

A Mild and Efficient Procedure for Asymmetric Michael Additions of α -Bromo-chalcone with Cyclohexanone Catalyzed by Different Bases

LI-GUO GAO, DONG-ZHI LIU, WEI LI and XUE-QIN ZHOU*

School of Chemical Engineering, Tianjin University, Tianjin 300072, P.R. China

*Corresponding author: Fax: +86 22 27400911; Tel: +86 22 27400911; E-mail: zhouxueqin@tju.edu.cn

(Received: 16 January 2012;

Accepted: 12 November 2012)

AJC-12401

A mild and efficient procedure for Michael addition of α -bromo-chalcone with cyclohexanone has been developed. In the presence of sodium ethoxide, α -bromo-chalcone reacted with cyclohexanone to afford Michael products in moderate to high yield and good diastereoselectivities. Especially, while $\text{CH}_3\text{CH}_2\text{ONa}$ or *t*-BuOK as catalyst, the unexpected products were obtained, which were the compound 4a((8*R*,9*S*)-4a,8a-dihydroxy-10-phenyl-tetradecahydro-phenanthren-9-yl)(phenyl)methanone) and 4b(((8*R*,9*R*)-4a,9-dihydroxy-10-phenyl-tetradecahydrophenanthren-9-yl)(phenyl)methanone).

Key Words: α -Bromo-chalcone, Cyclohexanone, Synthesis.

INTRODUCTION

Conjugate addition reactions of α,β -unsaturated ketones with donors is one of the most important carbon-carbon bond-forming reactions in organic synthesis¹. Over the past decade, there has been attracted increasing interest in the addition reaction of α,β -unsaturated ketones with cyclohexanone², particularly in Michael addition reactions. However, most of the reactions used highly activated nucleophiles, such as nitroalkenes³ or malonates⁴. Especially, asymmetric Michael addition of enones with ketones is still a challenging reaction. Ishrat⁵ reported the reactions of chalcones with cyclohexanone to generate 1,5-dicarbonyl compounds catalyzed by $\text{CH}_3\text{CH}_2\text{ONa}$ with good yields (79 %) and low diastereoselectivities which only is ((*S*)-2-((*R*)-3-oxo-1,3-diphenylpropyl)cyclohexanone: (*R*)-2-((*R*)-3-oxo-1,3-diphenylpropyl)cyclohexanone = 86:14). Many workers⁶ have reported imidazolidinones as organocatalysts to catalyze the reactions of aldehydes with enones, which had some drawbacks such as: long reaction time (more than 4 days) or high catalyst loading and these led to a high cost and limited its application in the pharmaceutical industry. The synthesis of (*R*)-2-((*R*)-3-oxo-1,3-diphenylpropyl)cyclohexanone with CH_3COOLi as catalyst also had the same shortcomings (poor diastereoselectivity). Melchiorre and Jørgensen⁷ have shown that pyrrolidine derivatives could promote the asymmetric conjugate addition smoothly with good results. The reactions were complete in a short time with a low catalyst loading (25 %), but preparation of the organocatalysts was complex and difficult. Therefore, the

design and discovery of efficient ways to generate single configuration products is still a challenge in organic synthetic chemistry.

It's noticed that dehydrobromination reaction preceded easily during Michael addition of 1,2,4-triazole to α -bromo-chalcone producing *E*-1,3-diaryl-3-(1*H*-1,2,4-triazol-1-yl)-2-propen-1-ones in high yields⁸. Considering the reactivity of bromine atom, this paper aims at studying the asymmetric Michael addition of α -bromo-chalcone with cyclohexanone using different catalysts. The compound 1,3-diphenyl-3-(2-oxo-cyclohexyl)-1-propanone was obtained with high diastereoselectivity. Besides, the other products was achieved while two mole ratio of cyclohexanones to α -bromo-chalcone in the presence of *t*-BuOK or NaH as catalyst, which has not been reported in the literature.

EXPERIMENTAL

All the solvents were purified according to standard procedures. The ¹H NMR spectra were recorded at 500 MHz, ¹³C NMR spectra were recorded at 500 MHz. ¹H and ¹³C NMR chemical shifts were calibrated to tetramethylsilane as an external reference. Coupling constants are given in hertz. HRMS were recorded on an IonSpec FT-ICR mass spectrometer with ESI resource. Melting points were measured on an RY-I apparatus and uncorrected. The reagents were used without purification. 2-Bromo-1,3-diphenyl-propenone was prepared following literature procedures⁹.

2-(3-Oxo-1,3-diphenyl-propyl)-cyclohexanone (3a¹⁰): Sodium (0.35 g, 0.015 mol) was dissolved in dry ethanol (30

mL) and then cooled to 20 °C, cyclohexanone (1.96 g, 0.02 mol) and α -bromochalcone (0.98 g, 0.01 mol) were added, the mixture was left at same temperature for 3 h. Filtered and the crude solid was washed with ethanol 30 mL \times 3 mL, dried, gave a white solid; yield: 80 %. (2.74 g,), m.p. 144.5-145.8 °C, IR: 3058, 3025, 2939, 2855, 1709, 1683, 1597, 1495 and 1448 cm^{-1} , ^1H NMR (CDCl_3 , 500 MHz): δ (ppm) 1.25-1.30 (m, 1H) 1.55-1.81 (m, 4H), 1.98-2.00 (m, 1H), 2.37-2.43 (m, 1H), 2.50-2.55 (m, 1H), 2.73 (dt, 1H, $J_1 = 5.5$ Hz, $J_2 = 5.0$ Hz), 3.264 (dd, 1H, $J_1 = 10.0$ Hz, $J_2 = 20$ Hz), 3.49 (dd, 1H, $J_1 = 4.0$ Hz, $J_2 = 4.0$ Hz), 3.73 (dd, 1H, $J_1 = 13.5$ Hz, $J_2 = 4.0$ Hz), 7.17 (t, 2H, $J = 7.5$ Hz), 7.258-7.274 (m, 3H), 7.399-7.449 (m, 2H), 7.50 (t, 1H, $J = 7.5$ Hz), 7.91 (d, 2H, $J = 8$ Hz). HRMS calcd. (%) for $\text{C}_{21}\text{H}_{22}\text{O}_2\text{H}^+$ ($\text{M} + \text{H}^+$) 307.1693, found (%) 307.1686.

2-(1-Benzyl-2-oxo-2-phenyl-ethyl)-cyclohexanone (3b¹¹): Catalyst (0.02 mol) was dissolved in dry solvent (20 mL), cyclohexanone (1.96 g, 0.02 mol) was added, α -bromochalcone (2.08 g, 0.01 mol) dissolved in 20 mL solvent was added, the mixture was kept at same temperature for 12 h, filtered. The crude red solid was purified by column chromatography (petroleum ether:ethyl acetate = 15:1) to give white solid; yield: 80 %. m.p. 144.5-145.8 °C, IR: 3058, 3025, 2939, 2855, 1709, 1683, 1597, 1495 and 1448 cm^{-1} , ^1H NMR (CDCl_3 , 500 MHz): δ (ppm) 1.55-1.70 (m, 4H), 1.90-1.91 (m, 1H), 2.00-2.09 (m, 2H), 2.24-2.30 (m, 1H), 2.38-2.41 (m, 1H), 2.70 (dt, 1H, $J_1 = 6$ Hz, $J_2 = 5.5$ Hz), 3.40 (dd, 1H, $J_1 = 9.5$ Hz), 3.53 (dd, 1H, $J_1 = 5.0$ Hz, $J_2 = 5.0$ Hz), 3.95 (dt, 1H, $J_1 = 4.5$ Hz, $J_2 = 5.0$ Hz), 7.149-7.184 (m, 1H), 7.258 (t, 3H, $J = 4.5$ Hz), 7.44 (t, 2H, $J = 7.5$ Hz), 7.53 (t, 1H, $J = 7$ Hz), 7.96 (d, 2H, $J = 7.5$ Hz). HRMS calcd (%) for $\text{C}_{21}\text{H}_{22}\text{O}_2\text{H}^+$ ($\text{M} + \text{Na}^+$) 329.1513, found (%) 329.1514.

2-[2-(2-Hydroxy-cyclohexylidene)-1-(hydroxy-phenyl-methyl)-2-phenyl-ethyl]-cyclohexanone (4a): Catalysts (0.02 mol) dissolved in dry THF (20 mL), cyclohexanone (1.96 g, 0.02 mol) was added, α -bromochalcone (2.08 g, 0.01 mol) dissolved in 20 mL THF was dropwised in 0.5 h. The mixture was maintained at same temperature for 12 h and filtered. The crude red solid was purified by column chromatography (petroleum ether:ethyl acetate = 20:1) to give additional white solid. Yield: 84 %. m.p. 184.3-186 °C. IR: 3442.61, 3061, 3026, 2930, 2854, 1645, 1595, 1578 and 1493 cm^{-1} . ^1H NMR (CDCl_3 , 500 MHz): δ (ppm) 0.99-1.11 (m, 3H), 1.21-1.41 (m, 6H), 1.59 (d, 1H, $J = 13.5$ Hz), 1.58-1.86 (m, 7H), 2.07 (d, 1H, $J = 13.5$ Hz), 3.26 (t, 1H, $J = 12.0$ Hz), 3.77 (d, 1H, $J = 11.5$ Hz), 4.78 (s, 1H), 5.18 (s, 1H), 6.89-6.96 (m, 2H), 7.01 (dd, 2H, $J = 7.5$ Hz), 7.19 (t, 1H, $J = 7.5$ Hz), 7.23 (t, 2H, $J = 7.5$ Hz), 7.39 (t, 1H, $J = 7.5$ Hz), 7.52 (d, 2H, $J = 7$ Hz), ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 19.90, 20.93, 21.30, 24.86, 25.97, 26.17, 36.06, 39.42, 45.59, 50.26, 50.37, 58.96, 72.47, 75.25, 126.02, 126.63, 128.22, 128.35, 128.35, 128.49, 128.49, 129.06, 131.15, 131.44, 133.39, 140.83, 209.14. HRMS calcd. (%) for $\text{C}_{27}\text{H}_{32}\text{O}_3\text{H}^+$ ($\text{M} + \text{H}^+$) 405.2424, found (%) 405.2422.

2-[2-(2-Hydroxy-cyclohexylidene)-1-(hydroxy-phenyl-methyl)-2-phenyl-ethyl]-cyclohexanone (4b): *t*-BuOK (0.02 mol) dissolved in dry ethanol (20 mL), cyclohexanone (1.96 g, 0.02 mol) was added, α -bromochalcone (2.08 g, 0.01 mol) dissolved in 20 mL ethanol was added in 0.5 h, the mixture was left at same temperature for 2 h under N_2 atmosphere,

cooled, filtered. The crude red solid was purified by column chromatography (petroleum ether:ethyl acetate = 20:1) to give additional white solid. Yield: 72 %. m.p. 184.5-186.1 °C. IR: 3445, 3060, 3021, 2930, 2854, 1647, 1595, 1578 and 1493 cm^{-1} . ^1H NMR (CDCl_3 , 500 MHz): δ (ppm) 1.07-1.57 (m, 7H) 1.68-1.95 (m, 4H), 2.08 (t, 2H, $J = 12.5$ Hz), 3.42 (t, 1H, $J = 14$ Hz), 4.24 (d, 1H, $J = 14$ Hz), 5.56 (s, 1H), 6.05 (s, 1H), 6.89-6.96 (m, 2H), 7.00-7.06 (m, 4H), 7.18-7.23 (m, 4H), 7.28 (s, 2H), 7.43 (d, 2H, $J = 7$ Hz), ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 19.92, 20.91, 21.34, 24.82, 25.98, 26.13, 36.07, 39.44, 45.53, 50.25, 50.34, 58.93, 72.44, 75.22, 126.08, 126.61, 128.27, 128.34, 128.37, 128.41, 128.40, 129.09, 131.11, 131.40, 133.33, 140.84, 209.10. HRMS calcd. (%) for $\text{C}_{27}\text{H}_{32}\text{O}_3\text{H}^+$ ($\text{M} + 2\text{Na}^+ - \text{H}^+$) 449.2058, found (%) 449.2060.

RESULTS AND DISCUSSION

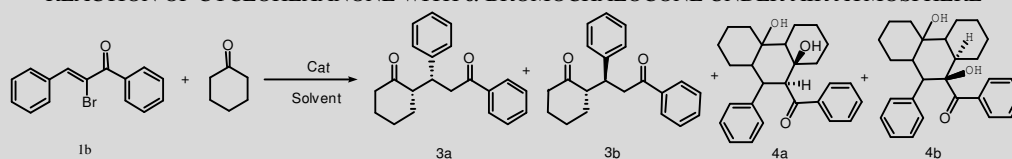
Sodium ethoxide was employed to catalyze the conjugated addition of cyclohexanone to α -bromochalcone firstly. When the reaction was performed in THF, the product **3a** was formed in high diastereoselectivity (>99:1) and low yield (21 %, Table-1, entry 1). When the reaction temperature was increased to 80 °C, the other configuration (**3b**) was obtained (dr 100 %) in good yield (Table-1, entry 2). While performed in ethanol, high yield was gained with lower diastereoselectivity (94:6, Table-1, entry 3) at room temperature and good results were observed when the temperature was increased to 80 °C (80 % yield, 99:1 diastereoselectivity) (Table-1, entry 4). However, low diastereoselectivities were obtained if toluene was used as solvent either in low temperature or in high temperature (Table-1 entry 5-6). If the temperature was increased to 120 °C, the yield of **3** nearly decreased to zero (Table-1 entry 7). Then *t*-BuOK was chose as catalyst, which could catalyze the reaction effectively in high yields, but with low diastereoselectivities (Table-1, entry 8-12). Using NaH as catalyst, the yields of **3** were nearly zero at different temperature.

An interesting phenomenon was found. While using *t*-BuOK as the catalyst and the reaction temperature was at 80 °C in ethanol and toluene, then new compounds (**4**) not **3** were formed (Table-1, entry 13-14) in high yield and mordrate diastereoselectivities. However, when the reaction was carried out under nitrogen atmosphere, only one configuration was obtained (Table-2, entry 1). Changing the catalyst to NaH, only the compound **4a** was afforded in good yield in THF and zero yields of **3** or **4** in toluene. While changing the feeding order, compounds **3** and **4** were obtained together as showed in Table-4. Then, the same reactions were done with **3a** and **3b** as starting material to find whether they were the intermediates of the reactions. **4a** was obtained in THF with NaH as catalyst, but no reaction occurred when *t*-BuOK was used as catalyst in ethanol (Table-4, entry 1).

This fact allowed us to hypothesize that synthesis of compounds **4** are preceded as follows: The order also affected the results which could be seen from the Tables 2 and 5.

From Table-1 (entry 1 and 2), we had believed that **3b** was the thermodynamic control product. But when we did the reactions as showed in Table-3, **3a** couldn't convert to **3b** except when THF was used as solvent. This revealed **3b** was not the thermodynamic control product.

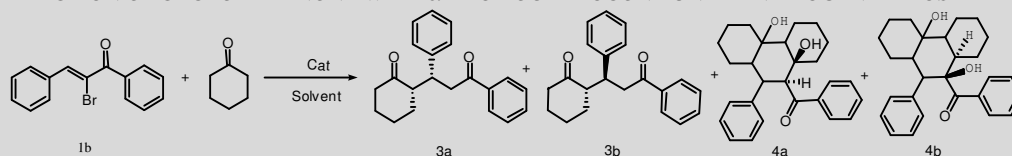
TABLE-1
REACTION OF CYCLOHEXANONE WITH α -BROMOCHALOCONE UNDER AIR ATMOSPHERE^a



Entry	Cat	Solvent (mL)	Temp. (°C)	Time (h)	Yield ^b (%)	
					3(dr ^c)	4(dr ^d)
1	CH ₃ CH ₂ ONa	THF	25	2	21 (>99:1)	0
2	CH ₃ CH ₂ ONa	THF	80	2	73 (<1:99)	0
3	CH ₃ CH ₂ ONa	Ethanol	25	2	78 (96:4)	0
4	CH ₃ CH ₂ ONa	Ethanol	80	2	80 (99:1)	0
5	CH ₃ CH ₂ ONa	Toluene	25	2	40 (82:18)	0
6	CH ₃ CH ₂ ONa	Toluene	80	2	67 (85:15)	0
7	CH ₃ CH ₂ ONa	Toluene	120	2	< 5	0
8	<i>t</i> -BuOK	THF	25	2	61 (78:22)	0
9	<i>t</i> -BuOK	THF	80	2	54 (88:12)	0
10	<i>t</i> -BuOK	Ethanol	25	2	76 (57:43)	0
11	<i>t</i> -BuOK	Toluene	14	5	71 (72:28)	0
12	<i>t</i> -BuOK	Toluene	80	5	75 (73:27)	0
13	<i>t</i> -BuOK	Toluene	120	5	61 (71:29)	17 (100:0)
14	<i>t</i> -BuOK	Ethanol	80	2	0	84 (86:14)
15	NaH	THF	25	2	0	67 (100:0)
16	NaH	THF	80	2	0	79 (100:0)
17	NaH	Toluene	14	2	<5 ^e	0
18	NaH	Toluene	80	5	<5 ^f	0

^aUnless, special remark, the order was mix cyclohexanone and catalyst (in THF) first and stirred for five minutes and then added α -bromochoalcone (in THF) slowly in 0.5 h in the given temperature. ^bIsolated yield. ^cdr (3a:3b) was determined by ¹H NMR spectroscopy (500 MHz). ^d(4a:4b) was determined by ¹H NMR spectroscopy (500 MHz). ^ePer cent conversion was 0. ^fPer cent conversion was 100 %.

TABLE-2
REACTION OF CYCLOHEXANONE WITH α -BROMOCHALOCONE UNDER NITROGEN ATMOSPHERE^a



Entry	Cat	Solvent (mL)	Temp. (°C)	Time (h)	Yield ^b (%)	
					3(dr ^c)	4(dr ^d)
1	<i>t</i> -BuOK	Ethanol	80	2	0	72 (0:100)
2	NaH	Toluene	25	2	< 5 ^e	0
3	NaH	Toluene	80	5	< 5 ^f	0

^aUnless, special remark, the order was mix cyclohexanone and catalyst (in THF) first and stirred for five minutes and then added α -bromochoalcone (in THF) slowly in 0.5 h in the given temperature. ^bIsolated yield. ^cdr (3a:3b) was determined by ¹H NMR spectroscopy (500 MHz). ^d(4a:4b) was determined by ¹H NMR spectroscopy (500 MHz). ^ePer cent conversion was 0. ^fPer cent conversion was 100 %.

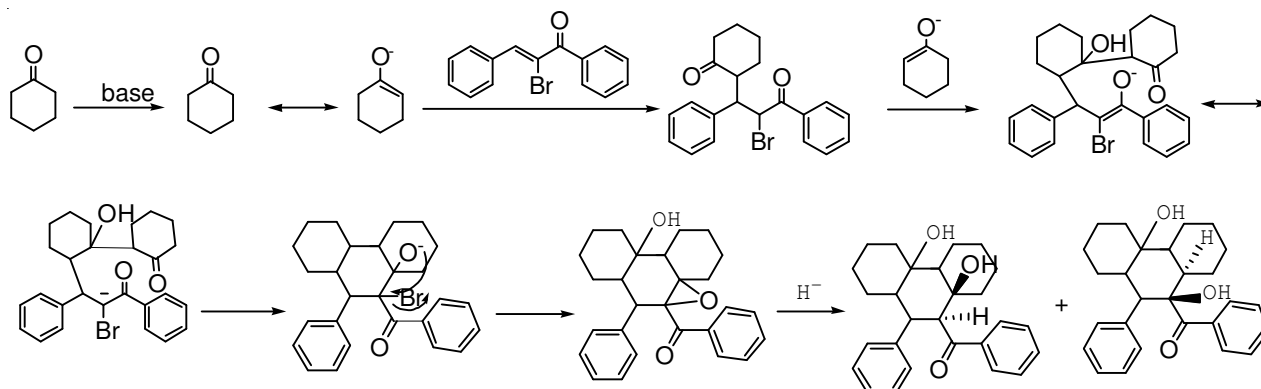
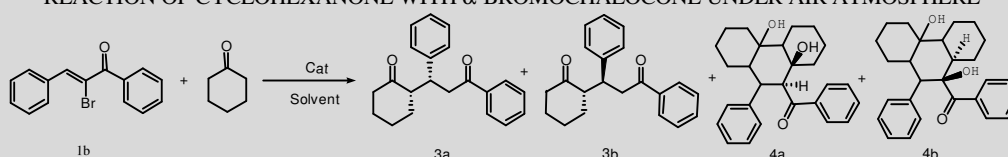


Fig. 1. Proposed mechanism forming compounds 4

TABLE-4
REACTION OF CYCLOHEXANONE WITH α -BROMOCHALCONE UNDER AIR ATMOSPHERE^a



Entry	Cat	Solvent (mL)	Temp. (°C)	Time (h)	Yield ^b (%)	
					3(dr ^c)	4(dr ^d)
1	NaH	THF	14	2	57(79:21)	10(100:0)
2	NaH	THF	25	2	56(70:30)	22(100:0)
3	NaH	THF	80	2	50(79:21)	27(100:0)

^aOrder was mix cyclohexanone and α -bromo-chalcone (in THF) first and stirred for 5 min and then added catalyst (in THF) in the given temperature. ^bIsolated yield. ^cdr (3a:3b) was determined by ¹H NMR spectroscopy (500 MHz). ^d(4a:4b) was determined by ¹H NMR spectroscopy (500MHz).

TABLE-3
RESULTS OF COMPOUND 3a CONVERTED TO 3b

Entry	Cat	Solvent (mL)	Temp. (°C)	Time (h)	Yield ^b (%)
1	CH ₃ CH ₂ ONa	Ethanol	80	2	19
2	CH ₃ CH ₂ ONa	Toluene	80	2	0
3	CH ₃ CH ₂ ONa	THF	80	2	90

^bIsolated yield.

We found that the addition order of reagents had a great influence on the products, which were showed in Table-4. The products changed as the order changed when THF was used as solvent.

TABLE-5
REACTION OF 3(a+b) TO 4a

Entry	Cat	Solvent (mL)	Temp. (°C)	Time (h)	Yield ^b (%)
1	NaH	THF	80	2	87
2	<i>t</i> -BuOK	Ethanol	80	2	0
3	NaH	Toluene	80	5	0

^bIsolated yield.

Conclusion

The reaction of α -bromo-chalcone with cyclohexanone generated good results. Different catalysts get different products. Good result was obtained when sodium ethoxide was employed as catalyst in the presence of ethanol. The other configuration was obtained under refluxed when performed in THF with sodium ethoxide as catalyst. Using *t*-BuOK in refluxed ethanol, new compounds 4 were generated. The single configuration was generated with NaH as catalyst in THF. At the same time, the feeding order also changed the results of the reaction. Further researches are still in progress.

REFERENCES

- P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon: Oxford (1992).
- (a) G. Wang and H.C. Sun, *Catal. Lett.*, **141**, 1324 (2011); (b) H. Gezezen, A. Dingil and M. Ceylan, *J. Heterocycl. Chem.*, **47**, 1017 (2010); (c) A. Mastracchio, A.A. Warkentin, A.M. Walji and D.C. MacMillan, *Proc. Natl. Acad. Sci. USA*, **107**, 20648 (2010); (d) Y.O. Sharma and M.S. Degani, *Green Chem.*, **11**, 526 (2009).
- (a) C.M. Yu, J. Qiu, F. Zheng and W.H. Zhong, *Tetrahedron Lett.*, **52**, 3298; (b) S. Anwar, H.J. Chang and K. Chen, *Org. Lett.*, **13**, 2200 (2011); (c) K. Albertshofer, R. Thayumanavan, N. Utsumi, F. Tanaka and C.F. Barbas, *Tetrahedron Lett.*, **48**, 693 (2007); (d) W. Wang, J. Wang and H. Li, *Angew. Chem., Int. Ed.*, **44**, 1369 (2005); (e) Y. Hayashi, H. Gotoh, T. Hayashi and M. Shoji, *Angew. Chem., Int. Ed.*, **44**, 4212 (2005); (f) T. Ishii, S. Fiujioka, Y. Sekiguchi and H.J. Kotsuki, *J. Am. Chem. Soc.*, **126**, 9558 (2004); (g) B.M. Nugent, R.A. Yoder, J.N. Johnson, *J. Am. Chem. Soc.*, **126**, 3418 (2004); (h) N. Mase, R. Thayumanavan, F. Tanaka and C.F. Barbas, *Org. Lett.*, **6**, 2527 (2004).
- N. Halland, T. Hansen and K.A. Jørgensen, *Angew. Chem. Int. Ed.*, **42**, 4955; (b) N. Halland, P.S. Aburel and K.A. Jørgensen, *Angew. Chem. Int. Ed.*, **42**, 661 (2003); (c) S. Hanessian and V. Pham, *Org. Lett.*, **2**, 2975 (2000); (d) A. Kawara and T. Taguchi, *Tetrahedron Lett.*, **35**, 8805 (1994).
- R. Ishrat, *J. Chem. Soc. Pak.*, **11**, 321 (1989).
- (a) M.T. Hechavarria Fonseca and B.B. List, *Angew. Chem., Int. Ed.*, **43**, 3958 (2004); (b) T.J. Peelen, Y.-G. Chi and S.H. Gellman, *J. Am. Chem. Soc.*, **127**, 11598 (2005); (c) Y.-G. Chi and S.H. Gellman, *Org. Lett.*, **7**, 4253 (2005).
- P. Melchiorre and K.A. Jørgensen, *J. Org. Chem.*, **68**, 4151 (2003).
- M.A. Rekhter, G.N. Grushetskaya, A.A. Panasenko and M.Z. Krimer, *Chem. Heterocycl. Comp.*, **31**, 792 (1995).
- (a) G.W. Kabalka, K. Yang, N.K. Reddy and C. Narayana, *Synth. Commun.*, **28**, 925 (1998); (b) Ch. Dufraisse, *Ann. Chim. Appl.*, **17**, 133 (1922).
- K. Miura, T. Nakagawa and A. Hosomi, *Synlett.*, 2068 (2003).
- N. Takashi, F. Hidehiko, N. Yuzo and M. Teruaki, *Chem. Lett.*, **33**, 1016 (2004).