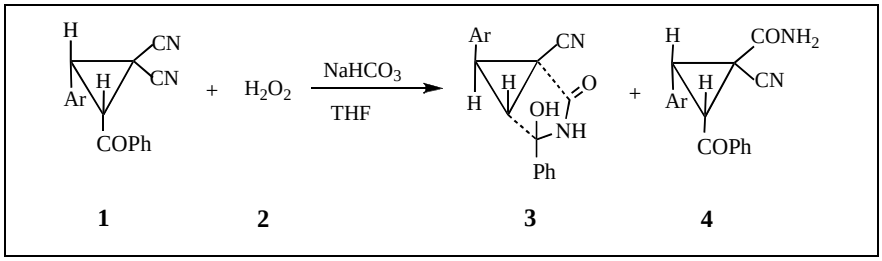
A Novel Synthesis of Cyclopropyl Lactam and Amide from *cis*-2-Aryl-3-Benzoyl-1,1-Dicynocyclopropane with H_2O_2 in the Presence of $NaHCO_3$

Zhongjiao Ren [a]*, Weiguo Cao [a, b], Jie Chen [a], Yeying Lu [a], Danyi Wu [a]

a. Department of Chemistry, Shanghai University, Shanghai, 200444, P. R. China
b. State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, 200032, P. R. China
Corresponding author, Fax: +86-21-6613-4856; E-mail: renrui198229@hotmail.com

Received September 13, 2006



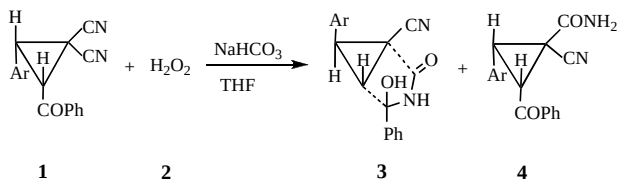
The process for preparation of cyclopropyl lactam and amide from *cis*-2-aryl-3-benzoyl-1,1-dicyno-cyclopropane with H_2O_2 in the Presence of $NaHCO_3$ is described. The highly stereoselective conversion of monocyano group to amide has been carried out in the present method.

J. Heterocyclic Chem., **44**, 999 (2007).

Cyclopropyl amides have attracted considerable attention due to their wide application as building block to construct complex molecule [1]. Moreover, cyclopropyl amides as structural unit are presence in a variety of natural and unnatural compounds with biological and pharmaceutical activity [2]. Although numerous methods for synthesis of cyclopropyl amide have been reported, the development of new method for synthesis of cyclopropyl amide is still demanded.

The interconversion of functional group is one of the most important processes in organic synthesis. We reported the preparation of *cis*-2-aryl-3-benzoyl-1,1-dicynocyclopropane [3]. The nitrile is a common precursor for preparing amide. As part of our program focused on the development of method for synthesis of highly functionalized cyclopropane, we studied the reaction involving the transformation of the cyano group incorporated on the cyclopropane into the amide group to provide new kind of highly functionalized cyclopropane. Here we report a novel process for preparation of cyclopropyl lactam and amide from *cis*-2-aryl-3-benzoyl-1,1-dicynocyclopropane with H_2O_2 in the presence of $NaHCO_3$ (Scheme 1).

Scheme 1



Nitrile hydration is a common method for preparation of amide. In all cases the reactions were monitored by TLC and stopped when the complete consumption of cyclopropane **1** was observed. We tested the hydrolysis reaction of *cis*-2-aryl-3-benzoyl-1,1-dicynocyclopropane in the presence of 10 % aqueous NaOH or K_2CO_3. When the reaction of cyclopropane **1** with 10 % NaOH was performed in THF at 40-50 ℃ or room temperature, an unidentified mixture was obtained. When the reaction of cyclopropane **1** with 10 % K_2CO_3 in THF was carried out at 40-50 ℃ a complex mixture was obtained, and no reaction occurred at room temperature. These results indicate that the cyclopropane **1** easily decomposes under higher temperature or stronger base. The conversion of nitrile to amide with an alkaline solution of hydrogen peroxide is a milder procedure. We turned our attention to the possibility of the transformation of the cyano group incorporated on the cyclopropane into the amide group with H_2O_2 in weaker bases, such as K_2CO_3, $NaHCO_3$ at room temperature. A complex mixture was obtained when 30% H_2O_2 (0.5 mL) was added dropwise to a stirred suspension of cyclopropane **1a** (1 equiv) and K_2CO_3 (3 equiv) in THF (5 mL). The cyclopropyl lactam **3a** and cyclopropyl amide **4a** were obtained in 72% and 11% in yields respectively in the presence of $NaHCO_3$ (3 equiv) under same condition. The reaction did not proceed at all in the absence of $NaHCO_3$ under same condition. The results of the reaction of some *cis*-2-aryl-3-benzoyl-1,1-dicynocyclopropanes with H_2O_2 in the presence of $NaHCO_3$ are shown in Table 1.

Table 1
The Synthesis of Cylopropyl Lactam **3 a-d** and Cylopropyl Amide **4 a-d**

Product	Ar	Time (h)	Yield (%)	Product	Ar	Yield (%)
3a	4-$CH_3OC_6H_4$	28	72	**4a**	4-$CH_3OC_6H_4$	11
3b	2,4-$(CHO_3)_2C_6H_3$	23	60	**4b**	2,4-$(CHO_3)_2C_6H_3$	20
3c	4-$CH_3C_6H_4$	30	54	**4c**	4-$CH_3C_6H_4$	34
3d	2,4-$Cl_2C_6H_3$	25	26	**4d**	2,4-$Cl_2C_6H_3$	52
3e	2-ClC_6H_4	26	17	**4e**	2-ClC_6H_4	56

Unless otherwise specified, the reaction was carried out with 30% H_2O_2 (0.5 mL) in the presence of $NaHCO_3$ (3 equiv) at room temperature in THF. Yields are of isolated product.

The structures of compound **3** and **4** were confirmed by ^{1}H NMR, MS, IR, elementary analysis and X-ray (**3b**).

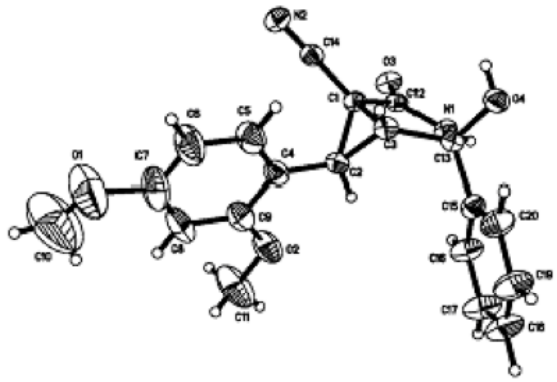


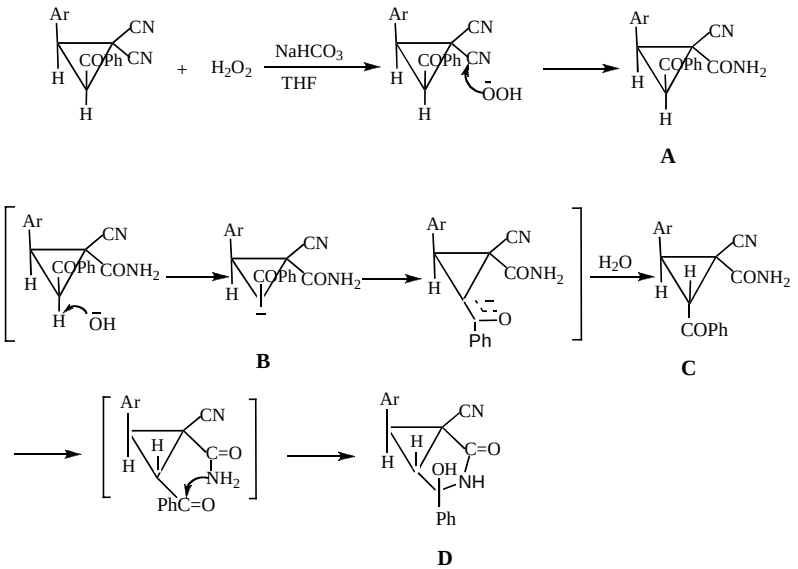
Figure 1. X-ray structure of compound **3b**.

Interestingly, the characteristic bands of the cyano groups (2233-2255 cm^{-1}) in the infrared spectra of compounds **3 a-e** and **4 a-e** are observed. This result indicates that the selective conversion of the monocyano group of dicyano groups on the cyclopropane **1** to amide occurs under the condition described above. To our knowledge, it is the first example of selective conversion of the monocyano group of dicyano groups to amide with H_2O_2 and $NaHCO_3$ as base.

It is known that cyclopropyl protons with a *cis* configuration have larger coupling constants (7-10 Hz), while those with a *trans* configuration have smaller coupling constants (3-7 Hz) [4]. The observed coupling constants for the cyclopropyl protons of **1 a-e** are 8.0-8.2 Hz [3] and those of the products **4 a-e** are 8.5 Hz respectively, whereas the coupling constants of cyclopropyl proton of the products **3 a-e** are 5.5 Hz. These observations show that the formation of product **3** undergoes *cis-trans* isomerization of cyclopropane ring.

We thought that the compound **3** could be given from the compound **4** *via* the *cis-trans* isomerization and intramolecular cyclization reactions. To verify this hypothesis, the reactions of the pure compound **4a** and **4e** with 30% H_2O_2 in the presence of $NaHCO_3$ were carried out under the same condition described above. As expected, compound **3a** and **3e** were obtained in 84%

Scheme 2



yield and in 30 % yield respectively. Considering on above data, a plausible mechanism for this process likely involves following key steps (Scheme 2). (1) The attack of H_2O_2 to cyano group occurs preferentially from the less hindered side of the *cis*-2-aryl-3-benzoyl-1,1-dicyno-cyclopropane **1**, bearing two hydrogen atoms, to afford the cyclopropyl amide **A** (product **4** in Scheme 1). (2) The carbanion **B** is formed by the removal of the proton of the cyclopropyl amide from the carbon *alpha* to benzoyl group with HCO_3^- as base. (3) The carbanion **B** is turned into cyclopropane **C**. (4) The intramolecular nucleophilic addition reaction between the benzoyl group and the amino group in the amide takes place and cyclopropyl Lactam **D** is afforded.

The results of our experiment showed that the yields of compounds **3** and **4** are related to the property of the substituents on aryl group (Table 1). A reasonable explanation for this might be given from the present mechanism. The fact that of the mixture of compound **3** and **4** are obtained in this reaction suggests that the steric repulsion between the amide and aryl groups on the same side of cyclopropane retards the isomerization of amide **A** to amide **C**; thus, a mixture of **3** and **4** is always afforded in this reaction. When the substituents on aryl group are electron-donating, such as CH_3, CH_3O, the electron density of the intermediate carbanion **B** is strengthened. Therefore, the carbanion intermediate **B** become higher energy and less stable, and is favour to transform into the intermediate **C** followed by leading in the lactam **D**. Conversely when the substituent on aryl group is electron-withdrawing group, such as Cl, the carbanion intermediate **B** become more stable and preferably regenerates the amide **A**. As a result, the yields of cyclopropyl lactam (**3a-c**) are higher than that of cyclopropyl amide (**4a-c**) and the yields of cyclopropyl lactam (**3d-e**) are lower than that of cyclopropyl amide (**4d-e**).

In summary, the novel process for synthesis of cyclo-propyl lactam and amide from *cis*-2-aryl-3-benzoyl-1,1-dicynocyclopropane with H_2O_2 in the presence of $NaHCO_3$ is achieved. It is noteworthy to mention that this process represents a highly stereoselective transformation, in which the one of the cyano groups of dicyano moiety is converted to amide from less sterically hindered side on *cis*-2-aryl-3-benzoyl-1,1-dicynocyclopropane.

EXPERIMENTAL

All reagents and solvents were obtained from commercial source and used without purification. All melting points are uncorrected. Melting points were determined on WRS-1 digital melting point apparatus made by Shanghai physical instrument factory (SPOIF), China. IR spectra were measured in KBr on a PE-580B spectrometer. ^{1}H NMR spectra were recorded using a Bruker AM-300, with CD_3COCD_3 or $CDCl_3$ as solvent and TMS as internal reference. Mass spectra were obtained on the Agilent 5973N spectrometer. Elemental analyses were measured on the elementar vario EL III. X-Ray crystal data sets were collected with Bruker Smart Apex2 CCD.

General procedure for preparing 1,6-*trans*-dihydro-6-aryl-3-aza-5-cyano-2-hydroxy-4-oxo-2-phenylbicyclo[3,1,0]hexane and *cis*-2-aryl-1-benzoyl-3-cyno-3-formamidecyclopropane. A 30% H_2O_2 solution (0.5 mL) was added dropwise to the suspension of *cis*-2-aryl-3-benzoyl-1,1-dicynocyclopropane **1** (1 mmol) and $NaHCO_3$ (0.25 g, 3 mmol) in THF (5 mL) at room temperature. Reaction progress was monitored by TLC and when the reaction was shown to be complete the suspension was filtered and all solvents were removed under reduced pressure. The residue was purified by a silica gel chromatographic column (petroleum ether/ethyl acetate (3:1)) and the product **3** and **4** were obtained respectively.

***trans*-1,6-Dihydro-3-aza-5-cyano-2-hydroxy-6-(4-methoxy-phenyl)-4-oxo-2-phenylbicyclo[3,1,0]hexane (3a).** This compound was obtained as a colorless solid, mp 174-175 °C; ^{1}H nmr (300 MHz, CD_3COCD_3) δ 2.84 (d, *J*=5.5 Hz, 1H, CH), 3.64 (d, *J*=5.5 Hz, 1H, CH), 3.76 (s, 3H, CH_3O), 6.33 (s, 1H, NH), 7.25 (d, *J*=6.9 Hz, 2H, Ar-H), 7.33-7.36 (m, 2H, Ar-H), 7.38-7.42 (m, 3H, Ar-H), 7.66 (d, *J*=6.9 Hz, 2H, Ar-H), 8.10 (s, br, 1H, OH); ir (potassium bromide) 3399, 3377, 2247, 1711, 1610 cm^{-1}; ms (m/z) (%): 105 (100), 77 (75), 51 (17), 44 (16), 145 (9), 128 (8), 199 (7), 106 (6); *Anal.* Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.11; H, 4.99; N, 8.53.

***trans*-1,6-Dihydro-3-aza-5-cyano-2-hydroxy-6-(2,4-dimeth-oxyphenyl)-4-oxo-2-phenylbicyclo[3,1,0]hexane (3b).** This compound was obtained as a colorless solid, mp 168-169 °C; ^{1}H nmr (300 MHz, CD_3COCD_3) δ 2.69 (d, *J*=5.5 Hz, 1H, CH), 3.65 (d, *J*=5.5 Hz, 1H, CH), 3.77 (s, 3H, CH_3O), 3.81 (s, 3H, CH_3O), 6.30 (s, 1H, NH), 6.46-6.51 (m, 2H, Ar-H), 6.55 (s, 1H), 7.08-7.11 (d, 1H, Ar-H), 7.33-7.43 (m, 3H, Ar-H), 7.64-7.68 (m, 2H, Ar-H), 8.08 (s, br, 1H, OH); ir (potassium bromide) 3385, 3237, 2248, 1716, 1613 cm^{-1}; ms (m/z) (%): 105 (100), 229 (45), 77 (27), 245 (15), 106 (9), 186 (8), 230 (7), 202 (5); *Anal.* Calcd. for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.45; H, 5.06; N, 8.03.

***trans*-1,6-Dihydro-3-aza-5-cyano-2-hydroxy-6-(4-methyl-phenyl)-4-oxo-2-phenylbicyclo[3,1,0]hexane (3c).** This compound was obtained as a colorless solid, mp 161-162 °C; ^{1}H nmr (300 MHz, CD_3COCD_3) δ 2.28 (s, 3H, CH_3), 2.80 (d, *J*=5.5 Hz, 1H, CH), 3.65 (d, *J*=5.5 Hz, 1H, CH), 6.34 (s, 1H, NH), 7.14 (d, *J*=8.0 Hz, 2H, Ar-H), 7.19-7.33 (m, 2H, Ar-H), 7.36-7.41 (m, 3H, Ar-H), 7.66 (d, *J*=8.0 Hz, 2H, Ar-H), 8.11 (s, br, 1H, OH); ir (potassium bromide) 3376, 2249, 1714 cm^{-1}; ms (m/z) (%): 199 (100), 105 (65), 77 (26), 129 (16), 200 (15), 183 (13), 140 (9), 286 (8); *Anal.* Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.99; H, 5.23; N, 9.00.

***trans*-1,6-Dihydro-3-aza-5-cyano-6-(2,4-dichlorophenyl)-2-hydroxy-4-oxo-2-phenylbicyclo[3,1,0]hexane (3d).** This compound was obtained as a colorless solid, mp > 180 °C decomp.; ^{1}H nmr (300 MHz, CD_3COCD_3) 2.80 (d, *J*=5.5 Hz, 1H, CH), 3.89 (d, *J*=5.5 Hz, 1H, CH), 6.43 (s, 1H, NH), 7.33-7.44 (m, 5H, Ar-H), 7.47 (s, 1H, Ar-H), 7.57-7.71 (m, 2H, Ar-H), 8.24 (s, br, 1H, OH); ir (potassium bromide) 3357, 3262, 2256, 1716 cm^{-1}; ms (m/z) (%):105 (100), 77 (67), 253 (34), 255 (22), 51 (15), 174 (13), 44 (10), 106 (8); *Anal.* Calcd. for $C_{18}H_{12}Cl_2N_2O_2$: C, 60.19; H, 3.37; N, 7.80. Found: C, 60.10; H, 3.45; N, 7.69.

***trans*-1,6-Dihydro-3-aza-6-(2-chlorophenyl)-5-cyano-2-hydroxy-4-oxo-2-phenylbicyclo[3,1,0]hexane (3e).** This

compound was obtained as a colorless solid, mp 154-155 °C; ^{1}H nmr (300 MHz, CD_3COCD_3) 2.80 (d, *J*=5.5 Hz, 1H, CH), 3.85 (d, *J*=5.5 Hz, 1H, CH), 6.41 (s, 1H, NH), 7.32-7.50 (m, 7H, Ar-H), 7.68-7.72 (m, 2H, Ar-H), 8.21 (s, br, 1H, OH); ir (potassium bromide) 3480, 3241, 2255, 1714, 1652 cm^{-1}; ms (m/z) (%):105 (100), 77 (93), 219 (25), 51 (24), 44 (12), 140 (10), 221 (8), 106 (7); *Anal.* Calcd. for $C_{18}H_{13}ClN_2O_2$: C, 66.57; H, 4.03; N, 8.63. Found: C, 66.56; H, 4.00; N, 8.62.

***cis*-1-Benzoyl-3-cyano-3-formamide-2-(4-methoxyphenyl)-cyclopropane (4a).** This compound was obtained as a colorless solid, mp 192-193 °C; ^{1}H nmr (300 MHz, CD_3COCD_3) δ 3.72 (d, *J*=8.5 Hz, 1H, CH), 3.82 (s, 3H, CH_3O), 4.07 (d, *J*=8.5 Hz, 1H, CH), 6.98 (s, br, 1H, NH), 7.01 (d, *J*=6.9 Hz, 2H, Ar-H), 7.47 (s, br, 1H, NH), 7.49-7.69 (m, 5H, Ar-H), 8.08 (d, *J*=6.9 Hz, 2H, Ar-H); ir (potassium bromide) 3466, 3334, 2237, 1690, 1596 cm^{-1}; ms (m/z) (%): 105 (100), 77 (37), 215 (10), 199 (9), 106 (8), 145 (7), 51 (6),128 (4); *Anal.* Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 70.90; H, 4.96; N, 8.43.

***cis*-1-Benzoyl-3-cyano-3-formamide-2-(2,4-dimethoxyphenyl)cyclopropane (4b).** This compound was obtained as a colorless solid, mp 188-189 °C; ^{1}H nmr (300 MHz, $CDCl_3$) δ 3.55 (d, *J*=8.5 Hz, 1H, CH), 3.75 (d, *J*=8.5 Hz, 1H, CH), 3.83 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O), 5.66 (s, br, 1H, NH), 6.38 (s, br, 1H, NH), 6.49-6.54 (m, 2H, Ar-H), 7.09-7.11 (d, 1H, Ar-H), 7.48-7.53 (m, 2H, Ar-H), 7.59-7.64 (m, 1H, Ar-H), 8.02-8.05 (m, 2H, Ar-H); ir (potassium bromide) 3420, 3315, 2236, 1699, 1612 cm^{-1}; ms (m/z) (%): 105 (100), 229 (31), 77 (29), 245 (12), 253 (9), 106 (8), 255 (6), 230 (5); *Anal.* Calcd. for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.51; H, 5.09; N, 7.91.

***cis*-1-Benzoyl-3-cyano-3-formamide-2-(4-methylphenyl)-cyclopropane (4c).** This compound was obtained as a colorless solid, mp 198-199 °C; ^{1}H nmr (300 MHz, CD_3COCD_3) δ 2.35 (s, 3H, CH_3), 3.73 (d, *J*=8.5 Hz, 1H, CH), 4.10 (d, *J*=8.5 Hz, 1H, CH), 6.93 (s, br, 1H, NH), 7.25 (d, *J*=8.3 Hz, 2H, Ar-H), 7.39 (s, br, 1H, NH), 7.42-7.46 (m, 1H, Ar-H), 7.55-7.60 (m, 2H, Ar-H), 7.64-7.70 (m, 2H, Ar-H), 8.09 (d, *J*=8.3 Hz, 2H, Ar-H); ir (potassium bromide) 3457, 3340, 2237, 1684, 1595 cm^{-1}; ms (m/z) (%): 199 (100), 105 (78), 77 (35), 129 (17), 200 (15), 156 (7), 106 (6), 51 (5); *Anal.* Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.60; H, 5.16; N, 8.94.

***cis*-1-Benzoyl-2-(2,4-dichlorophenyl)-3-cyano-3-formamidecyclopropane (4d).** This compound was obtained as a colorless solid, mp 216-217 °C; ^{1}H nmr (300 MHz, CD_3COCD_3) δ 3.80 (d, *J*=8.5 Hz, 1H, CH), 4.22 (d, *J*=8.5 Hz, 1H, CH), 7.04 (s, br, 1H, NH), 7.43 (s, br, 1H, NH), 7.49-7.71 (m, 6H, Ar-H), 8.07-8.11 (m, 2H, Ar-H); ir (potassium bromide) 3428, 3332, 2234, 1688, 1610 cm^{-1}; ms (m/z) (%): 105 (100), 77 (42), 253 (37), 255 (25), 229 (14), 106 (9), 209 (7), 51 (6); *Anal.* Calcd. for $C_{18}H_{12}Cl_2N_2O_2$: C, 60.19; H, 3.37; N, 7.80. Found: C, 60.02; H, 3.32; N, 7.68.

***cis*-1-Benzoyl-2-(2-chlorophenyl)–3-cyano-3-formamide-cyclopropane (4e).** This compound was obtained as a colorless solid, mp 202-203 °C; ^{1}H nmr (300 MHz, CD_3COCD_3) δ 3.82 (d, *J*=8.5 Hz, 1H, CH), 4.18 (d, *J*=8.5 Hz, 1H, CH), 7.01 (s, br, 1H, NH), 7.40 (s, br, 1H, NH), 7.42-7.49 (m, 2H, Ar-H), 7.55-7.71 (m, 5H, Ar-H), 8.08-8.11 (m, 2H, Ar-H); ir (potassium bromide) 3448, 3329, 2233, 1690, 1605 cm^{-1}; ms (m/z) (%): 219 (100), 105 (96), 77 (49), 221 (35), 220 (14), 140 (13), 149 (12), 184 (9); *Anal.* Calcd. for $C_{18}H_{13}ClN_2O_2$: C, 66.57; H, 4.03; N, 8.63. Found: C, 66.36; H, 3.99; N, 8.62.

Acknowledgements. Thanks are due to the National Natural Science Foundation of China for financial support (No. 20472047).

REFERENCES AND NOTES

[1] (a) Es-Sayed, M.; Devine, P.; Burgess, L. E.; Meijere, A.; Meyers, A. I. *J. Chem. Soc. Chem. Commun.* **1995**, 141. (b) Hanessian, S.; Buckle, R.; Bayrakdarian, M. *J. Org. Chem.* **2002,** *67*, 3387.

[2] (a) Zhong, R.; Mamai, A.; Madalengoitia, J. S. *J. Org. Chem.* **1999,** *64*, 547. (b) Romo, D.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 6265.

[3] Ren, Z.-J.; Cao, W.-G.; Ding, W.-Y.; Wang, Y. *Synthesis* **2005**, 2718.

[4] Gunther, H. NMR Spectroscopy; J. Wiley Sons: New York, **1980**, p. 108, 384.