Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 46 (2005) 5823–5826

Tetrahedron Letters

Copper catalyzed asymmetric conjugate addition-bromination of α,β-unsaturated ketones: a highly efficient one-pot reaction for the synthesis of chiral α-bromo-β-alkylketones

Kangying Li and Alexandre Alexakis*

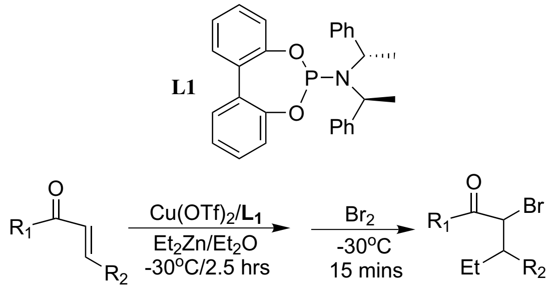
Department of Organic Chemistry, University of Geneva, 30 Quai Ernest Ansermet, CH-1211 Geneva, Switzerland

Received 30 May 2005; revised 23 June 2005; accepted 27 June 2005
Available online 14 July 2005

Abstract—An efficient one-pot reaction for the synthesis of chiral α-bromo-β-alkyl ketones was developed. The final products were obtained with excellent enantiomeric excess and good isolated yields. The synthetic potential was illustrated by the radical cyclization of the α-brominated ketone.

α-Brominated carbonyl compounds are important and useful organic intermediates.[1] Several methods such as the bromination of carbonyl compounds using bromine[2] and NBS[3] were applied to synthesize this type of compounds. However, to the best of our knowledge, no efficient approach has been reported so far for the preparation of α-bromo-β-alkyl ketones with two stereocontrolled chiral centres and highly enantiomeric purities. Recently we found that the bromination of zinc enolate, formed through the conjugate addition of diethyl zinc to α,β-unsaturated ketones in the presence of copper/chiral phosphoramidites ligands, proceeded cleanly and efficiently producing the chiral α-bromo-β-alkylketones with excellent enantioselectivity and good isolated yields. We present herein, our initial results of this one-pot reaction.

The copper catalyzed 1,4-addition[4] was successfully performed under the normal conditions developed in our lab, which afforded the zinc enolate with quantitative conversion in 2.5 h. The bromination was then conducted by directly adding molecular bromine to the zinc enolate, which cleanly afforded the corresponding α-bromo ketone in less than 15 min (Scheme 1).[5]



Scheme 1.

First of all, we used a series of structurally different α,β-unsaturated ketones in the presence of $Cu(OTf)_2$ and simple chiral phosphoramidite ligand (**L1**). The results are presented in Table 1.

We found that all the substrates were converted to the desired product with moderate to good isolated yields except for 2-cyclopenten-1-one (entry 1). We did not get the corresponding pure product due to too many impurities during the reaction. In all the cases, the products were formed as a mixture of two diastereomers with various ratios that depended on the substrate structure. The one-pot reaction of cyclohexenone (entry 2) afforded the corresponding product with moderate ratio (42:58), which could be equilibrated (DBU, MeOH, rt, 44 h) to 74:26. A slight improvement of the ratio was observed when 2-cyclohepten-1-one (entry 3) and 2-cyclopenten-1-one (entry 1) were used. The best ratio (27:73) was achieved using 2-cyclopentadecen-1-one (entry 4) as substrate. As expected, good enantioselectivities

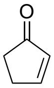
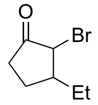
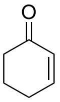
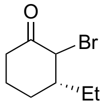
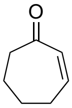
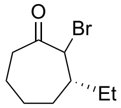
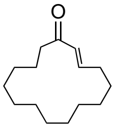
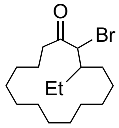
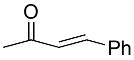
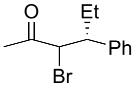
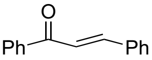
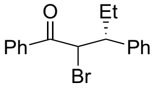
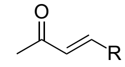
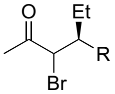
---

Keywords: Copper; Conjugate addition; Bromination; Chiral; One pot.

* Corresponding author. Fax: +41 22 379 652; e-mail: alexandre.alexakis@achiorg.unige.ch

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.06.144

Table 1. Conjugate addition–bromination of α,β-unsaturated ketones

Entry	Sub.	Conv.[a] (yield, %)[b]	dr[c]	Product	ee[f]
1		>99	31:69		ND
2		>99 (86)	42:58 (74:26)[e]		90
3		>99 (65)	68:32 (23:77)[e]		86
4		>99 (72)	27:73[d]		ND
5		>99 (60)	64:36[d]		58
6		>99 (82)	70:30		40
7	 R = $(CH_2)_3$–C≡C–Ph	>99 (84)	48:52		75

[a] GC–MS analysis.

[b] Isolated yields.

[c] Determined by GC–MS analysis.

[d] Determined by NMR.

[e] Equilibrated using DBU, in MeOH, rt.

[f] Determined by Chiral GCa or SFC in the first step (separation condition, see Note 6).

were obtained for these cyclic α,β-unsaturated ketones. For the linear α,β-unsaturated ketones (entries 5–7) also moderate diastereomeric ratios and enantiomeric excesses were obtained. *trans*-Chalcone was found to be the good substrate to get better ratio although the enantiomeric excess (40%) was not very high (entry 6).

On the other hand, some of the substrates mentioned above were tested in the presence of other bulky steric chiral ligands (**L2**–**L5**) (Fig. 1) and copper salt to get better enantiomeric excess. The results are summarized in Table 2.

From the results in Table 2, we did not find any obvious change for the diastereomeric ratio, which implies that ligands have no influence on the diastereomeric ratio. The enantioselectivity, however, was remarkably improved for all the substrates. The conjugate addition–bromination of cyclohexenone catalyzed by **L2**/$Cu(OTf)_2$ and **L2**/CuTC, for example, gave 97% (entry 1) and 96% (entry 2) enantiomeric excess, respectively. For the larger ring substrate like 2-cyclohepten-1-one the ee value was increased to 98% in the presence of **L3**/CuTC (entry 3). The enantioselectivities for the other three linear α,β-unsaturated ketones (entries 4–6) were

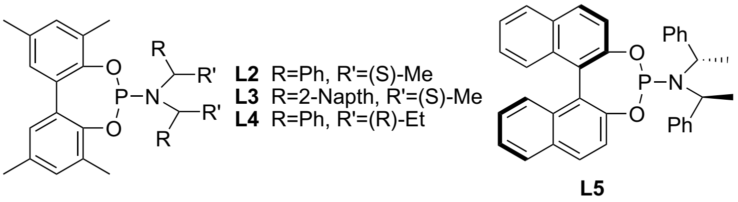
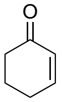
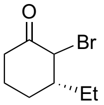
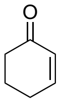
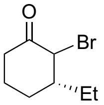
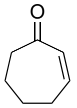
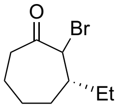
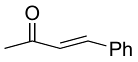
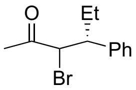
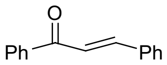
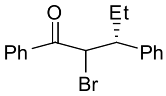
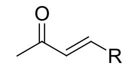
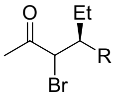
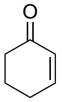
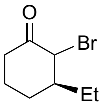
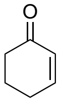
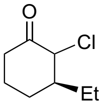
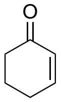
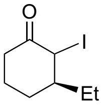


Figure 1.

Table 2. Results of the one-pot reaction in the presence of copper/**L2**–**L4**

Entry	Sub.	Ligand/Cu	Product	dr[a]	ee%[c] (yield, %[d])
1		**L2**/Cu(OTf)$_2$		39:61	97 (86)
2		**L2**/CuTC		41:59	96 (80)
3		**L3**/CuTC		68:32	98 (71)
4		**L2**/CuTC		67:33	90 (68)
5		**L5**/Cu(OTf)$_2$		70:30[b]	71 (87)
6	 R=$(CH_2)_3$–C≡C–Ph	**L5**/Cu(OTf)$_2$		49:51	80 (81)
7[e]		**L4**/Cu(OTf)$_2$		50:50	98
8[f]		**L4**/Cu(OTf)$_2$		47:53 (62:38)[g]	97
9[h]		**L4**/Cu(OTf)$_2$		74:26	98 (68)

[a] Determined by GC–MS.

[b] Determined by NMR.

[c] Determined by Chiral GC or SFC in the first step (separation conditions, see Note 6).

[d] Isolated yield.

[e] NBS used, 77% conv. after 16 h.

[f] NCS used, 100% conv. after 15 min.

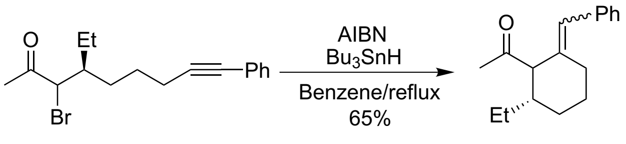
[g] Equilibrated with DBU in MeOH.

[h] I_2 used, 90% Conv. after 1 h.

much better than those obtained from the simple chiral ligand (Table 1, entries 5–7).

On the other hand, the reaction also worked using *N*-bromosuccinimide (NBS) as bromination reagent in the presence of **L4**/Cu(OTf)$_2$ (entry 7). Compared with bromine, it was found to be time consuming although NBS is relatively mild and easier to handle. Only 77% conversion resulted in the second step after 16 h at room temperature and the corresponding product was formed with a 50:50 diastereomeric ratio and with 98% ee. The chlorination of the zinc enolate using *N*-chlorosuccinimide (NCS) under the same conditions exhibited higher activity, which gave 100% conversion after 15 min (entry 8). The ratio of 47:53 was obtained, which could be equilibrated to 62:38 after DBU isomerization. Iodination of the zinc enolate using iodine efficiently gave the corresponding product with 74:26 diastereomeric ratio and 98% ee (entry 9).

In order to illustrate the synthetic potential of this transformation, we carried out a radical cyclization of the brominated product (Scheme 2). The cyclic product



Scheme 2.

was successfully obtained as a mixture of four isomers with a ratio of 9:47:8:36 and 65% isolated yield. No obvious change of the ratio was observed after isomerization using DBU in MeOH.

In conclusion, we disclosed a highly efficient one-pot reaction to prepare α-bromo-β-alkylketones with excellent enantioselectivity and good chemical yields. This reaction also provided a possible pathway for the construction of more elaborate cyclic compounds through radical reactions of the brominated products. This work is still in progress and further results will be reported in due course.

Acknowledgements

The authors thank Stephane Rosset and the Swiss National Research Foundation No. 200020-105368 and COST action D24/0003/01 (OFES contract No. C02.0027) for financial support.

References and notes

1. Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; VCH: New York, 1999, pp 715–719.
2. (a) Dowd, P.; Kaufman, C.; Kaufman, P. *J. Org. Chem.* **1985**, *50*, 882–885; (b) Hakam, K.; Thielmann, M.; Thielmann, T.; Winterfeldt, E. *Tetrahedron* **1987**, *43*, 2035–2044.
3. (a) Boyd, R. E.; Rasmussen, C. R.; Press, J. B. *Synth. Commun.* **1995**, *25*, 1045–1051; (b) Yang, D.; Yan, Y.-L.; Liu, B. *J. Org. Chem.* **2002**, *67*, 7429–7431; (c) Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Chem. Commun.* **2004**, 470–471; (d) Biswanath, D.; Katta, V.; Gurram, M.; Ibram, M. *Tetrahedron Lett.* **2005**, *46*, 3041–3044.
4. (a) Alexakis, A.; Polet, D.; Rosset, S.; March, S. *J. Org. Chem.* **2004**, *69*, 5660–5667; (b) Alexakis, A.; Polet, D.; Benhaim, C.; Rosset, S. *Tetrahedron: Asymmetry* **2004**, *15*, 2199–2203; (c) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221–3236; (d) Alexakis, A.; Benhaim, C.; Rosset, S.; Human, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262–5263; (e) Alexakis, A.; Burton, J.; Vastra, J.; Benhaim, C.; Fournioux, X.; Van den Heuvel, A.; Leveque, J.-M.; Maze, F.; Rosset, S. *Eur. J. Org. Chem.* **2000**, 4011–4027; (f) Alexakis, A.; Benhaim, C. *Org. Lett.* **2000**, *2*, 2579–2581.
5. Typical procedure: To a mixture of Cu(OTf)$_2$ (0.02 mmol) and ligand (0.04 mmol) was added 2 ml of dry diethyl ether under nitrogen. The solution was allowed to stir at room temperature for 30 min and then cooled to −30 °C. Diethyl zinc (1.5 ml, 1 M in hexane) was added dropwise in order that the temperature did not rise over −30 °C. The solution was stirred for 5 min, and the substrate (1 mmol) in 0.5 ml diethyl ether was added dropwise. The reaction mixture was stirred at −30 to −20 °C until all the starting material was consumed (~2.5 h). And then, neat bromine (3.5 mmol) was added dropwise below −30 °C. After the addition, stirring was continued for 15 min. To get full conversion, additional 15 min stirring is recommended. The solution was diluted with 20 ml ether and successively washed with saturated sodium thiosulfate solution and brine. The organic layer was dried over sodium sulfate. The pure product was obtained after chromatography on silica gel using cyclohexane/ethyl acetate as eluant.
6. Chiral GC separation conditions: temperature programs are described as follows: initial temperature (°C)–initial time (min)–temperature gradient (°C/min)–final temperature (°C)–final time (min).
   For (3*R*)-2-bromo-3-ethylcyclohexanone Lipodex E 50 cm s^{-1}, 60-45-20-170-5, t_R = 22.26 min (major), t_R = 26.67 min (minor).
   For (3*R*)-2-bromo-3-ethylcycloheptanone Lipodex E 45 cm s^{-1}, 60-45-20-170-5, t_R = 46.52 min (major), t_R = 46.99 min (minor). For (4*R*)-3-bromo-4-phenylhexan-2-one Lipodex E 40 cm s^{-1}, 70-60-15-170-5, t_R = 63.01 min (major) t_R = 63.38 min (minor).
   For (4*S*)-3-bromo-4-ethyl-9-phenylnon-8-yn-2-one Hydrodex-B-6-TBDM, 50 cm s^{-1}, 160-40-1-170-10 t_R = 50.80 min (major), t_R = 51.24 min (minor).
   For (3*R*)-2-bromo-1,3-diphenylpentan-1-one Chiral OD-H, 2%-6-1-15%, t_R = 10.87 min (minor), t_R = 11.82 min (major).