Aldol Reactions

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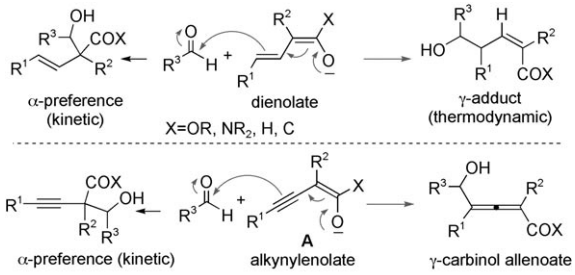
Thermodynamically Favored Aldol Reaction of Propargyl or Allenyl Esters: Regioselective Synthesis of Carbinol Allenoates**

*Bo Xu and Gerald B. Hammond**

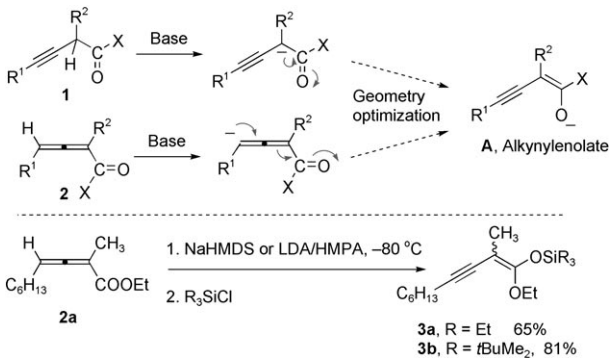
Dedicated to Professor David F. Wiemer

The aldol reaction is one of the cornerstones of synthetic organic chemistry, and as such it has been the subject of considerable optimization and multiple applications.[1] If a double bond is appended to the enolate precursor through conjugation, it gives rise to the so-called vinylogous aldol reaction depicted in Scheme 1 (top).[2] The inherent preference for α-functionalization (kinetic product) is attributed to the higher electron density at the α-carbon atom compared to the γ-carbon atom. The synthetic importance of the vinylogous aldol reaction has spurred the development of methods that address the regiochemistry problem but at the cost of increasing the experimental demands of the reaction or restricting the scope of substrates that can be utilized. A synthetically attractive yet unprecedented strategy is the aldol reaction of an enolate conjugated with a triple bond (Scheme 1, bottom). This reaction could be regarded as an alkynylogous[3] aldol reaction, and, as in the case of the vinylogous aldol reaction, this reaction is invariably prone to form the kinetic α-product. The reaction of an alkynylenolate with an aldehyde could lead to an interesting building block, namely, a substituted γ-carbinol allenoate (X = OEt), for which no general synthetic methodologies exist.[4] For this to occur, maximum control over the regioselectivity of this reaction must be exercised to favor the thermodynamic product.



Scheme 1. Regioselectivity considerations in the aldol reaction of extended enolates.

During our research on the synthesis and reactivity of fluorinated allenes,[5] we became interested in investigating whether the nature of the countercation could influence the outcome of base-mediated processes. Herein we report a practical and highly regioselective, TBAF-mediated synthesis (TBAF = tetra-*n*-butylammonium fluoride) of carbinol allenoates from either **1** or **2** (Scheme 2, X = OEt) by a thermodynamically controlled alkynylogous aldol reaction.



Scheme 2. Preparation of silylalkynylketene acetal **3**. HMDS = hexamethyldisilazide.

The synthetic potential of the carbinol allenoates was showcased by their efficient conversion to dihydrofurans or γ-lactones. Further, a silylalkynylketene acetal reacted under Mukaiyama conditions to yield hydroxyalkynoates or carbinol allenoates in highly regioselective fashion, or with an electrophilic fluorinating reagent to produce a α-fluoropropargyl ester.

In theory, if **1** or **2** were treated with a strong enough base, the deprotonation of the α-hydrogen atom of **1** or the γ-hydrogen atom of **2** should occur, furnishing alkynylenolate anion **A** (Scheme 2, top).[4a,e] Ab initio geometry optimization calculations (DFT/B3LYP/6.311G*) show that **A** is an energetically favored anionic species regardless of which hydrogen atom was abstracted. Thus, in principle, either **1** or **2** could be used as a synthetic precursor of **A**. The flexibility in the choice of starting material is an added advantage of conducting an aldol reaction with alkynylenolate **A**, because the propargyl and allenyl ester precursors **1** and **2** are readily prepared using standard protocols.[6]

[*] B. Xu, Prof. Dr. G. B. Hammond
Department of Chemistry
University of Louisville
Louisville, KY 40292 (USA)
Fax: (+1) 508-852-3899
E-mail: gb.hammond@louisville.edu

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The alkynylenolate anion **A** was generated under kinetic conditions by deprotonation of **2a** and trapped as its silylalkynylketene acetal **3** in good to very good yields (Scheme 2, bottom). Figure 1 illustrates the highest occupied molecular orbital (HOMO) of alkynylenolate anion **A** ($R^1 = R^2 = Me$) and its corresponding silylalkynylketene acetal **3**

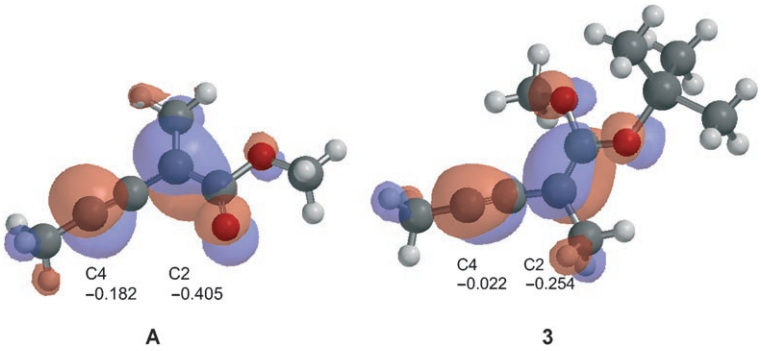
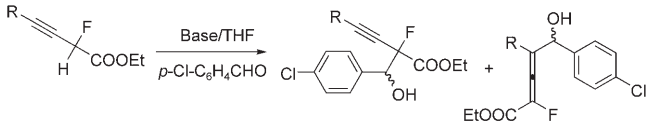


Figure 1. HOMO of optimized alkynylenolate anion **A** ($R^1 = R^2 = CH_3$, X = OEt) and corresponding silyl ether **3** (R = TMS).

along with the charge densities at C2 and C4. It is clear that these two carbon atoms correspond to the most nucleophilic sites in the molecule, but in an aldol reaction the higher electron density at C2 (α-position) should favor the kinetic product **4** (Table 1), in spite of the fact that the γ-adduct **5** is thermodynamically more stable, owing to its extended conjugation.

Table 1: Screening conditions for thermodynamic control.



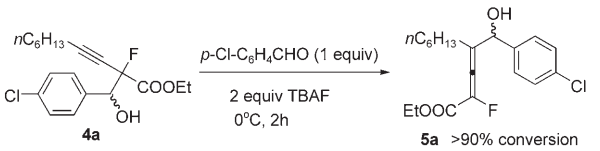
Entry	Base/additives	Equiv	*T* [°C]	*t* [h]	**4a** [%][a]	**5a** [%][a]	**1** [%][a]
1	LDA	1.5	−50	1	82	0	0
2	$Na[(TMS)_2N]$	1.5	−50	1	90	0	0
3	KF	2	RT	3	89	0	0
4	DBU	0.4	RT	3	61	0	5
5	CsF	2	RT	3	70	0	16
6	Et_3N	2	RT	48	44	0	27
7	LDA/HMPA	1	−50	1	73	27	0
8	$[(Bu)_4N][AcO]$	2	0	3	10	8	71
9	TBAF	2	0	1.5	trace	83	0
10	TBAF	0.2	0	1.5	70	3	17
11	Na_2CO_3	2	RT	12	0	0	100
12	pyridine	2	RT	12	0	0	100
13	$TBAF/H_2O$	2	RT	12	0	0	100
14	TBAF[b]	2	RT	12	0	0	100
15	TBAF[c]	2	0	3	71	5	2
16	$Na[(TMS)_2N]$/[15]c-5	2	−50	1	68	28	0

[a] Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as internal standard. [b] Ethanol as solvent. [c] *tert*-Butyl alcohol as solvent. LDA = lithium diisopropyl amide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, HMPA = hexamethyl phosphoramide.

The reaction of fluoropropargyl ester **1a** with *p*-chlorobenzaldehyde (Table 1) was used as model for our studies. The presence of fluorine in substrate **1a** allowed us to monitor the reaction using ^{19}F NMR spectroscopy with minimal steric disruption. As predicted, under kinetic conditions the α-isomer **4a** is obtained in very high yields (entries 1–2, Table 1).

According to computational calculations (Gaussian 03, DFT/B3LYP/6.311G*), the γ-product **5a** is 18 kJ mol^{-1} more stable than **4a**. This finding means that under purely thermodynamic control, the allenylic alcohol **5a** should predominate. In general, longer reaction times and higher temperatures will favor the thermodynamic product through the intermediacy of a retroaldol reaction, but those conditions may also lead to dehydration and other side reactions. Under standard thermodynamic conditions (entries 3–6, Table 1), the hydroxyalkynoate **4a** was the only product isolated. We hypothesized that the size and Lewis acidity of the countercation could influence the rate of the retroaldol reaction. When the size of the counterion is enlarged and its Lewis acidity is diminished, a chelated intermediate cannot be formed as easily, and an open alkoxide intermediate might be formed instead. This alkoxide intermediate may be energetically disfavored because of charge separation and loss of chelation, which in turn should enhance the rate of the retroaldol process, thus causing the reaction to fall under thermodynamic control. Experimentally, we observed that bases containing a rather large tetrabutylammonium cation tend to favor formation of the thermodynamic γ-product **5a**. TBAF (commercial solution in THF) gave the best yield and selectivity in THF (entry 9, Table 1). Alcoholic or predominantly aqueous media had a deleterious effect (entries 13–15, Table 1). Traditional kinetic bases like LDA or sodium hexamethyldisilazide, when complexed with HMPA or crown ether to increase the size of the counterion and reduce its complexing ability, augmented the production of the thermodynamic γ-product **5a** (compare entries 1 and 2 with entries 7 and 16, Table 1).

A crossover experiment that supported the occurrence of a retroaldol reaction is depicted in Equation (1). When the two diastereoisomers of the kinetic product **4a** were treated with one equivalent of chlorobenzaldehyde, conversion to the

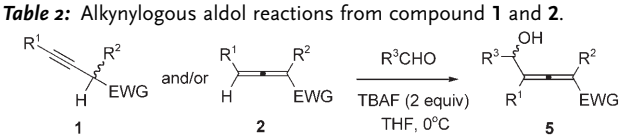


(1)

thermodynamic product **5a** occurred in high yield. This outcome is only possible if a mechanism involving a thermodynamically favored retroaldol reaction is invoked.

Because both **1** and **2** generate alkynylenolate **A** upon deprotonation, it should make no difference whether we use propargyl derivative **1**, allene compound **2**, or a mixture of both (Table 2). Indeed, the TBAF-mediated aldol reaction

Table 2: Alkynylogous aldol reactions from compound **1** and **2**.

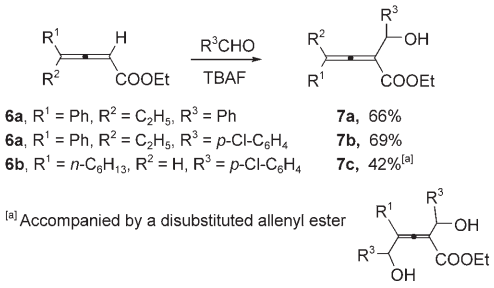


Entry	R^1	R^2	R^3	EWG	**1**:**2**	**5** [%][a]
1	nC_6H_{13}	F	*p*-Cl-C_6H_4	COOEt	100:0	**5a**, 56
2	nC_6H_{13}	F	*p*-Cl-C_6H_4	COO*t*Bu	100:0	**5b**, 60
3	nC_6H_{13}	Bn	*p*-Cl-C_6H_4	COOEt	4.5:1	**5c**, 56
4	Ph	CH_3	*p*-Cl-C_6H_4	COOEt	5:95	**5d**, 68
5	Ph	CH_3	*p*-NO_2-C_6H_4	COOEt	5:95	**5e**, 71
6	Ph	CH_3	*n*-C_5H_{11}	COOEt	5:95	**5f**, 51
7	Ph	CH_3	(*E*)-cinnamyl	COOEt	5:95	**5g**, 71
8	nC_6H_{13}	CH_3	Ph	COOEt	5:95	**5h**, 65
9	nC_6H_{13}	CH_3	*p*-Cl-C_6H_4	COOEt	5:95	**5i**, 90
10	nC_6H_{13}	CH_3	*p*-NO_2-C_6H_4	COOEt	5:95	**5j**, 70
11	nC_6H_{13}	CH_3	*o*-Br-C_6H_4	COOEt	5:95	**5k**, 77

[a] Yields of isolated compound. In all cases, traces or no compound **4** was detected. EWG = electron-withdrawing group, Bn = benzyl.

produced **5** regardless of the isomeric purity of **1** or **2** (compare entries 1, 3, and 9, Table 2). Not needing pure allenyl (**1**) or propargyl esters **2** as starting materials is an important feature of our procedure, because it is well-known that **1** and **2** tend to interconvert in the presence of base through a prototropic rearrangement.[7] Compounds **1** and **2** with alkyl or aryl substituents have been used successfully with hexanal, cinnamaldehyde, and other aromatic aldehydes in yields ranging from good to excellent (Table 2).

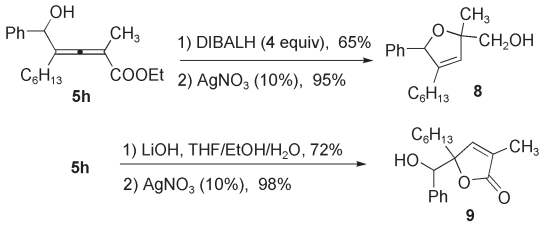
γ-Disubstituted allenoate **6** undergoes a facile α-aldolization under our standard conditions, yielding the corresponding α-carbinol allenoate **7** in satisfactory yields [Eq. (2)].



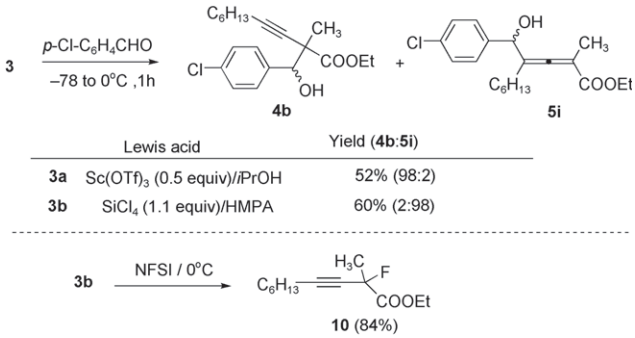
(2)

Carbinol allenoates have been reported to be good cycloaddition partners.[8] They also have been used in the synthesis of lactones through conjugate nucleophilic addition to the central carbon atom of the allene moiety.[4c] To showcase the synthetic potential of carbinol allenoate **5**, we conducted short and high-yielding syntheses of dihydrofuran **8** and γ-lactone **9**, both of which contain structural features found in numerous natural products (Scheme 3).

Finally, the silylalkynylketene acetal **3** can undergo a Mukaiyama aldol-type reaction[9] to produce α- or γ-aldol products **4** or **5** with excellent regioselectivity with the appropriate choice of Lewis acids, albeit in moderate yields thus far (Scheme 4, top). Silylalkynylketene acetal **3** can also



Scheme 3. Synthetic transformations of carbinol allenoate **5h**. DIBALH = diisobutylaluminum hydride.



Scheme 4. Synthetic transformations of silylalkynylketene acetal **3**. NFSI = *N*-fluorobenzenesulfonimide.

react with other electrophiles, as exemplified by the synthesis of a hitherto inaccessible quaternary α-fluoropropargyl ester **10** (Scheme 4, bottom).

In summary, we have described an extended aldol reaction of alkynylenolates with aldehydes in the presence of TBAF, in which the C–C bond formation takes place at the γ-position, thus yielding difficult-to-obtain carbinol allenoates under mild conditions. The latter were further converted into attractive structural motifs such as γ-lactones or dihydrofurans. Under Mukaiyama-type conditions, a silylalkynylketene acetal furnished α- or γ-aldol products depending on the choice of Lewis acid. The broader implications of this reaction in organic synthesis, including its asymmetric variant, are currently under investigation.

Experimental Section

3b: LDA (2 M in THF, 7.5 mL, 15 mmol) was added slowly over 5 min to a mixture of dry THF (50 mL) and HMPA (3.58 g, 20 mmol) at −80 °C. The reaction mixture was stirred at this temperature for 20 min, then a solution of **2a** (2.10 g, 10 mmol) in THF (10 mL) was introduced slowly over 5 min. The resulting solution was stirred for 10 min at −80 °C. *tert*-Butyldimethylsilyl chloride (TBDMSCl, 1.81 g, 12 mmol) in THF (6 mL) was then added by cannula. The reaction mixture was allowed to warm to 0 °C and was stirred for 30 min at 0 °C. The yellow solution was diluted with cold hexane (50 mL) and washed with cold saturated sodium bicarbonate solution (3 × 30 mL). The organic layer was dried over Na_2SO_4 and filtered, and the filtrate was concentrated in vacuo. The residue was purified by short-path distillation (85–95 °C, 1 Torr) to yield **3b** as a colorless oil (2.64 g, 81 %, *Z*/*E* 8:92). (*E*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.16$ (s, 6H; CH_3), 0.88 (t, $^3J(H,H) = 7.0$ Hz, 3H; CH_3), 0.94 (s, 3H; CH_3), 1.22–1.27 (m, 2H; CH_2), 1.27 (t, $^3J(H,H) = 7.5$ Hz, 3H; CH_3), 1.38–1.41 (m, 6H), 1.48–1.52 (m, 2H; CH_2), 1.65 (s, 3H; CH_3),

2.31 (t, ^3J(H,H) = 7.5 Hz, 2H; CH_2), 4.06 ppm (q, ^3J(H,H) = 7.0 Hz, 2H; CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): $\delta = -4.3$, 13.9, 15.0, 16.2, 17.9, 19.7, 22.5, 25.5, 28.5, 29.1, 31.4, 66.6, 78.8, 79.5, 90.5, 158.0 ppm. GC–MS (EI) $m/z = 324$ [M^+], 296, 268, 227, 149, 93.

5h: A solution of TBAF (1M in THF, 1.0 mL, 1 mmol) was added dropwise to a mixture of **2a** (105 mg, 0.5 mmol) and THF (0.5 mL) at 0 °C and the reaction mixture was stirred for 3 h at 0 °C. Then, saturated NH_4Cl solution (10 mL) was added to quench the reaction. After stirring for 5 min at about 0 °C, the resulting aqueous mixture was extracted with ether (3 × 15 mL). The extract was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel chromatography (10–20% ethyl acetate in hexane) to give **5h** (102 mg, 65%) as a colorless oil. **5h** was obtained as a mixture of two diastereomers in a ratio of 3.1:1. IR (neat): $\tilde{\nu} = 3418$, 2927, 1959, 1707, 1455, 1267, 1124 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS) Major isomer: $\delta = 0.85$ (t, ^3J(H,H) = 7.5 Hz, 3H; CH_3), 1.17–1.22 (m, 6H), 1.30–1.39 (m, 6H), 1.87–1.94 (m, 1H), 1.92 (s, 3H; CH_3), 2.72 (d, ^3J(H,H) = 4.5 Hz, 1H), 4.14–4.24 (m, 2H; CH_2), 5.15 (d, ^3J(H,H) = 4.5 Hz, 1H), 7.27–7.36 (m, 3H), 7.42–7.46 ppm (m, 2H); minor isomer: $\delta = 0.85$ (t, ^3J(H,H) = 7.5 Hz, 3H; CH_3), 1.17–1.22 (m, 6H), 1.30–1.39 (m, 6H), 1.87–1.94 (m, 1H), 1.89 (s, 3H; CH_3), 2.78 (d, ^3J(H,H) = 4.0 Hz, 1H), 4.14–4.24 (m, 2H), 5.26 (d, ^3J(H,H) = 4.0 Hz, 1H), 7.27–7.36 (m, 3H), 7.42–7.46 ppm (m, 2H); GC–MS (EI) $m/z = 300$, 253, 181, 149, 107; Elemental analysis (%) calcd. for $C_{20}H_{28}O_3$: C 75.91, H 8.92; found: C 75.97, H 9.09.

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