Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 62 (2006) 4728–4732
Tetrahedron

Direct conversion of aryl halides to phenols using high-temperature or near-critical water and microwave heating

Chad M. Kormos and Nicholas E. Leadbeater*

Department of Chemistry, University of Connecticut, 55 North Eagleville Road, Storrs, CT 06269-3060, USA

Received 10 December 2005; revised 3 January 2006; accepted 4 January 2006
Available online 30 March 2006

Abstract—The direct conversion of aryl halides to the corresponding phenols has been achieved using microwave heating. High-temperature or near-critical water is used as the solvent in conjunction with a copper catalyst and a mineral base.

1. Introduction

The concept of efficient and selective synthesis in water has been exemplified as the rates, yields, and selectivities observed for many reactions in water have begun to match, or in many cases, surpass those in organic solvents.[1] In contrast to many other solvents, water not only provides a medium for solution chemistry but also often participates in elementary chemical events on a molecular scale. Water also offers practical advantages over organic solvents. It is cheap, readily available, non-toxic, and non-flammable. Another area of current growing research interest is the use of microwave energy as a heating source. This is evidenced by the number of papers and recent reviews appearing in the literature.[2–4] As well as being energy efficient, microwave heating can also enhance the rate of reactions and in many cases improve product yields. With the advent of scientific focused microwave systems, it is possible to control the temperature, pressure, microwave power, and reaction times very easily and with a high degree of reproducibility. Bringing these two areas (chemistry in water and microwave heating) together offers a clean, easy, and efficient method for organic synthesis. An example of this is in the Suzuki coupling reaction where it is possible to use parts per million levels of palladium catalysts when using water as a solvent in conjunction with microwave heating.[5]

In addition to using water for chemistry at ambient pressure in open vessels there has been a growth of interest in the use of high-temperature, near-critical, and supercritical water.[6–8] High-temperature water is broadly defined as liquid water above 200 °C, near-critical water as that between 200 and 300 °C, and supercritical water as that above 374 °C and 218 atm. At these temperatures the water approaches properties more like polar organic solvents. Using conventional heating, a range of chemistries can be performed in superheated water and it has been found that acid or base-catalyzed reactions require less catalyst than normal, if any. Strauss and co-workers showed in 1997 that by using microwave heating, it is possible to open up new avenues for synthesis by working with water above 200 °C.[9] For example, they have performed etherifications and multi-component reactions that were not otherwise possible.[10] This work was performed in a specially designed microwave apparatus. The majority of chemistry undertaken using water as a solvent using commercially available single-mode apparatus has been undertaken at temperatures at or below 200 °C. This is because they have a pressure limit of 20–30 bar thereby limiting the temperature to which the water can be heated. However, using a dedicated multi-mode reactor it is possible to perform reactions in heavy-walled quartz reaction vessels with operating limits of 80 bar thus allowing water to be heated to temperatures close to 300 °C.[11] The use of this apparatus for some organic transformations in near-critical water has recently appeared in the literature.[12] We too have become interested in developing microwave methodologies for performing synthetic transformations using high-temperature (~200 °C) and near-critical (~300 °C) water. One particular transformation of interest to us was the direct conversion of aryl halides to the corresponding phenols. We present the results of our initial studies here.

2. Results and discussion

The conversion of aryl halides to the corresponding phenols in one step generally involves long reaction times and often harsh conditions are required. In addition, most of the work has been focused on chloro-, bromo- or iodo-benzene or on

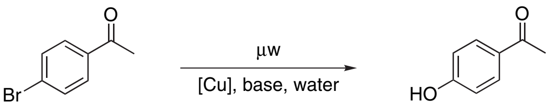
---

* Corresponding author. Tel.: +1 860 486 5076; fax: +1 860 486 2981; e-mail: nicholas.leadbeater@uconn.edu

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.01.103

electron-deficient aryl fluorides. Examples include performing the reaction in a steel bomb for 1½ days using CuI as a catalyst,[13] radical[14–16] and photochemical[17] reactions, and fluoride displacement from electron-deficient substrates.[18–20] To circumvent these methods, there have been numerous multi-step approaches reported.[21] A theme running through most of the direct methods is the use of water as a solvent, copper salt as catalysts, elevated temperatures, and lengthy reaction times. We were keen to see if, using microwave heating, it was possible to perform the reaction efficiently and rapidly using high-temperature or near-critical water as a solvent. We started our investigations working at the lower temperature of 200 °C using a monomode microwave apparatus and working on a 1 mmol scale. We screened a range of copper sources as catalysts in conjunction with mineral bases (3.1 M in water) for the direct conversion of 4-bromoacetophenone to 4-hydroxyacetophenone. The reaction mixtures were heated to 200 °C and then held at this temperature for 20 min before being allowed to cool. Our results are summarized in Table 1. Of those screened, copper dust was found to be the best catalyst for the reaction, the use of Cu (I) and Cu (II) sources leads to lower product yields (Table 1, entries 2, 4, and 5) and a catalyst loading of 10 mol % was found to be optimal (Table 1, entries 1–3). Using 3.1 equiv sodium hydroxide gave the best results, with less leading to lower yields because of incomplete conversion and more leading to product decomposition (Table 1, entries 6 and 7). Sodium carbonate and sodium acetate proved less successful as potassium hydroxide (Table 1, entries 8–10). Running the reaction for a shorter time led to lower conversion (Table 1, entry 11). We next decided to screen a range of aryl halide substrates using our conditions of 10 mol % copper powder, 3.1 equiv NaOH for a reaction time of 20 min at 200 °C. The results are shown in Table 2. Using activated aryl bromides and iodides, good yields of the corresponding phenols were obtained but with de-activated substrates product yields were significantly lower. In the case of 4-chloroacetophenone, no product was formed.

Table 1. Catalyst and base screening for the direct conversion of 4-bromoacetophenone to 4-hydroxyacetophenone[a]

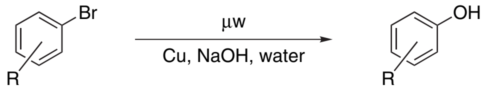


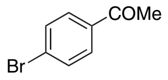
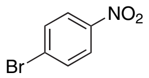
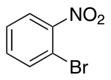
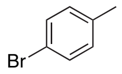
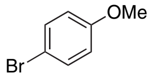
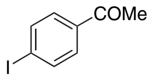
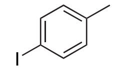
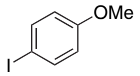
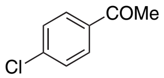
Entry	Copper source	Base	Yield (%)
1	Cu dust (5 mol %)	NaOH (3.1 equiv)	60
2	Cu dust (10 mol %)	NaOH (3.1 equiv)	65
3	Cu dust (20 mol %)	NaOH (3.1 equiv)	58
4	CuI (10 mol %)	NaOH (3.1 equiv)	40
5	$Cu(OAc)_2$ (10 mol %)	NaOH (3.1 equiv)	52
6	Cu dust (10 mol %)	NaOH (2.0 equiv)	32
7	Cu dust (10 mol %)	NaOH (5.0 equiv)	53
8	Cu dust (10 mol %)	KOH (3.1 equiv)	19
9	Cu dust (10 mol %)	Na_2CO_3 (3.1 equiv)	25
10	Cu dust (10 mol %)	NaOAc (3.1 equiv)	11
11[b]	Cu dust (10 mol %)	NaOH (3.1 equiv)	37

[a] Reactions were run in a sealed tube using 1 mmol 4-bromoacetophenone and base dissolved in water to give a 1 M solution. An initial microwave irradiation power of 75 W was used and the temperature being ramped from rt to 200 °C where it was then held for 20 min.

[b] Reaction mixture held at 200 °C for 10 min.

Table 2. Direct transformation of aryl halides to phenols in water using copper powder as a catalyst and sodium hydroxide as base[a]



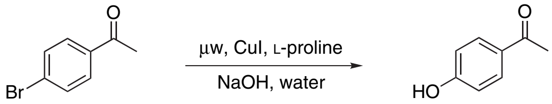
Entry	Aryl halide	Yield (%)
1		65
2		70
3		30
4		0
5[b]		17
6		74
7		12
8		31
9		0

[a] Reactions were run in a sealed tube using 1 mmol aryl halide, 10 mol % Cu powder and 1.0 mL of a 3.1 M NaOH solution. An initial microwave irradiation power of 75 W was used and the temperature being ramped from rt to 200 °C where it was then held for 20 min.

[b] Reaction mixture held at 200 °C for 30 min.

Ma and co-workers have recently reported the use of L-proline as a promoter for the CuI-catalyzed coupling reaction of aryl halides with amines.[22,23] We were interested to see if this catalytic system could also be applicable for our direct synthesis of phenols. Again working with 4-bromoacetophenone as a test substrate, we set out to probe this. Our results are summarized in Table 3. We found that using a 1:2 ratio of CuI (10 mol %) to L-proline as reported for the amination reactions led to a 60% yield of the desired phenol after heating at 200 °C for 20 min with NaOH as base (Table 3, entry 1). Reduction of this ratio to 1:0.5 led to an increase in product yield to 70% after heating at 200 °C for 20 min and to 82% if the reaction time at 200 °C was extended to 30 min (Table 3, entries 2 and 3). With these conditions in hand we screened representative substrates and the results being shown in Table 4. In the case of aryl iodides, yields of product were generally higher than those obtained using copper powder as the catalyst (Table 4, entries 1–3). Aryl bromides other than 4-bromoacetophenone proved less successful (Table 4, entries 4–7) and, in the case of 4-chloroacetophenone, some product was formed (Table 4, entry 8).

Table 3. Screening for the direct conversion of 4-bromoacetophenone to 4-hydroxyacetophenone using CuI as a catalyst and L-proline as an additive[a]

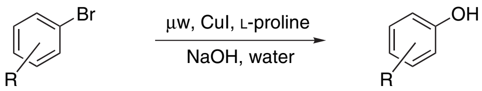


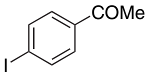
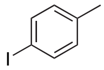
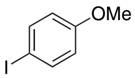
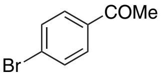
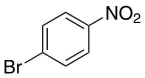
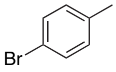
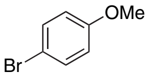
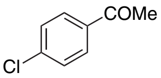
Entry	Catalyst mixture	Reaction time	Yield (%)
1	CuI/L-proline (1:1)	20 min at 200 °C	60
2	CuI/L-proline (1:0.5)	20 min at 200 °C	70
3	CuI/L-proline (1:0.5)	30 min at 200 °C	82

[a] Reactions were run in a sealed tube using 1 mmol aryl halide, 10 mol % CuI, and 3.1 mL of a 1 M NaOH solution. An initial microwave irradiation power of 35 W was used and the temperature being ramped from rt to 200 °C where it was then held for the allotted time.

In a further probe of the chemistry, we decided to use the same catalytic system (10 mol % CuI, 5 mol % L-proline, and NaOH as base) but work at 300 °C in the dedicated multi-mode reactor to see if the higher reaction temperature had a beneficial effect on product yield, especially in the case of aryl bromides. As shown in Table 5, we find that, with aryl iodides, product yields can be further improved by working at the higher temperature (Table 5, entries 1–4). The reaction mixtures are heated to 300 °C and then allowed to cool. Holding the reaction at 300 °C for 30 min is necessary when working with aryl bromides (Table 5, entries 5–7); shorter times lead to lower product yield. Using the same conditions, with 4-chloroacetophenone as a substrate a 44% yield of product was obtained (Table 5, entry 8).

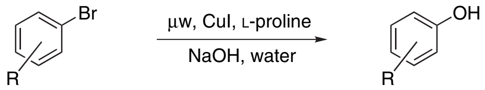
Table 4. Direct transformation of aryl halides to phenols in water at 200 °C using CuI as a catalyst, L-proline as an additive, and sodium hydroxide as base[a]

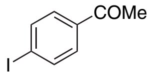
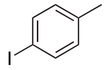
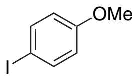
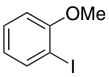
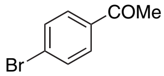
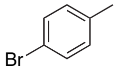
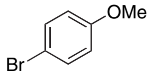
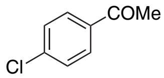


Entry	Aryl halide	Yield (%)
1		99
2		42
3		53
4		82
5		10
6		0
7		0
8		14

[a] Reactions were run in a sealed tube, using 1 mmol aryl halide, 10 mol % CuI, 5 mol % L-proline, and 1.0 mL of a 3.1 M NaOH solution. An initial microwave irradiation power of 35 W was used and the temperature being ramped from rt to 200 °C where it was then held for 30 min.

Table 5. Direct transformation of aryl halides to phenols in water at 300 °C using CuI as a catalyst, L-proline as an additive, and sodium hydroxide as base[a]



Entry	Aryl halide	Reaction time	Yield (%)
1		Heat to 300 °C and stop	100
2		Heat to 300 °C and stop	39
3		Heat to 300 °C and stop	65
4		Heat to 300 °C and stop	37
5		Heat to 300 °C and hold for 30 min	94
6		Heat to 300 °C and hold for 30 min	30
7		Heat to 300 °C and hold for 30 min	43
8		Heat to 300 °C and hold for 30 min	44

[a] Reactions were run in a sealed tube using 5 mmol aryl halide, 10 mol % CuI, 5 mol % L-proline, and 10 mL of a 1.5 M NaOH solution. An initial microwave irradiation power of 1400 W was used and the temperature being ramped from rt to 300 °C then cooled to 50 °C.

3. Conclusion

In conclusion, we have shown that it is possible to convert the aryl halides directly to the corresponding phenols using high-temperature or near-critical water as a solvent. The best base for the reaction is sodium hydroxide. Whilst simple copper powder is found to be a good catalyst (10 mol %) for the reaction, the optimum catalyst system is 10 mol % CuI together with 5 mol % L-proline as an additive. For aryl bromide substrates, best results are obtained by heating the reaction mixture to 300 °C and holding at this temperature for 30 min. The same was found to be true for an aryl chloride example. For aryl iodides, best results are obtained by heating the reaction mixture to 300 °C and then allowing the reaction mixture to cool. It is also possible to perform the reaction at a lower temperature of 200 °C but to the slight detriment of product yield.

4. Experimental

4.1. General

All materials were obtained from commercial suppliers and used without further purification. Standard distilled water was used throughout the study. All reactions were carried out in air. NMR spectra were recorded at 293 K on a 300 or 400 MHz spectrometer. All products are known and were characterized by comparison of NMR data with that in the literature.

4.2. Description of the microwave apparatus

For reactions performed at 200 °C, a commercially available monomode microwave unit (CEM Discover) was used. The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0–300 W. Reactions were performed in 10 mL capacity vessels sealed with a septum. The pressure was controlled by a load cell connected directly to the vessel and the temperature of the contents of the vessel was monitored using a calibrated IR sensor located outside the reaction vessel. The contents of the vessel were stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. Temperature, pressure, and power profiles were monitored using commercially available software provided by the microwave manufacturer. For reactions performed at 300 °C, a commercially available multimode microwave unit (Anton Paar Synthos 3000) was used. The instrument is equipped with two magnetrons, with combined continuous microwave output power from 0 to 1400 W. Heavy-walled quartz reaction vessels (80 mL capacity, up to 60 mL working volume) were used. These vessels are dedicated for reactions at high pressure (up to 80 bar) and temperatures. The quartz vessels were capped with special seals with a protective PEEK cap and then were placed inside protecting air cooling jackets made of PEEK. The seals comprise of a release valve that could be manually operated. The individual vessels were placed in an eight-position rotor and fixed in place by screwing down the upper rotor plate, and the rotor was finally closed with a protective hood. The temperature was monitored using an internal gas balloon thermometer placed in one reference vessel and additionally by exterior IR thermography. Pressure was monitored by a simultaneous hydraulic pressure-sensing device for all vessels, with recording of the highest pressure level and pressure increase. Reaction vessels were stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel.

4.3. General procedure for conversion of aryl halides to phenols using copper dust as a catalyst

In a 10 mL glass tube 4-bromoacetophenone (199 mg, 1.0 mmol), copper powder (6 mg, 0.1 mmol), and 1.0 mL of a 3.1 M NaOH solution was placed. The vessel was then sealed with a septum and placed into the microwave cavity. Initial microwave irradiation of 75 W was used and the temperature being ramped from rt to the desired temperature of 200 °C. Once this was reached, the reaction mixture was held at this temperature for 20 min. The reaction mixture was stirred continuously during the reaction. After allowing the mixture to cool to rt, the reaction vessel was opened and the contents were acidified with 2 M hydrochloric acid to pH 5–7. The aqueous layer was extracted with ethyl acetate (3×15 mL). The organic washings were combined, dried over $MgSO_4$, and then ethyl acetate was removed in vacuo. This left the crude product, which was isolated and characterized by comparison of NMR data with that in the literature.

4.4. General procedure for conversion of aryl halides to phenols at 200 °C using copper iodide as a catalyst and L-proline as an additive

In a 10 mL glass tube 4-bromoacetophenone (199 mg, 1.0 mmol), copper iodide (19 mg, 0.1 mmol), L-proline (5 mg, 0.05 mmol), and 1.0 mL of a 3.1 M NaOH solution was placed. The vessel was then sealed with a septum and placed into the microwave cavity. Initial microwave irradiation of 35 W was used and the temperature being ramped from rt to the desired temperature of 200 °C. Once this was reached, the reaction mixture was held at this temperature for 30 min. The reaction mixture was stirred continuously during the reaction. After allowing the mixture to cool to rt, the reaction vessel was opened and the contents were acidified with 2 M hydrochloric acid to pH 5–7. The aqueous layer was extracted with ethyl acetate (3×15 mL). The organic washings were combined, dried over $MgSO_4$, and then ethyl acetate was removed in vacuo. This left the crude product, which was isolated and characterized by comparison of NMR data with that in the literature.

4.5. General procedure for conversion of aryl halides to phenols at 300 °C using copper iodide as a catalyst and L-proline as an additive

In an 80 mL quartz tube 4-bromoacetophenone (996 mg, 5.0 mmol), copper iodide (95 mg, 0.5 mmol), L-proline (25 mg, 0.25 mmol), and 10 mL of a 1.55 M NaOH solution was placed. The vessel was sealed and loaded onto the rotor. Three other vessels were prepared similarly. The loaded rotor was subjected to a maximum of 1400 W microwave power in a ramp to 300 °C (limited by a maximum pressure of 80.0 bar) over a period of 10 min and then held at this temperature for 30 min before being allowed to cool to 50 °C, this takes around 30 min. The reaction mixture was stirred continuously during the reaction. The vessel was vented, removed from the rotor, and the contents were acidified with 2 M hydrochloric acid to pH 5–7. The aqueous layer was extracted with ethyl acetate (3×15 mL). The organic washings were combined, dried over $MgSO_4$, and then ethyl acetate was removed in vacuo. This left the crude product, which was isolated and characterized by comparison of NMR data with that in the literature.

Acknowledgments

The University of Connecticut is thanked for funding. Anton Paar GmbH and CEM Microwave Technology are thanked for equipment support.

References and notes

1. For a general introduction to organic synthesis in water see: (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Klewer Academic: Dordrecht, 1997; (b) Li, C.-J.; Chen, T.-H. *Organic Reactions in Aqueous Media*; Klewer Academic: Dordrecht, 1997.
2. For books on microwave heating in synthesis: (a) Kappe, O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinhiem, 2005; (b) *Microwave Assisted Organic Synthesis*; Tierney, J. P., Lidström, P., Eds.; Blackwell: Oxford, 2005; (c) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002; (d) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM: Matthews, 2002.
3. For reviews on the area see: (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250; (b) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717–727; (c) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlain, A. R. *J. Comb. Chem.* **2002**, *4*, 95–105; (d) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283.
4. For a review on the concepts see: Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213–233.
5. For reports of microwave-promoted Suzuki couplings in water, see: (a) Blettner, C. G.; Konig, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885; (b) Han, J. W.; Castro, J. C.; Burgess, K. *Tetrahedron Lett.* **2003**, *44*, 9359; (c) Appukkuttan, P.; Orts, A.; Chandran, R. P.; Goeman, J. L.; Van der Eycken, J.; Dehaen, W.; Van der Eycken, E. *Eur. J. Org. Chem.* **2004**, 3277; (d) Gong, Y.; He, W. *Org. Lett.* **2002**, *4*, 3803; (e) Namboodiri, V. V.; Varma, R. S. *Green Chem.* **2001**, *3*, 146; (f) Zhang, W.; Chen, C. H.-T.; Lu, Y.; Nagashima, T. *Org. Lett.* **2004**, *6*, 1473; (g) Solodenko, W.; Schön, U.; Messinger, J.; Glinschert, A.; Kirschning, A. *Synlett* **2004**, 1699.
6. For a recent review see: Akiya, N.; Savage, P. E. *Chem. Rev.* **2002**, *102*, 2725–2750.
7. For a recent review see: Broll, D.; Kaul, C.; Kramer, A.; Krammer, P.; Richter, T.; Jung, M.; Vogel, H.; Zehner, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2999–3014.
8. For a recent review see: (a) Siskin, M.; Katritzky, A. R. *Chem. Rev.* **2001**, *102*, 825–837; (b) Siskin, M.; Katritzky, A. R. *Chem. Rev.* **2001**, *102*, 838–892.
9. For a recent review see: Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653–661.
10. An, J.; Bagnell, L.; Cablewski, T.; Strauus, C. R.; Trainor, R. W. *J. Org. Chem.* **1997**, *62*, 2505–2511.
11. For an overview of the apparatus see: Stadler, A.; Yousefi, B. H.; Dallinger, D.; Walla, P.; Van der Eycken, E.; Kaval, N.; Kappe, C. O. *Org. Process Res. Dev.* **2003**, *7*, 707–716.
12. Kremsner, J. M.; Kappe, C. O. *Eur. J. Org. Chem.* **2005**, 3672–3679.
13. Weller, D. D.; Stirchak, E. P.; Yokoyama, A. *J. Org. Chem.* **1984**, *49*, 2061–2063.
14. Cram, D. J.; Day, A. C. *J. Org. Chem.* **1966**, *31*, 1227–1232.
15. Das Sarma, K.; Maitra, U. *Tetrahedron* **1998**, *54*, 4965–4976.
16. Eberhardt, M. K.; Ramirez, G.; Ayala, E. *J. Org. Chem.* **1989**, *54*, 5922–5926.
17. Orvis, J.; Weiss, J.; Pagni, R. M. *J. Org. Chem.* **1991**, *56*, 1851–1857.
18. Heilman, W. P.; Battershell, R. D.; Pyne, W. J.; Goble, P. H.; Magee, T. A. *J. Med. Chem.* **1978**, *21*, 906–913.
19. Kalir, A.; Szara, S. *J. Med. Chem.* **1963**, *6*, 716–719.
20. Makosza, M.; Sienkiewicz, K. *J. Org. Chem.* **1990**, *55*, 4979–4981.
21. (a) Gotteland, J. P.; Halazy, S. *Synlett* **1995**, 931–932; (b) Halterman, R. L.; McEvoy, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 6690–6695; (c) Levin, J. I.; Du, M. T. *Synth. Commun.* **2002**, *32*, 1401–1406; (d) Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3527–3533; (e) Rogers, J. F.; Green, D. M. *Tetrahedron Lett.* **2002**, *43*, 3585–3587; (f) Sheehan, M.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3544–3552; (g) Skowronska-Ptasinska, M.; Aarts, V. M. L. J.; Egberink, R. J. M.; Van Eerden, J.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1988**, *53*, 5484–5491.
22. Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453–2457.
23. Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164–5173.