DOI 10.5012/bkcs.2011.32.3.1087

Remarkable Rate Acceleration of Baylis-Hillman Reaction of Notorious α,β-Unsaturated Aldehydes Catalyzed by Proton Donor

Ko Hoon Kim, Hyun Seung Lee, Yu Mi Kim, and Jae Nyoung Kim*

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Korea
**E-mail: kimjn@chonnam.ac.kr*
Received January 8, 2011, Accepted January 18, 2011

Key Words : Baylis-Hillman reaction, α,β-Unsaturated aldehydes, Proton donor, Phenol

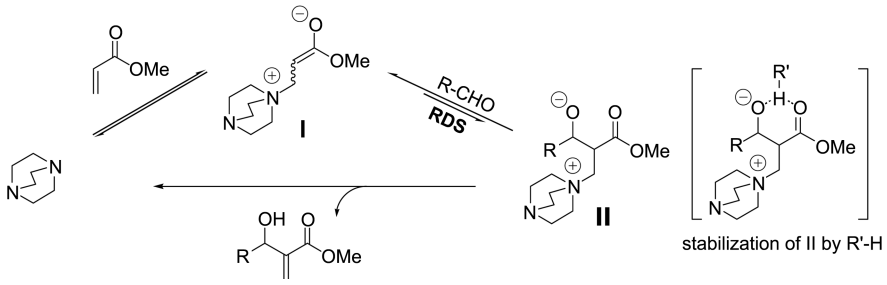
The Baylis-Hillman reaction is an efficient carbon-carbon bond-forming reaction between aldehyde and α,β-unsaturated carbonyl compound catalyzed by a tertiary amine such as DABCO.[1] However, the reaction has suffered from low reaction rates and yields in many aldehydes.[2,3] Especially the Baylis-Hillman reaction of cinnamaldehyde and its derivatives is notorious.[2] As an example, the highest yield of Baylis-Hillman adduct of cinnamaldehyde is at best 66% even though a variety of ways have been examined.[2a-f] The situation is more severe for the Baylis-Hillman adducts of α-substituted cinnamaldehyde, crotonaldehyde, and β-substituted crotonaldehyde. The yields in these entries remained extremely low (13-31%) until now.[2b,f,g]

During our recent studies, various Baylis-Hillman adducts were required of α,β-unsaturated aldehydes.[4] However, the reaction of α-methylcinnamladehyde under normal conditions (cat. DABCO, rt) with methyl acrylate did not produce any trace amounts of the desired Baylis-Hillman adduct even after 7 days. Similarly, the reactions of *p*-methoxycinnamaldehyde and β-phenylcinnamaldehyde were very sluggish. Thus we decided to develop an efficient protocol for the Baylis-Hillman reaction of cinnamaldehyde and its derivatives.

The rate-determining step of the Baylis-Hillman reaction is the reaction between the ammonium enolate **I** and the aldehyde,[5a,d-f] as shown in Scheme 1. Thus, increasing the amount of the enolate, activation of the aldehyde, or stabilization of the zwitterion **II** would increase the reaction rate. In this context, various proton donors[5,6] and Lewis acids[5i-k] have been known to increase the reaction rate by stabilizing the zwitterion **II**.

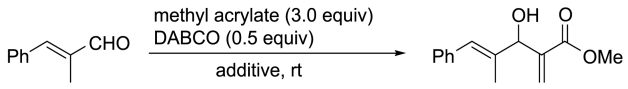
Thus, we carried out the reaction of α-methylcinnamaldehyde (**1a**) with methyl acrylate in the presence of DABCO (50 mol %) and various proton donors, as shown in Table 1. The reaction did not produce any trace amount of product **2a** in the presence of phloroglucinol, dimethylglyoxime, three trifluoroacetamides, PEG-3400, and picolinic acid (entries 12, 21-24, 26, 29). Trace amounts of **2a** (< 5%) was observed on TLC in the presence of three nitrophenols, 8-hydroxyquinoline, phthalimide, MeOH, *N*-hydroxyphthalimide, and NH_4Cl (entries 8-10, 11, 25, 27, 28, 31). The use of naphthols (entries 6 and 7), acetaldoxime (entries 13-15), benzophenone oxime (entry 16), 4-methoxybenzaldehyde oxime (entry 20), and pivalic acid (entry 30) showed the formation of low yield of **2a**. Fortunately, the use of phenol (entries 1-4) and 4-chlorobenzaldehyde oxime (entries 17 and 18) showed moderate yields of **2a**, and the yield was dependent on the ratio of DABCO/additive. When we increased the amounts of additive (1.0 equiv) and DABCO (2.0 equiv), the yield of **2a** increased to 56-70% (entries 5 and 19). It is interesting to note that 4-chlorobenzaldehyde oxime increased the yield of **2a** to 56% (entry 19); however, phenol (entry 5) was found to be the best choice of proton donor.

Encouraged by the above results we carried out the synthesis of Baylis-Hillman adducts of various α,β-unsaturated aldehydes, as shown in Table 2. Three cinnamaldehydes **1b-d** showed high yields (80-93%) of the corresponding Baylis-Hillman adducts **2b-d** (entries 2-4) under the influence of excess DABCO (2.0 equiv) and phenol additive (1.0 equiv). The Baylis-Hillman adduct of crotonaldehyde **2e** was also synthesized in high yield (78%, entry 5). In addition, β-phenylcinnamaldehyde (**1f**) and 3-(9-anthryl)acrolein (**1g**) also produced the corresponding Baylis-Hillman



Scheme 1

Table 1. Synthesis of **2a** in the presence of various additives

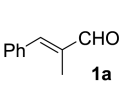
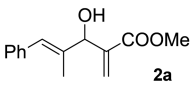
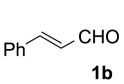
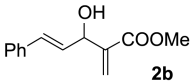
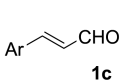
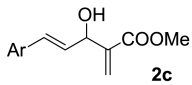
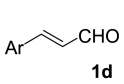
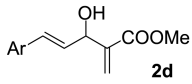
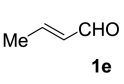
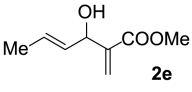
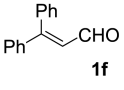
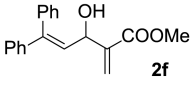
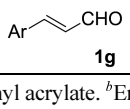
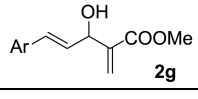


1a (1.0 equiv) **2a**

Entry	Additive (equiv)	Time (d)	Yield (%)[a]	Entry	Additive (equiv)	Time (d)	Yield (%)[a]
1	PhOH (0.3)	4	27	17	4-chlorobenzaldehyde oxime (0.3)	4	27
2	PhOH (0.3)	5.5	36	18	4-chlorobenzaldehyde oxime (0.3)	5.5	36
3	PhOH (0.5)	4	25	19	4-chlorobenzaldehyde oxime (1.0)[b]	5.5	56
4	PhOH (1.0)	4	21	20	4-methoxybenzaldehyde oxime (0.3)	2	15
5	PhOH (1.0)[b]	5.5	70	21	dimethylglyoxime (0.3)	2	NR
6	1-naphthol (0.3)	2	10	22	2,2,2-trifluoro-*N*-pnenylacetamide (0.3)	2	NR
7	2-naphthol (0.3)	2	11	23	*N*-(4-chlorophenyl)-2,2,2-trifluoroacetamide (0.3)	2	NR
8	2-nitrophenol (0.3)	2	trace	24	2,2,2-trifluoroacetamide (0.3)	2	NR
9	3-nitrophenol (0.3)	2	trace	25	phthalimide (0.3)	2	trace
10	4-nitrophenol (0.3)	2	trace	26	PEG-3400[c]	2	NR
11	8-hydroxyquinoline (0.3)	2	trace	27	MeOH[c]	2	trace
12	phloroglucinol (0.3)	2	NR	28	*N*-hydroxyphthalimide (0.3)	2	trace
13	acetaldoxime (0.3)	4	21	29	picolinic acid (0.3)	2	NR
14	acetaldoxime (0.6)	2	12	30	pivalic acid (0.3)	4	21
15	acetaldoxime (3.0)	2	trace	31	NH_4Cl (0.3)	2	trace
16	benzophenone oxime (0.3)	4	25				

[a]Isolated yield and NR is no reaction. [b]DABCO was used in 2.0 equiv. [c]Arbitrary amount was used.

Table 2. Synthesis of Baylis-Hillman adducts of α,β-unsaturated aldehydes

Entry	Aldehyde	Product	Conditions[a]	Yield (%)
1	 **1a**	 **2a**	MA (3.0 equiv), DABCO (0.5 equiv), PhOH (0.3 equiv), rt, 4 days MA (3.0 equiv), DABCO (2.0 equiv), PhOH (1.0 equiv), rt, 5.5 days	27[b] 70[c]
2	 **1b**	 **2b**	MA (3.0 equiv), DABCO (2.0 equiv), PhOH (1.0 equiv), rt, 12 h	92
3[d]	 **1c**	 **2c**	MA (2.0 equiv), DABCO (1.0 equiv), rt, 2 days MA (5.0 equiv), DABCO (0.5 equiv), PhOH (0.3 equiv), rt, 12 h MA (3.0 equiv), DABCO (2.0 equiv), PhOH (1.0 equiv), rt, 12 h	56 78 93
4[e]	 **1d**	 **2d**	MA (5.0 equiv), DABCO (0.5 equiv), rt, 24 h MA (5.0 equiv), DABCO (0.5 equiv), PhOH (0.3 equiv), rt, 4 days MA (3.0 equiv), DABCO (2.0 equiv), PhOH (1.0 equiv), rt, 2 days	0 67 80
5	 **1e**	 **2e**	MA (2.0 equiv), DABCO (0.5 equiv), PhOH (0.3 equiv), rt, 4 days MA (3.0 equiv), DABCO (2.0 equiv), PhOH (1.0 equiv), rt, 3 days	62 78
6	 **1f**	 **2f**	MA (2.0 equiv), DABCO (0.3 equiv), rt, 5 days MA (5.0 equiv), DABCO (0.5 equiv), PhOH (0.3 equiv), rt, 4 days MA (3.0 equiv), DABCO (2.0 equiv), PhOH (1.0 equiv), rt, 2 days	7 63 81
7[f]	 **1g**	 **2g**	MA (4.0 equiv), DABCO (0.3 equiv), rt, 2 days MA (10.0 equiv), DABCO (1.0 equiv), DMF, rt, 12 days MA (3.0 equiv), DABCO (2.0 equiv), PhOH (1.0 equiv), DMF, rt, 5 days	0 75 77

[a]MA is methyl acrylate. [b]Entry 1 in Table 1. [c]Entry 5 in Table 1. [d]Ar is 4-fluorophenyl. [e]Ar is 4-methoxyphenyl. [f]Ar is 9-anthryl.

adducts **2f** and **2g** in good yields (77-81%), under the optimized conditions (entries 6 and 7). For the reaction of **1g**, a small amount of DMF was added for the solubility. As can be seen in entries 3-7, the reactions with lesser amounts of DABCO and phenol showed sluggish reactivity and completely no reaction in some entries.

In summary, various Baylis-Hillman adducts of α,β-unsaturated aldehydes have been synthesized in high yields using excess amounts of DABCO (2.0 equiv) and phenol additive (1.0 equiv).

Experimental Section

Typical Procedure for the Synthesis of 2a. A mixture of α-methylcinnamaldehyde (**1a**, 146 mg, 1.0 mmol), methyl acrylate (258 mg, 3.0 mmol), DABCO (224 mg, 2.0 mmol), and phenol (94 mg, 1.0 mmol) was stirred at room temperature for 5.5 days under nitrogen atmosphere. After the usual extractive workup and column chromatographic purification process (hexanes/EtOAc, 15:1) compound **2a** was obtained as colorless oil, 162 mg (70%). Other compounds were synthesized analogously and the spectroscopic data of unknown compounds, **2a** and **2c-g**, are as follows.

Compound 2a: 70%; colorless oil; IR (KBr) 3464, 2951, 1718, 1442, 1276 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.83 (d, J = 1.2 Hz, 3H), 2.85 (d, J = 5.4 Hz, 1H), 3.77 (s, 3H), 5.08 (d, J = 5.4 Hz, 1H), 5.92 (t, J = 1.2 Hz, 1H), 6.34 (dd, J = 0.9 and 0.6 Hz, 1H), 6.65 (s, 1H), 7.18-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.27, 51.95, 75.90, 126.13, 126.56, 127.31, 128.07, 128.95, 136.90, 137.38, 140.51, 166.93; ESIMS *m/z* 233 $[M+H]^+$. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.57; H, 7.12.

Compound 2c: 93%; colorless oil; IR (KBr) 3493, 2953, 1716, 1510, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.06 (d, J = 6.0 Hz, 1H), 3.79 (s, 3H), 5.12 (t, J = 6.0 Hz, 1H), 5.92 (t, J = 0.9 Hz, 1H), 6.21 (dd, J = 15.9 and 6.0 Hz, 1H), 6.29 (s, 1H), 6.63 (dd, J = 15.9 and 0.9 Hz, 1H), 6.95-7.03 (m, 2H), 7.31-7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.98, 71.91, 115.41 (d, J = 21.1 Hz), 125.84, 128.08 (d, J = 7.9 Hz), 128.94 (d, J = 1.7 Hz), 130.20, 132.58 (d, J = 2.9 Hz), 141.15, 162.39 (d, J = 245.0 Hz), 166.69; ESIMS *m/z* 237 $[M+H]^+$. Anal. Calcd for $C_{13}H_{13}FO_3$: C, 66.09; H, 5.55. Found: C, 66.34; H, 5.67.

Compound 2d: 80%; pale yellow solid; mp 47-48 °C; IR (KBr) 3493, 2952, 1717, 1512, 1251 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.93 (d, J = 6.3 Hz, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 5.10 (t, J = 6.3 Hz, 1H), 5.91 (t, J = 1.2 Hz, 1H), 6.15 (dd, J = 15.9 and 6.3 Hz, 1H), 6.28 (s, 1H), 6.60 (d, J = 15.9 Hz, 1H), 6.82-6.87 (m, 2H), 7.29-7.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.96, 55.24, 72.21, 113.93, 125.65, 126.94, 127.78, 129.18, 131.08, 141.40, 159.38, 166.78; ESIMS *m/z* 249 $[M+H]^+$. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.95; H, 6.46.

Compound 2e:[2b] 78%; colorless oil; IR (KBr) 3423, 2954, 1723, 1440, 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.70-1.73 (m, 3H), 3.03 (d, J = 5.7 Hz, 1H), 3.78 (s, 3H), 4.90 (app t, J = 5.7 Hz, 1H), 5.54-5.62 (m, 1H), 5.70-5.82 (m, 1H), 5.85 (t, J = 1.2 Hz, 1H), 6.22-6.23 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.59, 51.77, 71.71, 125.04, 128.10, 130.97, 141.66, 166.76; ESIMS *m/z* 157 $[M+H]^+$.

Compound 2f: 81%; colorless oil; IR (KBr) 3474, 3024, 1719, 1275 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.09 (d, J = 6.0 Hz, 1H), 3.77 (s, 3H), 4.95 (dd, J = 9.3 and 6.0 Hz, 1H), 5.75 (s, 1H), 6.23 (s, 1H), 6.24 (d, J = 9.3 Hz, 1H), 7.19-7.23 (m, 2H), 7.25-7.27 (m, 5H), 7.30-7.40 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.96, 69.77, 126.14, 127.49, 127.58, 127.62, 127.76, 128.14, 128.23, 129.59, 138.92, 141.38, 141.50, 144.79, 166.94; ESIMS *m/z* 295 $[M+H]^+$. Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.62; H, 6.33.

Compound 2g: 77%; pale yellow solid; mp 98-100 °C; IR (KBr) 3441, 3049, 1719, 1440, 1153 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.23 (d, J = 6.6 Hz, 1H), 3.84 (s, 3H), 5.39 (dd, J = 6.6 and 5.7 Hz, 1H), 6.03 (t, J = 0.9 Hz, 1H), 6.13 (dd, J = 16.2 and 5.7 Hz, 1H), 6.37 (s, 1H), 7.41-7.46 (m, 5H), 7.93-7.98 (m, 2H), 8.19-8.25 (m, 2H), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.08, 72.52, 125.07, 125.40, 125.76, 126.12, 126.40, 127.55, 128.56, 129.40, 131.31, 131.90, 137.86, 141.18, 166.85; ESIMS *m/z* 319 $[M+H]^+$. Anal. Calcd for $C_{21}H_{18}O_3$: C, 79.22; H, 5.70. Found: C, 79.59; H, 5.97.

Acknowledgments. This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2010-0015675). Spectroscopic data were obtained from the Korea Basic Science Institute, Gwangju branch.

References and Notes

1. For the leading reviews on Baylis-Hillman reaction, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811-891. (b) Gowrisankar, S.; Lee, H. S.; Kim, S. H.; Lee, K. Y.; Kim, J. N. *Tetrahedron* **2009**, *65*, 8769-8780. (c) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627-645. (d) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481-1490. (e) Radha Krishna, P.; Sachwani, R.; Reddy, P. S. *Synlett* **2008**, 2897-2912. (f) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1-48. (g) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511-4574. (h) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447-5674 and further references cited therein.
2. For the synthesis of Baylis-Hillman adducts of cinnamaldehyde derivatives, see: (a) Song, Y.; Ke, H.; Wang, N.; Wang, L.; Zou, G. *Tetrahedron* **2009**, *65*, 9086-9090. (b) Hsu, J.-C.; Yen, Y.-H.; Chu, Y.-H. *Tetrahedron Lett.* **2004**, *45*, 4673-4676. (c) Jeong, Y.; Ryu, J.-S. *J. Org. Chem.* **2010**, *75*, 4183-4191. (d) Johnson, C. L.; Donkor, R. E.; Nawaz, W.; Karodia, N. *Tetrahedron Lett.* **2004**, *45*, 7359-7361. (e) Rosa, J. N.; Afonso, C. A. M.; Santos, A. G. *Tetrahedron* **2001**, *57*, 4189-4193. (f) Chandrasekhar, S.; Narsihmulu, C.; Sartitha, B.; Sultana, S. S. *Tetrahedron Lett.* **2004**, *45*, 5865-5867. (g) Cho, J.-H.; Ko, S. Y.; Oh, E.; Park, J. C.; Yoo, J. U. *Helv. Chim. Acta* **2002**, *85*, 3994-3999.
3. For the use of special acrylates in order to increase the reaction rate, see: (a) Lee, W.-D.; Yang, K.-S.; Chen, K. *Chem. Commun.* **2001**, 1612-1613. (b) Nakano, A.; Kawahara, S.; Akamatsu, S.; Morokuma, K.; Nakatani, M.; Iwabuchi, Y.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Tetrahedron* **2006**, *62*, 381-389. (c) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219-10220. (d) Leadbeater, N. E.; van der Pol, C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2831-2835. (e) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 1539-1542. (f) Bhuniya, D.; Narayanan, S.; Lamba, T. S.; Krishna Reddy, K. V. S. R. *Synth. Commun.* **2003**, *33*, 3717-3726.
4. The manuscript on palladium-catalyzed synthesis of cyclobuta-[*a*]indene scaffold from the modified Baylis-Hillman adducts of cinnamaldehydes will be published in due course.
5. For the rate increase by proton donor additive in DABCO-catalyzed Baylis-Hillman reactions, see: (a) Maher, D. J.; Connon, S. J. *Tetrahedron Lett.* **2004**, *45*, 1301-1305. (b) Shi, M.; Liu, X.-G. *Org. Lett.* **2008**, *10*, 1043-1046. (c) Amarante, G. W.; Benassi,

M.; Milagre, H. M. S.; Braga, A. A. C.; Maseras, F.; Eberlin, M. N.; Coelho, F. *Chem. Eur. J.* **2009**, *15*, 12460-12469. (d) Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem*. **2003**, *68*, 692-700. (e) Aggarwal, V. K.; Dean, D. K.; Mereu, A.; Williams, R. *J. Org. Chem*. **2002**, *67*, 510-514. (f) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem*. **2001**, *66*, 5413-5418. (g) de Souza, R. O. M. A.; Pereira, V. L. P.; Esteves, P. M.; Vasconcellos, M. L. A. A. *Tetrahedron Lett*. **2008**, *49*, 5902-5905. (h) Gruttadauria, M.; Giacalone, F.; Meo, P. L.; Marculescu, A. M.; Riela, S.; Noto, R. *Eur. J. Org. Chem*. **2008**, 1589-1596. Various Lewis acids have also been used for the same purpose, see: (i) Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem*. **1998**, *63*, 7183-7189. (j) Yang, K.-S.; Lee, W.-D.; Pan, J.-F.; Chen, K. *J. Org. Chem*. **2003**, *68*, 915-919. (k) Yukawa, T.; Seelig, B.; Xu, Y.; Morimoto, H.; Matsunaga, S.; Berkessel, A.; Shibasaki, M. *J. Am. Chem. Soc*. **2010**, *132*, 11988-11992.

6. For the rate increase by proton donor additive in phosphine or other Lewis base-catalyzed Baylis-Hillman reactions, see: (a) Shi, M.; Liu, Y.-H. *Org. Biomol. Chem*. **2006**, 1468-1470. (b) Shi, M.; Chen, L.-H.; Li, C.-Q. *J. Am. Chem. Soc*. **2005**, *127*, 3790-3800. (c) Liu, Y.-h.; Shi, M. *Adv. Synth. Catal*. **2008**, *350*, 122-128. (d) Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Lett*. **2000**, 41, 2165-2169. (e) Zhong, W.; Zheng, Y.; Zhou, J.; Shen, Y. *Synlett* **2010**, 3057-3060. (f) Garnier, J.-M.; Anstiss, C.; Liu, F. *Adv. Synth. Catal*. **2009**, *351*, 331-338. (g) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc*. **2003**, *125*, 12094-12095. (h) McDougal, N. T.; Trevellini, W. L.; Rodgen, S. A.; Kliman, L. T.; Schaus, S. E. *Adv. Synth. Catal*. **2004**, *346*, 1231-1240. (i) Narender, P.; Gangadasu, B.; Ravinder, M.; Srinivas, U.; Swamy, G. Y. S. K.; Ravikumar, K.; Rao, V. J. *Tetrahedron* **2006**, *62*, 954-959. (j) Grainger, R. S.; Leadbeater, N. E.; Pamies, A. M. *Catal. Commun*. **2002**, *3*, 449-452. (k) Abermil, N.; Masson, G.; Zhu, J. *Org. Lett*. **2009**, 11, 4648-4651. (l) Abermil, N.; Masson, G.; Zhu, J. *J. Am. Chem. Soc*. **2008**, 130, 12596-12597. (m) Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett*. **2002**, *4*, 4723-4725.