Stereoelectronic Effect on Stereoselective Olefination of Ketones Providing Tetrasubstituted Olefins via Ynolates

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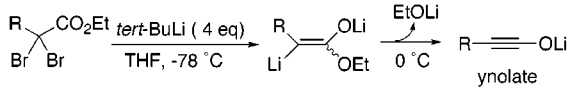
Olefination of a carbonyl group is one of the fundamental reactions in synthetic organic chemistry. Conventional methods such as the Horner−Wadsworth−Emmons reaction[1] and its variants[2] provide convenient routes to olefins from aldehydes. However, in the synthesis of tetrasubstituted olefins, which would be important units for organic synthesis,[3] high stereoselectivity has not been achieved using such reagents with *ketones*.[4] Therefore, development of a reaction with a novel mechanism is required for this process.

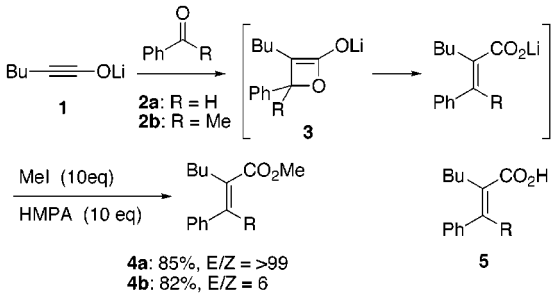
We previously reported a novel methodology for the generation of ynolate anions via cleavage of ester dianions (Scheme 1)[5] as well as new reactions using these unique anions.[6] More recently, we reported the olefination reaction of aldehydes and ketones with ynolates.[7] We now describe the unprecedented stereoelectronic effect on the stereocontrol in the formation of tetrasubstituted olefins using ynolates and the first successful achievement of high stereoselectivity.

Previously, we reported that ynolates (**1**) react with aldehydes (e.g., **2a**) at ambient temperature to give trisubstituted olefins (**5**, R = H) with excellent *E*-selectivity via ring opening of the resulting *β*-lactone enolates (**3**) (Scheme 2). The reaction of the ynolate (**1**) with acetophenone also provided the tetrasubstituted olefins (**5**, R = Me) with an *E*/*Z* ratio of 6:1. For easier isolation and purification of the desired olefins, instead of acidifying the resulting carboxylates, methyl iodide (10 equiv) was added to the solution along with HMPA or DMF to afford the corresponding methyl esters (**4**) in good yields without any loss of stereoselectivity.

Scheme 1



Scheme 2



In an attempt to elucidate the reaction mechanism, para-substituted acetophenones were used as substrates. Surprisingly, the *E*/*Z* selectivity in the olefination reaction with the ynolate was found to be strongly dependent on the electronic nature of the para-substituents, as shown in Table 1. The acetophenones with electron withdrawing groups gave lower *E*-selectivity (entries 1−3), compared to the unsubstituted case (entry 4). When nitro was the substituent, the *Z*-olefin was preferred. On the other hand, substrates with electron donating groups gave higher *E*-selectivity (entries 5−7). Finally we achieved complete *E*-selectivity in the synthesis of a tetrasubstituted olefin by using *p*-dimethylaminoacetophenone. As far as we know, this is the first example of a highly stereoselective olefination of ketones providing tetrasubstituted olefins. Since the para-substituents are positioned far from the reaction center (*β*-lactone enolate), presumably the stereochemistry is controlled by a stereoelectronic effect as well as by a steric effect.

To confirm this remarkable stereoelectronic effect, we then examined the olefination of para-substituted benzophenones, in which the steric effect should be negligible. The reactions proceeded smoothly to afford the desired tetrasubstituted olefins in excellent yields. As shown in Table 2, the benzophenones with an electron donating group (methyl, methoxy, dimethylamino) were converted into the desired tetrasubstituted olefins with *E*-selectivity, up to a ratio of 5:1 (entry 7). On the other hand, the benzophenones with an electron-withdrawing group gave the *Z*-olefin preferentially (entries 1 and 2).

Thus, to investigate the relationship between the selectivity and the degree of electron donation of the para-substituents, plots of $\Delta\Delta G^{\ddagger}$ ($\Delta G^{\ddagger}_{E} - \Delta G^{\ddagger}_{Z}$(kcal/mol)) versus σ values of the Hammett equation were constructed. As shown in Figure 1, the plot gave straight lines. This good linear relationship indicates that increasing electron density on the phenyl substituents tends to increase *E*-selectivity. Electron-rich aryl groups tend to wind up trans to the ester.

The reaction with 4-methoxy-4′-nitrobenzophenone gave the expected tetrasubstituted olefin with an *E*/*Z* ratio of 4:1, where the electron-donating group and the withdrawing group work concertedly (Scheme 3). Clearly, in these reactions, the stereochemistry was controlled only by a stereoelectronic effect.

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(2) For example: Marshall, J. A.; DeHoff, B. S.; Cleary, D. G. *J. Org. Chem.* **1986**, *51*, 1735−1741.

(3) For examples, Sharpless asymmetric epoxidation to trisubstituted allylic alcohols (tetrasubstituted olefins) provide the corresponding epoxides with high enantioselectivity. Since the products possess contiguous asymmetric carbons, they would be useful for synthesis of natural products. See: Erickson, T. J. *J. Org. Chem.* **1986**, *51*, 934−935; Marshall, J. A.; Jenson, T. M.; *J. Org. Chem.* **1984**, *49*, 1707−1712.

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(5) (a) Shindo, M. *Tetrahedron Lett.* **1997**, *38*, 4433−4436. (b) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, *54*, 2411−2422. For review: (c) Shindo, M, *Chem. Soc. Rev.* **1998**, *27*, 367−374.

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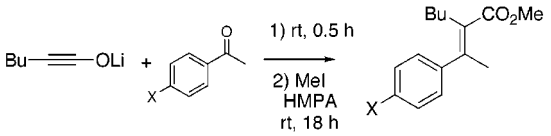
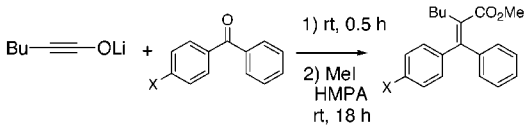
Table 1. Olefination of Para-Substituted Acetophenones via Ynolates[a]



entry	X	yield[b] (%)	*E*/*Z*[c]	$\Delta\Delta G^{\ddagger}$ [d]	σ[e]
1	NO_2	61	0.67	0.24	0.778
2	Cl	68	2.45	−0.53	0.227
3	F	88	4.0	−0.82	0.062
4	H	82[f]	6.0	−1.07	0
5	Me	89	10	−1.36	−0.17
6	MeO	80	20	−1.77	−0.268
7	Me_2N	64	>99	<−2.7	−0.83

[a] The dibromoester (1.0 mmol) and acetophenones (1.5 mmol) were used. [b] The yields were based on the dibromoesters. [c] The stereochemistry was determined by NOE experiments. [d] $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}_E - \Delta G^{\ddagger}_Z$ (kcal/mol). T = 298 K. [e] Substituent constant of Hammett equation. [f] The yield of the carboxylic acids.

Table 2. Olefination of Para-Substituted Benzophenones via Ynolates[b]



entry	X	yield[b] (%)	*E*/*Z*[c]	$\Delta\Delta G^{\ddagger}$ [d]	σ[e]
1	NO_2	92	0.34	0.64	0.778
2	Cl	92	0.67	0.24	0.227
3	F	>99	1.0	0.0	0.062
4	H	82[f]	1.0	0.0	0
5	Me	90	1.5	−0.24	−0.17
6	MeO	99	2.0	−0.41	−0.268
7	Me_2N	90	5.0	−0.95	−0.83

[a] The dibromoester (1.0 mmol) and benzophenones (0.8 mmol) were used. [b] The yields were based on the benzophenones. [c] The stereochemistry was determined by NOE experiments. [d] $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}_E - \Delta G^{\ddagger}_Z$ (kcal/mol). T = 298 K. [e] Substituent constant of Hammett equation. [f] The yield of the carboxylic acids.

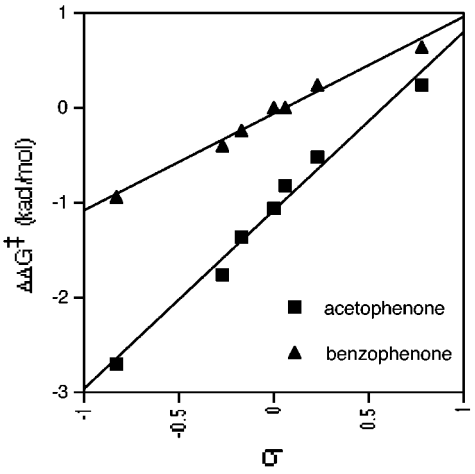
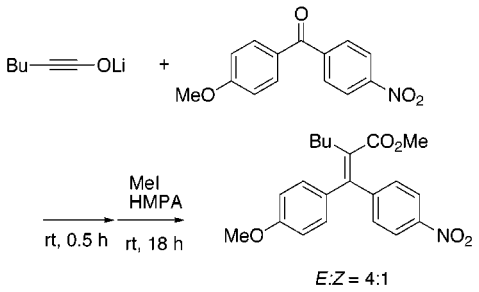


Figure 1. Plots of σ value vs $\Delta\Delta G^{\ddagger}$ for the olefination of para-substituted acetophenones and benzophenones.

It is known that Lewis acid activates reactions of aldehydes or ketones with alkynyl ethers to provide olefins.[8−10] The mechanism proposed is that an intermediate alkoxyoxetene is formed and its conrotatory ring-opening gives the corresponding α,β-unsaturated ester.[11,12] Our reaction may also be regarded as an electrocyclic ring-opening reaction of an oxetene, although

Scheme 3



not activated by Lewis acid.[13] Rondan and Houk reported substituent electronic effects on the ring-opening of cyclobutenes and their theoretical caliculations.[14] Our results may also be explained by their effects, since π-orbitals on the phenyl group can be considered as donor orbitals. The differences of selectivity found for the acetophenones and the benzophenones may be attributed to steric interaction between the butyl and methyl groups. For further detail mechanistic consideration, theoretical calculations are in progress.

In conclusion, we have found a novel stereoelectronic effect on the stereoselectivity in the ring-opening reaction of β-lactone enolates derived from ynolates. We have also achieved, for the first time, the highly stereoselective olefination of ketones providing tetrasubstituted alkenes. This work represents a new methodology for stereoselective construction of olefins and also shows the synthetic utility of ynolates.

Experimental Section

General Methods. ^{1}H NMR were measured in $CDCl_3$ solution and referenced to TMS (0.00 ppm). ^{13}C NMR were measured in $CDCl_3$ solution and referenced to $CDCl_3$ (77.0 ppm). All reactions were performed in oven-dried glassware under positive pressure of argon, unless otherwise noted. Reaction mixtures were stirred magnetically. Solutions of alkyllithium reagents were transferred by syringe or cannula and were introduced into reaction vessels through rubber septa.

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(10) The Lewis acid-catalyzed addition of alkynylsulfides to imines giving olefins: Ishitani, H.; Nagayama, S.; Kobayashi, S. *J. Org. Chem.* **1996**, *61*, 1902−1903.

(11) Isolation of the intermediate alkoxyoxetenes: (a) Middleton, W. J. *J. Org. Chem.* **1965**, *30*, 1307. (b) Oblin, M.; Parrain, J.-L.; Rajzmann, M.; Pons, J.-M. *Chem. Commun.* **1998**, 1619−1620.

(12) Theoretical calculations for the ring opening of oxetene: Yu, H.; Chan, W.-T.; Goddard, J. D. *J. Am. Chem. Soc.* **1990**, *122*, 7529−7537.

(13) The conversion of the β-lactone enolate into an olefin via "forbidden" β-elimination has been reported by Mulzer. This mechanism cannot be ruled out: see ref 7c.

(14) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989−7991. Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099−2111. Spellmeyer, D. C.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3412−3416. Kallel, E. A.; Wang, Y.; Spellmeyer, D. C.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 6759−6763. Li, Y.; Rubin, Y.; Diederich, F.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 1618−1623.

General Procedure for the Synthesis of Methyl 2-Butyl-3-(4-nitrophenyl)-2-butenoate (5b) from Butyl-Substituted Lithium Ynolate (Table 1, Entry 1). To a solution of ethyl 2,2-dibromohexanoate (302 mg, 1.0 mmol) in 6 mL of dry THF, cooled to −78 °C under argon, was added dropwise a solution of *tert*-butyllithium (2.70 mL, 4.0 mmol, 1.48 M in pentane). The yellow solution was stirred for 3 h at −78 °C and allowed to warm to 0 °C. After 30 min, the resulting colorless reaction mixture was warmed to room temperature and then a solution of *p*-nitroacetophenone (248 mg, 1.5 mmol) in THF (2 mL) was added dropwise. After 0.5 h, methyl iodide (0.62 mL, 10 mmol) and HMPA (1.7 mL, 10 mmol) were added. After 15 h, NH_4Cl solution (8 mL) was added, and then the resulting mixture was extracted with ethyl acetate (10 mL × 3). The organic phase was washed with water (10 mL × 3), saturated $NaHCO_3$ solution, saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil, which was chromatographed over silica gel (2% ethyl acetate in hexane) to yield 170 mg (69%) of ester as a pale yellow oil. It was separated into the *E*- and *Z*-olefins with preparative HPLC (eluent: 2% AcOEt in hexane).

(*E*)-Methyl 2-Butyl-3-(4-nitrophenyl)-2-butenoate. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 0.76 (t, J = 7.2 Hz, 3 H,), 1.15 (tq, J = 7.2, 7.2 Hz, 2H), 1.28 (m, 2H), 2.09 (dd, J = 7.2, 7.2 Hz, 2H), 2.17 (s, 3H), 3.83 (s, 3H), 7.31 (d, J = 8.6 Hz, 2H), 8.23 (d, J = 8.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.7 (q), 22.3 (t), 22.9 (q), 30.8 (t), 31.0 (t), 51.7 (q), 123.8 (d), 128.3 (d), 132.2 (s), 140.8 (s), 146.9 (s), 149.8 (s), 169.8 (s). IR (neat): 1715, 1600, 1519 cm^{-1}. MS *m*/*z*: 277 (M^+), 278 (M + 1), 129 (100). HRMS (EI) calcd for $C_{15}H_{19}NO_4$ (M^+) 277.1314, found 277.1292. Preparative HPLC (2% EtOAc/hexane, 10 mL/min, LiChrosorb Si 60 (7 mm)) retention time: 67.5 min.

(*Z*)-Methyl 2-Butyl-3-(4-nitrophenyl)-2-butenoate. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 0.95 (t, J = 7.0 Hz, 3 H,), 1.33−1.52 (m, 4H), 2.11 (s, 3H), 2.47 (dd, J = 7.4, 7.4 Hz, 2H), 3.42 (s, 3H), 7.29 (d, J = 8.6 Hz, 2H), 8.17 (d, J = 8.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9 (q), 21.0 (q), 22.5 (t), 30.2 (t), 30.7 (t), 51.4 (q), 123.4 (d), 127.8 (d), 133.2 (s), 140.6 (s), 146.7 (s), 151.2 (s), 169.8 (s). IR (neat): 1717, 1600, 1520 cm^{-1}. MS *m*/*z*: 277 (M^+), 278 (M + 1), 128 (100%). HRMS (EI): calcd for $C_{15}H_{19}NO_4$ (M^+) 277.1314, found 277.1306. Preparative HPLC (2% EtOAc/hexane, 10 mL/min, LiChrosorb Si 60 (7 mm)) retention time: 55.1 min. NOE experiments: irradiation of CH_2 of allylic position produced an enhancement of the allylic CH_3 resonance.

General Procedure. Synthesis of (*E*)-Methyl 2-Butyl-3-(4-nitrophenyl)-3-phenylacrylate from Butyl-Substituted Lithium Ynolate (Table 2, Entry 1). To a solution of ethyl 2,2-dibromohexanoate (302 mg, 1.0 mmol) in 6 mL of dry THF, cooled to −78 °C under argon, was added dropwise a solution of *tert*-butyllithium (2.70 mL, 4.0 mmol, 1.48 M in pentane). The yellow solution was stirred for 3 h at −78 °C and allowed to warm to 0 °C. After 30 min, the resulting colorless reaction mixture was warmed to room temperature and then a solution of *p*-nitrobenzophenone (182 mg, 0.8 mmol) in THF (2 mL) was added dropwise. After 0.5 h, methyl iodide (0.62 mL, 10 mmol) and HMPA (1.7 mL, 10 mmol) were added. After 15 h, NH_4Cl solution (8 mL) was added and then the resulting mixture was extracted with ethyl acetate (10 mL × 3). The organic phase was washed with water (10 mL × 3), saturated $NaHCO_3$ solution, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil, which was chromatographed over silica gel (2% ethyl acetate in hexane) to yield 170 mg (69%) of ester as a pale yellow oil. It was separated into the *E*- and *Z*-olefins with preparative HPLC (eluent: 5% AcOEt in hexane).

(*E*)-Methyl 2-Butyl-3-(4-nitrophenyl)-3-phenylacrylate. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 0.86 (t, J = 7.2 Hz, 3H), 1.30 (tq, J = 7.2, 7.2 Hz, 2H), 1.47 (m, 2H), 2.32 (dd, J = 8.0, 8.0 Hz, 2H), 3.50 (s, 3H), 7.09 (m, 2H), 7.27 (m, 3H), 7.35 (d, J = 8.6 Hz, 2H), 8.21 (d, J = 8.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.8 (q), 22.5 (t), 30.9 (t), 32.0 (t), 51.7 (q), 123.6 (d), 128.0 (d), 128.3 (d), 128.4 (d), 130.1 (d), 135.7 (s), 140.8 (s), 142.8 (s), 147.5 (s), 170.7 (s). IR (Neat): 1717, 1598, 1520 cm^{-1}. MS *m*/*z*: 339 (M^+), 340 (M + 1), 43 (100). HRMS (EI): calcd for $C_{20}H_{21}NO_4$ (M^+) 339.1471, found 339.1495. Preparative HPLC (5% EtOAc/hexane, 10 mL/min, LiChrosorb Si 60 (7 mm)) retention time: 33.8 min.

(*Z*)-Methyl 2-Butyl-3-(4-nitrophenyl)-3-phenylacrylate. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 0.86 (t, J = 7.2 Hz, 3H), 1.30 (tq, J = 7.2, 7.2 Hz, 2 H,), 1.46 (m, 2 H,), 2.38 (dd, J = 8.0, 8.0 Hz, 2H), 3.51 (s, 3H), 7.13 (dd, J = 8.0, 1.6 Hz, 2H), 7.32 (m, 5H), 8.12 (d, J = 8.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.7 (q), 22.5 (t), 30.9 (t), 31.9 (t), 51.7 (q), 123.3 (d), 128.1 (d), 128.5 (d), 128.9 (d), 129.3 (d), 136.0 (d), 139.5 (s), 143.6 (s), 146.9 (s), 149.1 (s), 170.4 (s). IR (neat): 1718, 1595, 1519 cm^{-1}. MS *m*/*z*: 339 (M^+, 100), 340 (M + 1). HRMS (EI) calcd for $C_{20}H_{21}NO_4$ (M^+) 339.1471, found 339.1458. Preparative HPLC (5% EtOAc/hexane, 10 mL/min, LiChrosorb Si 60 (7 mm)) retention time: 29.1 min. NOE experiments: irradiation of CH_2 of allylic position produced an enhancement of the ortho protons of the phenyl group without the nitro substituent.

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Supporting Information Available: Synthetic procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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