoxic DMSO and does not require an inert atmosphere. In CD_3CN, the treatment of **1** with 10 mol % of DABCO generated **2** with a high *E*-selectivity (>10:1) but in somewhat lower yield (60−70% determined by ^1H NMR; entry 12). Suitable concentrations of **1** were determined to be 0.2−0.25 M; at higher concentrations (>0.5 M), the yield of ***E*2** is significantly lower, and at lower concentrations (<0.13 M), the reaction is slower, requiring more than 20 h, although the yield remains nearly the same.

After the discovery of the DABCO-catalyzed isomerization of **1** to **E2**,[14] our mechanistic studies were reported (Scheme 3).[15] Briefly, DABCO abstracts 4-H from **1** to generate the cumulene intermediate **3** as the rate-determining step. This intermediate then reacts with the protonated DABCO to form allenol **4**, which tautomerizes to form **Z2**. Finally, this putative intermediate undergoes DABCO-catalyzed isomerization to generate **E2**.

With this mechanistic insight, we set out to determine the scope of this method with 20 mol % of DABCO (Table 2). In almost all of the cases, Z-isomers were nearly undetectable. Analogously to methyl ester **1**, ethyl ester **5** (entry 1) was converted to its corresponding *E*-isomer **6** within 4 h in 72% isolated yield, showing the redox isomerization is tolerant of different ester functionalities.

The more electron-deficient (trifluoromethyl)phenyl derivative **7** (entry 2) and the electron-rich methoxyphenyl derivaitve **9**

SCHEME 3. Mechanism of DABCO-Catalyzed Redox Isomerization[15]

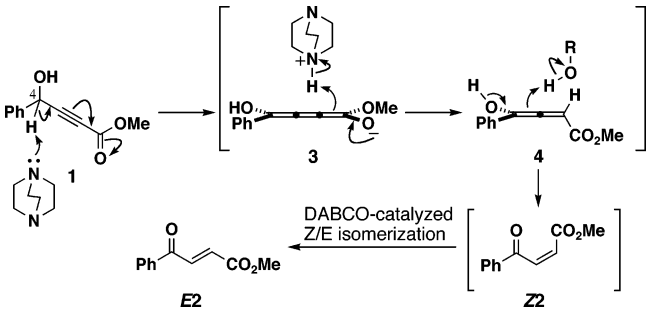
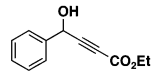
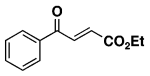
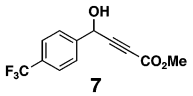
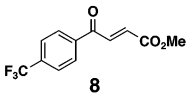
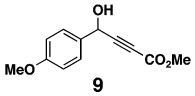
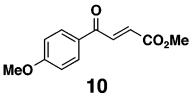
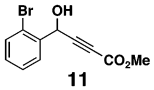
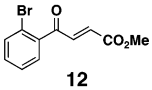
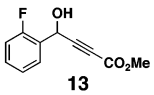
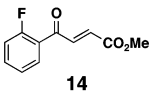
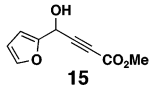
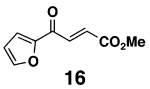
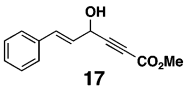
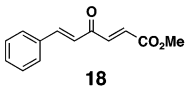
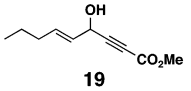
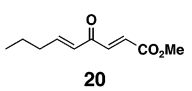
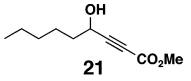
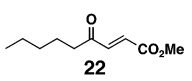
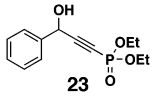
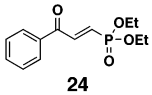
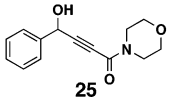
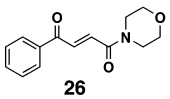


TABLE 2. Scope of DABCO-Catalyzed Isomerizations[a]

Entry	Substrate	Product	Time (h)	Yield (%)
1[a]	 **5**	 **6**	4	72
2[a]	 **7**	 **8**	2	62
3[a]	 **9**	 **10**	25	77
4[a]	 **11**	 **12**	23	34
5[a]	 **13**	 **14**	20	60
6[a]	 **15**	 **16**	9	78
7[a]	 **17**	 **18**	0.5	quant.
8[a]	 **19**	 **20**	24	0
9[b]	 **21**	 **22**	5	0
10[c]	 **23**	 **24**	30	95 (E:Z = 10:1)
11[d]	 **25**	 **26**	22	76

[a] Conditions: (a) DABCO (20 mol %), DMSO, 23 °C; (b) DABCO (20 mol %), DMSO, 23 → 95 °C; (c) DABCO (20 mol %), DMSO, 40 °C; (d) DABCO (20 mol %) and NaOAc (20 mol %), 23 °C.

(entry 3) underwent the isomerizations, providing the *E*-isomers **8** and **10** in 62% and 77%, respectively. The shorter (2 h) and

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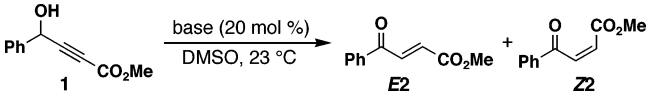
(15) Sonye, J. P.; Koide, K. *Org. Lett.* **2006**, *8*, 199−202.

TABLE 3. ***E*-Redox Isomerization Revisited**[a]



entry	base	time (h)	yield (%)	*E*2/*Z*2
1	DABCO	7	70	33:1
2	NaOAc	0.5	n/a[b]	1:2.4
3	DABCO/NaOAc	0.8	62	30:1

[a] Conditions: 20 mol % of base in DMSO at 23 °C. [b] Not isolated.

longer (25 h) reaction times compared to that in entry 1 (4 h) are consistent with the proposed mechanism due to the lower and higher pK_a values for the hydrogen atoms abstracted by DABCO. In addition to these para-substituted derivatives, ortho-substituted compounds were examined; unexpectedly, treatment of aryl bromide **11** (entry 4) with catalytic DABCO gave **12** only in 34% isolated yield and the reaction was slow (23 h). We are currently investigating side reactions of the **11** → **12** conversion. We postulate that steric hindrance posed by the bromide atom toward DABCO may be the cause of the longer reaction time. Aryl fluoride **13** (entry 5) underwent the isomerization in 20 h to give **14** in 60% isolated yield. According to the recent work of Bernotas,[8] this product is capable of undergoing a cascade sequence with 1,2-diamines (1,4-addition, lactamization, and intramolecular S_NAr-type reaction) to form medicinally important arylpyrazine derivatives.

The furan derivative **15** (entry 6) generated the corresponding product **16** in 78% yield, showing that the reaction is amenable to heteroaromatics. Interestingly, the isomerization of the cinnamyl alcohol derivative **17** (entry 7) was rapid (0.5 h), affording diene **18** in quantitative yield. However, the treatment of aliphatic alkene **19** (entry 8) with 20 mol % of DABCO in DMSO at 23 °C generated an intractable mixture with no detectable **20**. Compound **21** (entry 9) could not be transformed into **22** in the presence of DABCO; instead, the starting material was recovered even when the reaction was heated to 95 °C in the presence of 20 mol % of DABCO. Treatment of **21** with 75 mol % of $NaHCO_3$ in DMSO at 23 °C resulted in a complex mixture with no detectable olefin.

In addition to alkynoic esters, other electron-deficient alkynes were examined. Under the conditions used in entry 1−9 (20 mol % of DABCO in DMSO, 23 °C), diethyl phosphonate **23** (entry 11) was isomerized to **24** and its *Z*-isomer in an *E*/*Z* = 6:1 ratio. This ratio was improved to *E*/*Z* = 10:1 at 40 °C in 95% yield as a mixture of the stereoisomers. It is noteworthy that 50 mol % of $CsHCO_3$ was also capable of producing **24** with no detectable *Z*-isomer, but the isolated yield was moderate (50%).

The amide derivative **25** (entry 10) did not isomerize to **26** under the above conditions (20 mol % DABCO in DMSO at 23 °C), which is not surprising because the propargylic proton of **25** is not as acidic as that of the ester derivatives shown above. However, after screening efforts, we found that the isomerization proceeded under the modified conditions (20 mol % of NaOAc and 20 mol % of DABCO in DMSO, 23 °C, 22 h) to form **26** in 76% yield. To the best of our knowledge, this is the first example of the redox isomerization of an electron-deficient propargylic alcohol conjugated to an amide.

The facile reaction of amide **25** with NaOAc prompted us to apply these conditions to **1**. Our optimized conditions using DABCO gave ***E*2** selectively in 7 h (Table 3, entry 1) while NaOAc gave a shorter time scale (0.5 h) for the redox isomerization but with poor *E*/*Z* selectivity (entry 2). From these results, we hypothesized that the combination of DABCO and NaOAc would accelerate the redox isomerization without a loss of *E*/*Z* selectivity. In effect, treatment of **1** with 20 mol % of DABCO and 20 mol % of NaOAc gave ***E*2** in slightly lower 62% yield but in a much shorter reaction time (0.8 h; entry 3). We postulate that the stronger base, NaOAc, accelerates the rate-determining methine deprotonation step while the DABCO facilitates the *Z* to *E* isomerization to give excellent *E*/*Z* selectivity.[15]

In conclusion, we have developed a convenient method to isomerize γ-hydroxy-α,β-alkynyl esters to γ-oxo-α,β-(*E*)-alkenyl esters using catalytic DABCO. The modified methods were applied to propargylic alcohols conjugated with an amide and phosphonate, respectively. The corresponding highly *Z*-selective isomerization method will be reported in due course.[16]

Experimental Section

Alkynes were synthesized by one of the two following methods.

Preparation of 7 (Method A). Using the procedure as shown in ref 17, silica gel chromatography (5 → 20% EtOAc in hexanes) afforded **7** (303.0 mg, 61%) as a yellow oil: R_f = 0.33 (30% EtOAc in hexanes); IR (film) 3420 (br, OH), 3011, 2959, 2242 (C≡C), 1717 (C═O), 1438, 1329, 1260, 1167, 1128, 1017, 857 cm^{-1}; ^{1}H NMR (300 MHz, 293 K, $CDCl_3$) δ 7.65 (br s, 4H), 5.61 (br s, 1H), 3.80 (s 3H); ^{13}C NMR (125 MHz, 293 K, $CDCl_3$) δ 153.8, 142.4, 130.7 (q, J = 32.3 Hz), 126.8, 125.6 (q, J = 3.8 Hz), 123.8 (q, J = 270.4 Hz), 86.2, 77.5, 63.1, 52.9; HRMS (EI$^+$) calcd for $C_{12}H_9F_3O_3$ (M^+) 258.0503, found 258.0500.

Preparation of 11 (Method B). Using the procedure as shown in ref 18, silica gel chromatography (5 → 20% EtOAc in hexanes) afforded **11** (459.0 mg, 46%) as a yellow oil: R_f = 0.40 (30% EtOAc in hexanes); IR (film) 3411 (br, OH), 2954, 2923, 2238 (C≡C), 1716 (C═O), 1436, 1255, 1019, 942, 751 cm^{-1}; ^{1}H NMR (500 MHz, 293 K, $CDCl_3$) δ 7.72 (dd, 1H, J = 7.8, 1.5 Hz), 7.57 (d, 1H, J = 8.0 Hz), 7.38 (t, 1H, J = 7.6 Hz), 7.22 (td, 1H, J = 7.8, 1.6 Hz), 5.87 (s, 1H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, 293 K, $CDCl_3$) δ 153.8, 137.7, 132.9, 130.2, 128.4, 127.9, 122.4, 86.0, 76.9, 63.4, 52.9; HRMS (EI$^+$) calcd for $C_{11}H_9BrO_3$ (M^+) 267.9735, found 267.9742.

General Procedure for the Formation of Trans Olefins. Preparation of 8. To a solution of **7** (64.5 mg, 0.2500 mmol) in DMSO (1.25 mL) at 23 °C was added DABCO (5.6 mg, 0.050 mmol) in one portion, and the resulting solution was stirred at the same temperature for 2 h. The reaction was then diluted with water (25 mL) and then acidified to pH 3 with pH 3 phosphate buffer. The resulting aqueous mixture was extracted with Et_2O (25 mL × 3). The combined organic layers were then washed with water (25 mL) and brine (25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (5 → 20% EtOAc in hexanes) to afford **8** (40.0 mg, 62%) as a pale yellow solid: R_f = 0.41 (20% EtOAc in hexanes); mp = 73.5−74.0 °C; IR (film) 3079, 2927, 1731 (C═O), 1669 (C═O), 1628, 1410, 1319, 1306, 1164, 1126, 970, 773, 722 cm^{-1}; ^{1}H NMR (300 MHz, 293 K, $CDCl_3$) δ 8.11 (br d, 2H, J = 8.8 Hz), 7.90 (d, 1H, J = 15.6 Hz), 7.79 (br d, 1H, J = 8.8 Hz), 6.93 (d, 1H, J = 15.6 Hz), 3.87 (s, 3H); ^{13}C NMR (125 MHz, 293 K, $CDCl_3$) δ 188.6, 165.6, 139.1, 135.7, 135.0 (q, J = 32.5 Hz), 133.0, 129.0, 125.9, 123.4 (q, J = 273.8 Hz), 52.4; HRMS (ES$^+$) calcd for $C_{12}H_9F_3O_3$ (M^+) 258.0504, found 258.0538.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, IR, and HRMS analysis data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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