A Kinetic Study on Michael-type Reactions of 1-(X-Substituted Phenyl)-2-propyn-1-ones with Amines: Effect of Amine Nature on Reactivity and Mechanism

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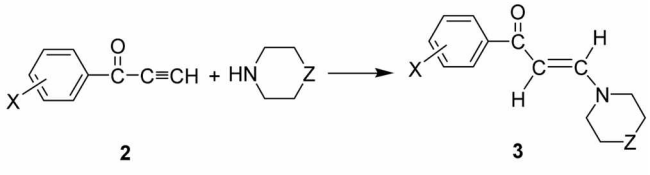
Second-order rate constants have been measured spectrophotometrically for the Michael-type reaction of 1-(X-substituted phenyl)-2-propyn-1-ones (**2a-f**) with amines in H_2O at 25.0 ± 0.1 °C. A linear Bronsted-type plot is obtained with $\beta_{nuc} = 0.25 \pm 0.02$, a typical β_{nuc} value for reactions which proceed through a stepwise mechanism with attack of amine on the electrophilic center being the rate-determining step. Secondary alicyclic amines are found to be more reactive than isobasic primary amines. The Hammett plot for the reactions of **2a-f** with morpholine is not linear, *i.e.*, the substrate with a strong electron-donating group (*e.g.*, 4-MeO) exhibits a negative deviation from the Hammett plot. However, the Yukawa-Tsuno plot for the same reactions exhibits an excellent linear correlation with $\rho = 0.62$ and $r = 0.82$. Thus, it has been proposed that the nonlinear Hammett plot is not due to a change in the rate-determining step but due to ground-state stabilization through resonance interactions.

Key Words : Michael-type reaction, Enaminone, Bronsted-type plot, Hammett plot, Yukawa-Tsuno plot

Introduction

Addition reactions of amines to carbon-carbon double bonds conjugated with a strong electron withdrawing group (EWG) have been intensively investigated and their reaction mechanisms are fairly well understood.[1-4] The corresponding reactions of carbon-carbon triple bonds with amines have also been performed widely.[5-11] However, most studies have been focused on the stereochemistry of the reaction products (*e.g.*, *Z*- or *E*-isomers of enamines) due to synthetic interests.[5-8] Thus, the mechanism for additions of amines to electron-deficient acetylene derivatives is not fully understood.

We have performed kinetic studies for Michael-type reactions of a series of aliphatic primary amines to activated acetylene derivatives such as 3-butyn-2-one (**1**)[9] and 1-(X-substituted phenyl)-2-propyn-1-ones (**2a-f**).[10] The reactions have been suggested to proceed through a stepwise mechanism with rate-determining nucleophilic attack on the electrophilic carbon atom followed by fast proton transfer.[9,10] However, the reactions of **1** with substituted anilines have been reported to proceed through specific acid catalysis and the catalytic effect is remarkable for the reaction with weakly basic aniline such as 4-cyanoaniline.[11]



2 **3**

X = 4-MeO (**2a**), 4-Me (**2b**), H (**2c**), 4-Cl (**2d**), 4-CN (**2e**), 3-NO_2 (**2f**)
Z = CH_2, NH, NCH_2CH_2OH, O, NCHO, NH_2^+.

Scheme 1

We have extended our study to reactions of **2a-f** with a series of secondary alicyclic amines as shown in Scheme 1. The kinetic data obtained in the current study have been compared with those reported for the corresponding reactions with aliphatic primary amines to investigate the effect of amine nature (*i.e.*, primary *vs.* secondary amines) on reactivity and reaction mechanism.

Results and Discussion

All reactions obeyed pseudo-first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln (A_\infty - A_t) = -k_{obsd}t + C$. The plots of k_{obsd} *vs.* amine concentrations were linear passing through the origin, indicating that general acid/base catalysis is absent. Thus, the rate equation is given by eq. (1). Five different amine concentrations were used to determine the second-order rate constants (k_N) from the slope of the linear plots of k_{obsd} *vs.* amine concentrations. Correlation of coefficients of the plots were usually higher than 0.9995. It is estimated from the replicate runs that the uncertainty in the rate constants is less than ± 3%. The second-order rate constants obtained in this way are summarized in Table 1. The k_N values reported for the corresponding reactions with primary amines are also included for comparison purpose.

$$\text{Rate} = k_{obsd}[\text{substrate}], \text{ where } k_{obsd} = k_N[\text{amine}] \quad (1)$$

Effect of Amine Basicity on Reactivity and Reaction Mechanism. As shown in Table 1, the second-order rate constant decreases as the basicity of amines decreases, *i.e.*, k_N decreases from 41.9 $M^{-1}s^{-1}$ to 11.5 and 2.21 $M^{-1}s^{-1}$ as the

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Table 1. Summary of Second-order Rate Constants for the Michael-Type Reactions of 1-Phenyl-2-propyn-1-one (**2c**) with Primary and Secondary Alicyclic Amines in H_2O at 25.0 0.1 °C[a]

Entry	amine	pK_a	$k_N/M^{-1}s^{-1}$
1	piperidine	11.22	41.9
2	piperazine	9.82	44.0
3	1-(2-hydroxyethyl)piperazine	9.38	20.8
4	morpholine	8.36	11.5
5	1-formylpiperazine	7.98	8.67
6	piperazinium ion	5.68	2.21
7	ethylamine	10.63	1.33
8	glycine	9.76	1.13
9	ethanolamine	9.50	0.703
10	benzylamine	9.34	1.22
11	glycylglycine	8.25	0.595
12	glycine ethyl ester	7.75	0.466
13	trifluoroethylamine	5.70	0.0467

[a]The k_N values for reactions with primary amines were taken from ref. 10.

pK_a of the conjugate acid of amines decreases from 11.22 to 8.36 and 5.68, in turn. The effect of amine basicity on reactivity is illustrated in Figure 1. The Bronsted-type plot exhibits a good linear correlation with β_{nuc} = 0.25 for the reactions of 1-phenyl-2-propyn-1-one (**2c**) with secondary alicyclic amines, when k_N and pK_a are statistically corrected using p and q (*i.e.*, p = 2 except p = 4 for piperazinium ion and q = 1 except q = 2 for piperazine).[12] A similar result is demonstrated for the corresponding reactions with primary amines. The magnitude of β_{nuc} values for the two series of reactions is almost identical within the experimental error

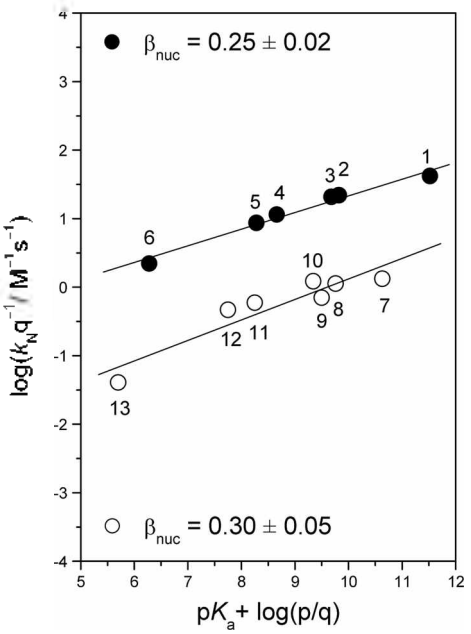
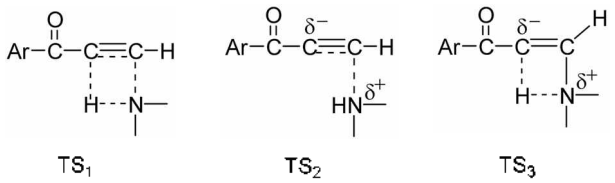


Figure 1. Bronsted-type plots for the Michael-type reactions of 1-phenyl-2-propyn-1-one (**2c**) with primary (○) and secondary alicyclic amines (●) in H_2O at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

range, implying that these reactions proceed through the same mechanism.

The current reactions can proceed either through a concerted mechanism with a transition-state (TS) structure similar to TS_1 or through a stepwise mechanism with TS_2 or TS_3 depending on the rate-determining step (RDS). One might expect a large primary kinetic isotope effect (KIE) if the reactions proceed through TS_1 or TS_3, in which proton transfer is partially advanced in the RDS. Since we found that KIE is absent for the reactions of **2c** with the primary amines, the reactions have been concluded to proceed through a stepwise with TS_2, in which proton transfer does not occur.[10] Thus, one can suggest that the reactions of **2c** with secondary amines also proceed through TS_2.



The above argument can be further supported by the β_{nuc} value of 0.25, which is typical for reactions proceeding through a stepwise mechanism with addition of amines to an unsaturated bond (*e.g.*, C=C or C=O bond) being the RDS. In fact, Bernasconi et al. have reported that β_{nuc} = 0.22-0.32 for addition of amines to benzylidene Meldrum's acids[2a,2f] and 1,2,3,4-tetrachloro-6-phenylfulvene.[2e] A similar β_{nuc} value has often been reported for aminolysis of various esters, in which the RDS is the attack of amines on the C=O bond to form an addition intermediate.[13-16]

Effect of Amine Nature on Reactivity and Reaction Mechanism. As shown in Figure 1, secondary alicyclic amines are more reactive than isobasic primary amines toward substrate **2c**. This result is consistent with the report that primary amines are less reactive than secondary or tertiary amines of similar basicity, *e.g.*, in deprotonation of carbon acids such as nitroethane,[17a] 4-nitrophenyl and 2,4-dinitrophenylacetonitriles,[18] in nucleophilic displacement on chloramines,[15] and in aminolysis of various esters.[17b,20] Since solvation energy was reported to increase in the order $R_3NH^+ < R_2NH_2^+ < RNH_3^-$, solvent effect has been suggested to be responsible for the lower reactivity shown by primary amines compared with secondary or tertiary amines.[17,18]

Steric hindrance would be more significant for the reactions with secondary amines than for those with primary amines. Accordingly, one might expect that secondary amines are less reactive than isobasic primary amines if steric hindrance is an important factor to determine the reactivity of amines. However, the current result shows that secondary amines are more reactive than primary amines of similar basicity, indicating that steric effect is insignificant for the present reactions.

One can expect that steric hindrance would be significant for reactions in which the bond formation between the nucleophile and the substrate is greatly advanced in the TS.

Table 2. Summary of Second-order Rate Constants for the Michael-type Reactions of 1-(X-Substituted Phenyl)-2-propyn-1-ones (**2a-f**) with Morpholine in H_2O at 25.0 ± 0.1 °C

Entry	X	k_N /$M^{-1}s^{-1}$
2a	4-MeO	4.64
2b	4-Me	8.59
2c	H	11.5
2d	4-Cl	14.4
2e	4-CN	31.4
2f	3-NO_2	34.5

The β_{nuc} value of 0.25 obtained in this study suggests that the bond formation is advanced only a little in the TS, which is responsible for the result that steric effect is insignificant in the current system. This argument is consistent with the reports that primary amines are more reactive than secondary or tertiary amines of similar basicity in the nucleophilic substitution reaction of phenyl acetate in which β_{nuc} = 1.05,[17b] while the reverse is true in the reactions of phosphate and sulfate esters in which β_{nuc} = 0.20[20a] and 0.13,[20b] respectively.

Effect of Substituents on Reactivity and Reaction Mechanism. To get further information on the reaction mechanism, second-order rate constants have been determined for the reactions of 1-(X-substituted phenyl)-2-propyn-1-ones (**2a-f**) with morpholine. As shown in Table 2, the reactivity increases as the substituent X changes from an electron donating group (EDG) to a strong EWG, *i.e.*, k_N increases from 4.64 $M^{-1}s^{-1}$ to 11.5 and 34.5 $M^{-1}s^{-1}$ as the substituent X changes from 4-MeO to H and 3-NO_2, in turn.

The effect of substituent X on reactivity is illustrated in Figure 2. The Hammett plot is not linear since **2a** exhibits a

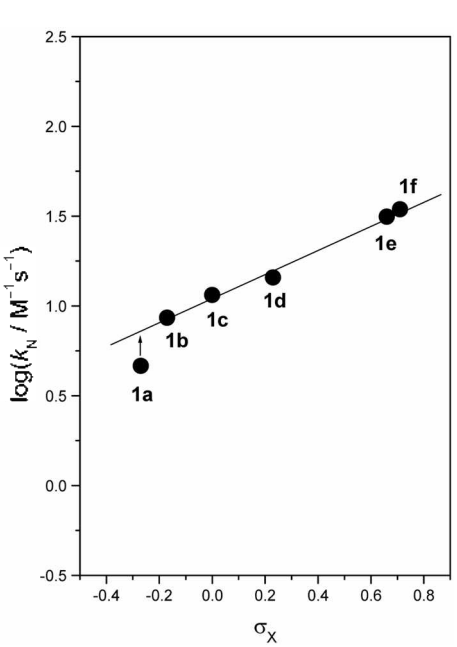


Figure 2. Hammett plot for the Michael-type reactions of 1-(X-substituted phenyl)-2-propyn-1-ones (**2a-f**) with morpholine in H_2O at 25.0 ± 0.1 °C. The identity of the points is given in Table 2.

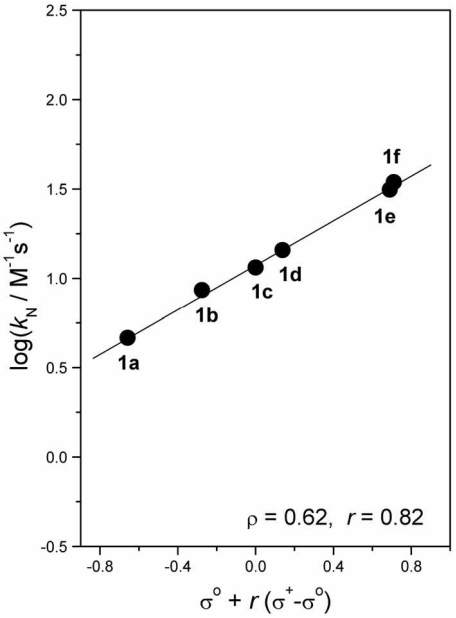


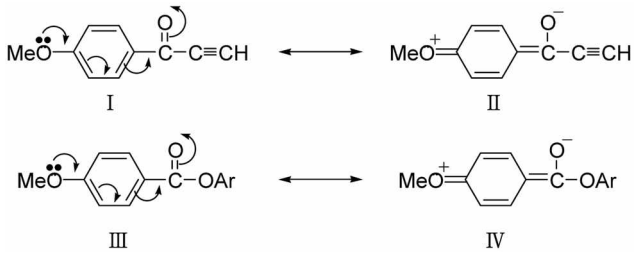
Figure 3. Yukawa-Tsuno plot for the Michael-type reactions of 1-(X-substitute phenyl)-2-propyn-1-ones (**2a-f**) with morpholine in H_2O at 25.0 ± 0.1 °C. The identity of the points is given in Table 2.

negative deviation. We have reported a similar result for aminolyses of 4-nitrophenyl X-substituted benzoates[21] and 2,4-dinitrophenyl X-substituted benzenesulfonates[22] as well as alkaline hydrolysis of *O*-4-nitrophenyl X-substituted thionobenzoates,[23] and nucleophilic substitution reactions of 2,4-dinitrophenyl X-substituted benzoates with OH^-, CN^-, and N_3^-.[24] In all cases, the substrate with a strong EDG in the benzoyl or sulfonyl moiety exhibited a negative deviation from the Hammett plot.[21-24] Traditionally, such a deviation has been interpreted as a change in the RDS on changing the substituent X from an EWG to an EDG since the rate of amine attack would be slow when X = EDG but becomes fast when X = EWG. However, we have proposed that the nonlinear Hammett plots were not due to a change in the RDS, since the corresponding Yukawa-Tsuno plots exhibited an excellent linear correlation.[21-24]

We have constructed a Yukawa-Tsuno plot for the reactions of **2a-f** with morpholine. Figure 3 demonstrates an excellent linearity with ρ = 0.62 and r = 0.82. Such a linear plot clearly indicates that the reactions of **2a-f** proceed without changing the RDS.

The r value in the Yukawa-Tsuno equation, eq. (2) represents the resonance demand of the reaction center or the extent of resonance contribution.[25] Accordingly, one can suggest that ground-state (GS) stabilization through the resonance interaction as illustrated in the resonance structures I and II is responsible for the negative deviation shown by the substrate with an EDG (*e.g.*, **2a**). This argument is consistent with our previous proposal that resonance structures III and IV are the cause of the negative deviation shown by the substrate with a strong EDG from the Hammett plot for aminolysis of aryl X-substituted benzoates.[21-24]

$$\log k^N/k^H = \rho[\sigma^o + r(\sigma^+ - \sigma^o)] \quad (2)$$



Conclusions

Our present study has allowed us to conclude the following: (1) The reactions of **2a-f** with all the amines studied proceed without general acid/base catalysis. (2) The reactions of **2c** with secondary alicyclic amines result in a linear Bronsted-type plot with β_{nuc} = 0.25, which is a typical β_{nuc} value for reactions proceeding through a rate-determining attack of amines on the electrophilic center (*e.g.*, TS_2). (3) Secondary amines are more reactive than isobasic primary amines toward **2c**. (4) The Hammett plot for the reactions of **2a-f** with morpholine is not linear, while the Yukawa-Tsuno plot for the same reactions results in an excellent linear correlation with r = 0.82. (5) The nonlinear Hammett is not due to a change in the RDS but due to GS stabilization through resonance interactions.

Experimental Section

Materials. 1-(X-substituted phenyl)-2-propyn-1-ones (**2a-f**) were readily prepared from oxidation of the corresponding carbinols.[26] which were obtained from the reactions of X-substituted benzaldehydes with ethynylmagnesium bromide in dried diethyl ether as reported in the literature.[27] The purity of **2a-f** was checked by means of their melting points and ^{1}H NMR spectra. Doubly glass distilled water was further boiled and cooled under nitrogen to eliminate CO_2 just before use. Amines and other chemicals employed were of the highest quality available.

Kinetics. The kinetic studies were performed using a UV-vis spectrophotometer for slow reactions ($t_{1/2}$ > 10 s) or a stopped-flow spectrophotometer for fast ones ($t_{1/2}$ ≤ 10 s) equipped with a constant-temperature circulating bath. The reactions were followed by monitoring the appearance of enaminone **3** at a fixed wavelength corresponding to the maximum absorption. Typically, the reaction was initiated by adding 5 μL of *ca.* 0.02 M substrate stock solution in CH_3CN by a 10 μL syringe to a 10 mm UV cell containing 2.50 mL of the reaction medium and the amine. All reactions were carried out under pseudo-first-order conditions in which the amine concentration was at least 20 times greater than that of **2a-f**. The amine stock solution of *ca.* 0.2 M was prepared in a 25.0 mL volumetric flask under nitrogen by adding 2 equiv of amine to 1 equiv of standardized HCl solution to obtain a self-buffered solution. All the transfers of solutions were carried out by means of gastight syringes.

Product analysis. The enaminones **3a-f** were identified to be *E*-isomers from their ^{1}H NMR spectra.

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References

1. Reviews: (a) Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301-308. (b) Bernasconi, C. F. *Tetrahedron* **1989**, *45*, 4017-4090. (c) Kutyrev, A. A.; Moskva, V. V. *Russ. Chem. Rev.* **1991**, *60*, 72-106.
2. (a) Ali, M.; Biswas, S.; Rappoport, Z.; Bernasconi, C. F. *J. Phy. Org. Chem.* **2006**, *19*, 647-653. (b) Bernasconi, C. F.; Ali, M.; Nguyen, K.; Ruddat, V.; Rappoport, Z. *J. Org. Chem.* **2004**, *69*, 9248-9254. (c) Bernasconi, C. F.; Leyer, A. E.; Rappoport, Z. *J. Org. Chem.* **1999**, *64*, 2897-2902. (d) Bernasconi, C. F.; Zitomer, J. L.; Schuck, D. F. *J. Org. Chem.* **1992**, *57*, 1131-1139. (e) Bernasconi, C. F.; Stronach, M. W. *J. Am. Chem. Soc.* **1990**, *112*, 8448-8454. (f) Bernasconi, C. F.; Murray, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 5251-5257.
3. (a) Sung, D. D.; Kang, S. S.; Lee, J. P.; Jung, D. I.; Ryu, Z. H.; Lee, I. *Bull. Korean Chem. Soc.* **2007**, *28*, 1670-1674. (b) Ku, M. H.; Oh, H. K.; Ko, S. *Bull. Korean Chem. Soc.* **2007**, *28*, 1217-1220. (c) Oh, H. K.; Lee, J. M.; Sung, D. D.; Lee, I. *J. Org. Chem.* **2005**, *70*, 3089-3093. (d) Oh, H. K.; Kim, I. K.; Lee, H. W.; Lee, I. *J. Org. Chem.* **2004**, *69*, 3806-3810. (e) Oh, H. K.; Yang, J. H.; Lee, H. W.; Lee, I. *J. Org. Chem.* **2000**, *65*, 5391-5395. (f) Oh, H. K.; Yang, J. H.; Lee, H. W.; Lee, I. *J. Org. Chem.* **2000**, *65*, 2188-2191.
4. (a) Varghese, B.; Kothari, S.; Banerji, K. K. *Int. J. Chem. Kinet.* **1999**, *31*, 245-252. (b) Varghese, B.; Kothari, S.; Banerji, K. K. *J. Chem. Res. (S)* **1998**, 422. (c) Jalani, N.; Kothari, S.; Banerji, K. K. *Can. J. Chem.* **1996**, *74*, 625-629.
5. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992, and references cited therein.
6. (a) Truce, W. E.; Onken, D. W. *J. Org. Chem.* **1975**, *40*, 3200-3208. (b) Truce, W. E.; Heuring, D. L.; Wolf, G. C. *J. Org. Chem.* **1974**, *39*, 238-244. (c) Truce, W. E.; Tichenor, G. J. *J. Org. Chem.* **1972**, *37*, 2391-2396.
7. (a) Sun, X.; Sengupta, S.; Petersen, J. L.; Wang, H.; Lewis, J. P.; Shi, X. *Org. Lett.* **2007**, *9*, 4495-4498. (b) Sopbue Fondjo, E.; Doepp, D.; Henkel, G. *Tetrahedron* **2006**, *62*, 7121-7131. (c) Crisp, G. T.; Millan, M. J. *Tetrahedron* **1998**, *4*, 637-648. (d) Sinsky, M. S.; Bass, R. G. *J. Heterocyclic Chem.* **1984**, *21*, 759-768.
8. (a) Shen, Z.; Lu, X. *Tetrahedron* **2006**, *62*, 10896-10899. (b) Zhao, L.; Lu, X.; Xu, W. *J. Org. Chem.* **2005**, *70*, 4059-4063. (c) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031-5041. (d) Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709-713. (e) Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1990**, 1643-1644.
9. Um, I. H.; Lee, J. S.; Yuk, S. M. *J. Org. Chem.* **1998**, *63*, 9152-9153.
10. Um, I. H.; Lee, E. J.; Seok, J. A.; Kim, K. H. *J. Org. Chem.* **2005**, *70*, 7530-7536.
11. Um, I. H.; Lee, E. J.; Min, J. S. *Tetrahedron* **2001**, *57*, 9585-9589.
12. Bell, R. P. *The Proton in Chemistry*; Methuen: London, 1959; p 159.
13. (a) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511-527. (b) Castro, E. A. *Chem. Rev.* **1999**, *99*, 3505-3524. (c) Page, M. I.; Williams, A. *Organic and Bio-organic Mechanisms*; Longman: Harlow, U.K., 1997; Chapter 7.
14. (a) Castro, E. A.; Aliaga, M.; Gazitua, M.; Santos, J. G. *Tetrahedron* **2006**, *62*, 4869. (b) Castro, E. A.; Campodonico, P. R.; Contreras, R.; Fuentealba, P.; Santos, J. G.; Leis, J. R.; Garcia-Rio, L.; Saez, J. A.; Domingo, L. R. *Tetrahedron* **2006**, *62*, 2555-2562. (c)

Castro, E. A.; Gazitua, M.; Santos, J. G. *J. Org. Chem.* **2005**, *70*, 8088-8092. (d) Campodonico, P. R.; Fuentealba, P.; Castro, E. A.; Santos, J. G.; Contreras, R. *J. Org. Chem.* **2005**, *70*, 1754-1760.
15. (a) Oh, H. K.; Oh, J. Y.; Sung, D. D.; Lee, I. *J. Org. Chem.* **2005**, *70*, 5624-5629. (b) Oh, H. K.; Jin, Y. C.; Sung, D. D.; Lee, I. *Org. Biomol. Chem.* **2005**, *3*, 1240-1244. (c) Oh, H. K.; Park, J. E.; Sung, D. D.; Lee, I. *J. Org. Chem.* **2004**, *69*, 9285-9288. (d) Oh, H. K.; Park, J. E.; Sung, D. D.; Lee, I. *J. Org. Chem.* **2004**, *69*, 3150-3153.
16. (a) Um, I. H.; Chun, S. M.; Akhtar, K. *Bull. Korean Chem. Soc.* **2007**, *28*, 220-224. (b) Um, I. H.; Park, Y. M.; Fujio, M.; Mishima, M.; Tsuno, Y. *J. Org. Chem.* **2007**, *72*, 4816-4821. (c) Um, I. H.; Jeon, S. E.; Seok, J. A. *Chem. Eur. J.* **2006**, *12*, 1237-1243. (d) Um, I. H.; Kim, E. J.; Park, H. R.; Jeon, S. E. *J. Org. Chem.* **2006**, *71*, 2302-2306. (e) Um, I. H.; Lee, J. Y.; Lee, H. W.; Nagano, Y.; Fujio, M.; Tsuno, Y. *J. Org. Chem.* **2005**, *70*, 4980-4987. (f) Um, I. H.; Han, H. J.; Baek, M. H.; Bae, S. K. *J. Org. Chem.* **2004**, *69*, 6365-6370. (g) Um, I. H.; Lee, J. Y.; Kim, H. T.; Bae, S. K. *J. Org. Chem.* **2004**, *69*, 2436-2441. (h) Um, I. H.; Seok, J. A.; Kim, H. T.; Bae, S. K. *J. Org. Chem.* **2003**, *68*, 7742-7746.
17. (a) Gregory, M. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1967**, *89*, 2327-2330. (b) Bruice, T. C.; Donzel, A.; Huffman, R. W.; Butler, A. R. *J. Am. Chem. Soc.* **1967**, *89*, 2106-2121.
18. (a) Bernasconi, C. F.; Hibdon, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 4343-4348. (b) Bernasconi, C. F.; Perez-Lorenzo, M.; Brown, S. D. *J. Org. Chem.* **2007**, *72*, 4416-4423. (c) Spencer, T. A.; Kendall, M. C. R.; Reingold, I. D. *J. Am. Chem. Soc.* **1972**, *94*, 1250-1254.
19. Yagil, G.; Anbar, M. *J. Am. Chem. Soc.* **1962**, *84*, 1797-1803.
20. (a) Kirby, A. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1965**, *87*, 3209-3216. (b) Benkovic, S. J.; Benkovic, P. A. *J. Am. Chem. Soc.* **1966**, *88*, 5504-5511.
21. (a) Um, I. H.; Lee, J. Y.; Ko, S. H.; Bae, S. K. *J. Org. Chem.* **2006**, *71*, 5800-5803. (b) Um, I. H.; Min, J. S.; Ahn, J. A.; Hahn, H. J. *J. Org. Chem.* **2000**, *65*, 5659-5663.
22. (a) Um, I. H.; Hong, J. Y.; Seok, J. A. *J. Org. Chem.* **2005**, *70*, 1438-1444. (b) Um, I. H.; Chun, S. M.; Chae, O. M.; Fujio, M.; Tsuno, Y. *J. Org. Chem.* **2004**, *69*, 3166-3172.
23. Um, I. H.; Lee, J. Y.; Kim, H. T.; Bae, S. K. *J. Org. Chem.* **2004**, *69*, 2436-2441.
24. Um, I. H.; Han, H. J.; Ahn, J. A.; Kang, S.; Buncel, E. *J. Org. Chem.* **2002**, *67*, 8475-8480.
25. (a) Tsuno, Y.; Fujio, M. *Adv. Phys. Org. Chem.* **1999**, *32*, 267-385. (b) Tsuno, Y.; Fujio, M. *Chem. Soc. Rev.* **1996**, *25*, 129-139. (c) Yukawa, Y.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 965-970.
26. Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39-45.
27. (a) Bagley, M. C.; Dale, J. W.; Ohnesorge, M.; Xiong, X.; Bower, J. *J. Comb. Chem.* **2003**, *5*, 41-44. (b) McMullen, C. H.; Stirling, C. J. M. *J. Chem. Soc.* **1966**, 1221-1223. (c) Jones, E. R. H.; McCombie, J. T. *J. Chem. Soc.* **1942**, 733-735. (d) Hennion, G. F.; Murray, W. S. *J. Am. Chem. Soc.* **1942**, *64*, 1220-1222. (e) Froning, J. F.; Hennion, G. F. *J. Am. Chem. Soc.* **1940**, *62*, 653-655.