JOC*Note*

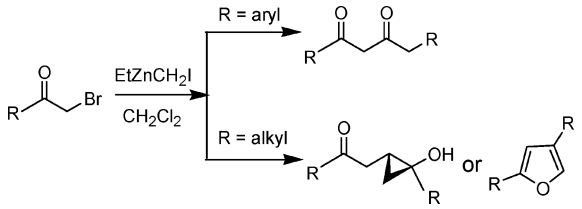
Zinc-Mediated C−C Bond Sigmatropic Rearrangement: A New and Efficient Methodology for the Synthesis of β-Diketones

Lezhen Li,[‡] Peijie Cai,[‡] Da Xu,[‡] Qingxiang Guo,[‡] and Song Xue*,[†,‡]

Department of Applied Chemistry, Tianjin University of Technology, Tianjin 300191, P.R. China, and Department of Chemistry, University of Science and Technology of China, Hefei 230026, P.R. China

xuesong@ustc.edu.cn

Received June 29, 2007



A new and efficient methodology has been developed for the synthesis of β-diketones from aromatic α-bromo ketones in the presence of Furukawa reagent under mild conditions. The present transformation is proposed to proceed via a Reformatsky-type reaction of α-bromo ketones, followed by C−C bond sigmatropic rearrangement of the aldolate intermediate to give β-diketones in moderate to good isolated yields, while aliphatic α-bromomethyl ketones resulted in the formation of 2,4-disubstituted furans or *cis*-1,2-disubstituted cyclopropanols in moderate yields. The scope of this process was investigated, and a tentative mechanism was proposed.

β-Diketones have been important intermediates in organic synthesis. They have served as key building blocks in the preparation of heterocyclic compounds such as pyrazoles,[1] isoxazoles,[2] triazoles,[3] and benzopyran-4-ones.[4] Moreover, they have also been used as chelating ligands for lanthanides and transition metals.[5] A variety of synthetic methods have been developed for the preparation of β-diketones.[6,7] 1-Aroylbenzimidazoles[8] and 1-aroylbenzotriazoles[9] have been used for the aroylations of the anion from acetylacetone or ketones and the subsequent obtainment of the desired β-diketones. Recently, an operationally simple and new approach to synthesize the α-aroylacetones from α-aminonitriles and propargyl bromide was reported.[10] Although these methods provide reliable routes for the preparation of β-diketones, most of them follow lengthy procedures and require multistep-preparation of a special reagent. Therefore, the development of direct and efficient procedures for these classes of compounds from facile materials has been the target of synthetic organic chemistry. In 1966, Furukawa reported that cyclopropanation reagent $EtZnCH_2I$ could be generated by the alkyl exchange between Et_2Zn and CH_2I_2.[11] From then on, the Furukawa reagent ($EtZnCH_2I$), as cyclopropanation reagent, has been widely used in organic synthetic chemistry.[12] However, the applicability of Furukawa reagent in organic synthesis has not been fully explored. Our ongoing interest in organozinc reagents prompted us to investigate the new application in organic synthetic chemistry. During the course of our investigation on the reaction of α-bromo ketones with Furukawa reagent ($EtZnCH_2I$), it was found that the self-coupling reaction of α-bromo ketones proceeded to furnish β-diketones, which appears to proceed via a C−C bond sigmatropic rearrangement. Herein, we wish to report a new and efficient methodology to synthesize β-diketones from α-bromo ketones in the presence of Furukawa reagent under mild reaction conditions.

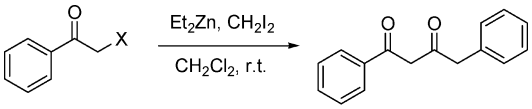
Initially, we examined the reactivity of α-halo acetophenone with organozinc species to optimize the reaction conditions. The results are shown in Table 1. The reaction of α-bromo acetophenone with 1.2 equiv of Furukawa reagent ($EtZnCH_2I$) in CH_2Cl_2 at room-temperature gave β-diketone **2a** in 48% yield along with recovered α-bromo acetophenone. When the reaction was performed in the presence of 2.0 equiv of organozinc

[†] Tianjin University of Technology.
[‡] University of Science and Technology of China.

(1) Nagpal, A.; Unny, R.; Joshi, Y. C. *Heterocycl. Commun.* **2001**, *32*, 589.
(2) Simoni, D.; Invidiata, F. P.; Rondanin, R.; Grimaudo, S.; Cannizzo, G.; Barbusca, E.; Porretto, F.; D'Alessandro, N.; Tolomeo, M. *J. Med. Chem.* **1999**, *42*, 4961.
(3) Alekseev, V. V.; Zelinin, K. N.; Yakimovich, S. I. *Russ. J. Org. Chem.* **1995**, *31*, 705.
(4) (a) Ellis, G. P. The Chemistry of Heterocyclic Compounds. In *Chromanones and Chromones*; Ellis, G. P., Ed.; Interscience: New York; Vol. 33, pp 495. (b) Raston, C. L.; Salem, G. *J. Chem. Soc., Chem. Commun.* 1984, 1702.
(5) Garnovskii, A. D.; Kharixov, B. I.; Blanco, L. M.; Garnovskii, D. A.; Burlov, A. S.; Vasilchenko, I. S.; Bondarenko, G. I. *J. Coord. Chem.* **1999**, *46*, 365−375.
(6) (a) Hauser, C. R.; Swamer, F. W.; Adams, J. T. *Org. React.* **1954**, *8*, 59. (b) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrel, R. *J. Am. Chem. Soc.* **1963**, *85*, 216. (c) Kopka, I.; Rathke, M. W. *J. Org. Chem.* **1981**, *46*, 3771. (d) Beck, A. K.; Hoekstra, M. S.; Seebach, D. *Tetrahedron Lett.* **1977**, 1187. (e) Fargeas, V.; Baalouch, M.; Metay, E.; Baffreau, J.; Menard, D.; Gosselin, P.; Berge, J.-P.; Barthomeuf, C.; Lebreton, J. *Tetrahedron* **2004**, *60*, 10359.
(7) (a) Hampton, K. G.; Harris, T. M.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 3511. (b) Padwa, A.; Hornbuckle, S. F.; Zhang, Z.; Zhi, L. *J. Org. Chem.* **1990**, *55*, 5297. (c) Pellicciari, R.; Fringuelli, R.; Sisani, E.; Curini, M. *J. Chem. Soc., Perkin Trans.* **1981**, *1*, 2566. (d) Gong, L.; Leung-Toung, R.; Tidwell, T. T. *J. Org. Chem.* **1990**, *55*, 3634. (e) Sato, T.; Inoue, M.; Kobara, S.; Otera, J.; Nozaki, H. *Tetrahedron Lett.* **1989**, *30*, 91. (f) Kel'in, A. V.; Kozyrkov, Y. Y. *Synthesis* **1998**, 729.
(8) Karnik, A. V.; Rane, J. P. *Indian J. Chem., Sect. B* **1998**, *37*, 1191.
(9) (a) Katritzky, A. R.; Wang, Z.; Wang, M.; Wilkerson, C. R.; Hall, C. D.; Akhmedov, N. G. *J. Org. Chem.* **2004**, *69*, 6617. (b) Katritzky, A. R.; Meher, N. K.; Singh, S. K. *J. Org. Chem.* **2005**, *70*, 7792.
(10) Mahalingam, S. M.; Aidhen, I. S. *J. Org. Chem.* **2006**, *71*, 349.
(11) (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, 3353. (b) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53. (c) Nishimura, J.; Furukawa, J.; Kawabata, N.; Kitayama, M. *Tetrahedron* **1971**, *27*, 1799.
(12) (a) Brogan, J, B.; Zercher, C. K. *J. Org. Chem.* **1997**, *62*, 6444. (b) Verbicky, C. A.; Zercher, C. K. *J. Org. Chem.* **2000**, *65*, 5615. (c) Lai, S.; Zercher, C. K.; Jasinski, J. P.; Reid, S. N.; Staples, R. J. *Org. Lett.* **2001**, *3*, 4169. (d) Hilgenkamp, R.; Zercher, C. K. *Tetrahedron* **2001**, *57*, 8793. (e) Xue, S.; Liu, Y. K.; Li, L. Z.; Guo, Q. X. *J. Org. Chem.* **2005**, *70*, 8245. (f) Long, J.; Yuan, Y.; Shi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 13632 and references therein.

10.1021/jo7013627 CCC: $37.00
Published on Web 09/21/2007

TABLE 1. Reaction of α-Halo Acetophenone with Organozinc Species



2a

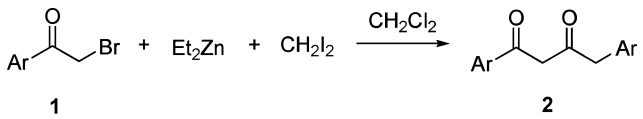
entry	X	solvent	organozinc species	time (h)	**2a** yield (%)[a]
1[b]	Br	CH_2Cl_2	$EtZnCH_2I$ 1.2 equiv	6	48
2	Br	CH_2Cl_2	$EtZnCH_2I$ 2.0 equiv	6	84
3	Br	CH_2Cl_2	Et_2Zn 2.0 equiv	8	complex mixture
4	Br	toluene	$EtZnCH_2I$ 2.0 equiv	6	32
5[c]	Br	CH_2Cl_2	$EtZnCH_2I$ 2.0 equiv	6	0
6	Cl	CH_2Cl_2	$EtZnCH_2I$ 2.0 equiv	5	–
7[d]	I	CH_2Cl_2	$EtZnCH_2I$ 2.0 equiv	5	62

[a] Isolated yields. [b] The recovery of α-bromo acetophenone was observed. [c] The reaction was performed at 0 °C. [d] Trace amount of 1-phenylcyclopropanol was obtained.

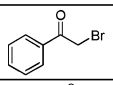
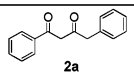
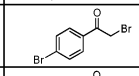
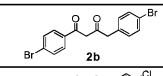
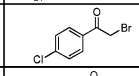
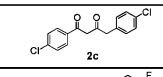
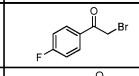
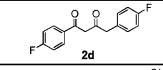
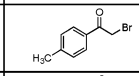
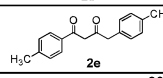
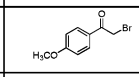
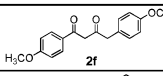
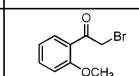
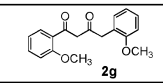
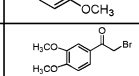
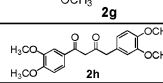
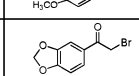
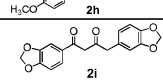
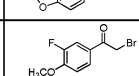
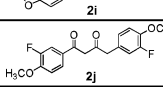
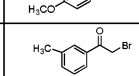
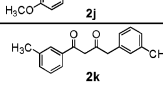
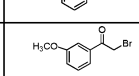
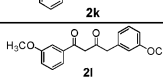
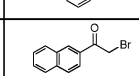
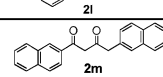
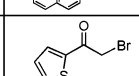
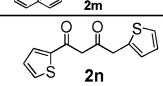
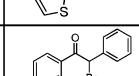
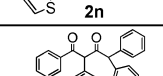
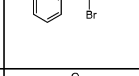
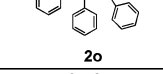
species, the desired product **2a** was obtained in 84% yield (entry 2). Nevertheless, no desired product **2a** was detected when using 2.0 equiv of Et_2Zn in CH_2Cl_2 for 8h at room temperature (entry 3). Solvent was also crucial for the course of the reaction. When the reaction was run in toluene, the desired product **2a** was obtained in 32% yield. The reaction performed in Et_2O or THF afforded a complex reaction mixture. Therefore, CH_2Cl_2 was chosen as the most effective solvent for the reaction. Decreasing reaction temperature to 0 °C gave no desired product **2a** (entry 5). Noted that the α-bromo ketones reacted with Furukawa reagent effectively, the reaction of α-chloro acetophenone with Furukawa reagent proceeded smoothly in the same reaction conditions, however, it gave a complicated mixture. Additionally, exposure of α-iodo acetophenone to 2.0 equiv of Furukawa reagent at room-temperature provided the desired product **2a** in 62% isolated yield along with trace amount of 1-phenylcyclopropanol.

With the optimal reaction conditions in hand, subsequently, we investigated the scope and limitation of this reaction. Various α-bromo ketones were subjected to the reaction under the standard conditions, and the representative results are shown in Table 2. Aromatic α-bromo ketones reacted smoothly with Furukawa reagent to give the desired *β*-diketones in moderate to good yields. Clearly, the substituents on the phenyl ring have an effect on the yields of the reaction. When the substrates contained an electron-withdrawing group, such as bromo or chloro, on its phenyl ring, the yields of the corresponding *β*-diketones decreased obviously (entries 2 and 3, Table 2). With a fluoro group in the para position on the benzene ring, the desired product **2d** was obtained in 82% yield (entry 4). However, when the fluoro or bromo group was on the meta position of its phenyl ring, the corresponding *β*-diketones were not formed under the same conditions. On the other hand, the substrates containing an electron-donating group in the para position of the phenyl ring should be carried out at 0 °C, which gave rise to the desired products in good isolated yields (entries 5−10, Table 2). When the reaction was performed at room

TABLE 2. Reaction of Aromatic α-Bromo Ketones with Furukawa Reagent ($EtZnCH_2I$)



1 **2**

Entry	Substrate	Time (h)	Product	Yield (%)[a]
1		6	 **2a**	84
2		6	 **2b**	44
3		6	 **2c**	46
4		6	 **2d**	82
5[b]		3	 **2e**	85
6[b]		3	 **2f**	81
7[b]		3	 **2g**	60
8[b]		3	 **2h**	70
9[b]		3	 **2i**	78
10[b]		3	 **2j**	80
11		4	 **2k**	62
12		6	 **2l**	40
13		4	 **2m**	73
14		4	 **2n**	62
15		5	 **2o**	72
16		5	 **2p**	0

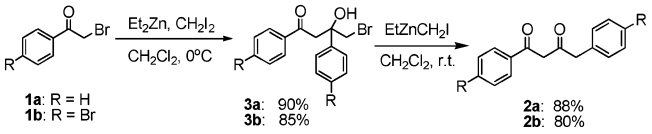
[a] Isolated yields. [b] Reactions were performed at 0 °C.

temperature, the yields of *β*-diketones decreased, due to the formation of cyclopropanols from the corresponding *β*-diketones.[13] However, if an electron-donor substituent, such as a methyl- or methoxyl group, was on the meta position of its phenyl ring, the reaction should be performed at room temperature, and would afford the desired *β*-diketones in 62% and 40% yields, respectively (entries 11 and 12, Table 2).

It is notable that when substrate **1a** or an electron-withdrawing group on its phenyl ring was carried out at 0 °C, the

(13) Xue, S.; Li, L. Z.; Liu, Y. K.; Guo, Q. X. *J. Org. Chem.* **2006**, *71*, 215.

SCHEME 1



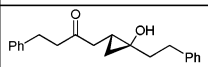
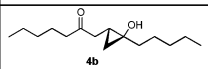
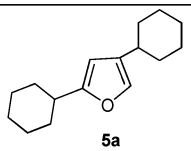
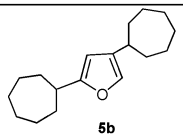
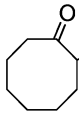
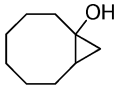
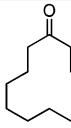
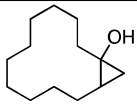
corresponding β-diketone was not detected by TLC analysis, but a new polar compound was formed. For example, exposure of α-bromo acetophenone, **1a**, and 2-bromo-1-(4-bromophenyl)-ethanone, **1b**, to 2.0 equiv of Furukawa reagent at 0 °C for 8 h gave the corresponding polar compounds in 90% and 85% yields, respectively (Scheme 1). These two compounds were determined to be 4-bromo-3-hydroxy ketones **3a** and **3b** by NMR spectra. These results indicated that [1,2]-sigmatropic migration of the electron-withdrawing aryl group to form β-diketones did not occur at 0 °C, even prolonging the reaction time. Thus, the reaction temperature is crucial for the success of the electron-withdrawing aryl group migration in this reaction. For better understanding of this reaction, the desired β-diketone **2a** was obtained in 88% yield when compound **3a** was treated with 3.0 equiv of Furukawa reagent in CH_2Cl_2 for 5 h at room temperature. However, compound **3b** was converted into the product **2b** in 80% yield at similar conditions, and longer reaction time (20 h) was needed necessarily.[14] The moderate yields of **2b** and **2c** in Table 2 might be ascribed to the slow conversion from the intermediate **3** to the product **2**.

The heteroaromatic α-bromo ketone, such as 2-bromo-1-(thiophen-2-yl)ethanone, was submitted to this reaction, and the desired product **2n** was obtained in 62% isolated yield. Employment of 2-bromo-1,2-diphenylethanone as a substrate resulted in the corresponding product **2o** with 72% yield. However, treatment of 2-bromo-1-phenylpentan-1-one with 2.0 equiv of Furukawa reagent under the same conditions gave no desired β-diketone **2p** as judged by the ^{1}H NMR spectra of the crude reaction mixtures (entry 16). The structure of products **2** was confirmed unambiguously by microanalysis, which was in accordance with NMR and HRMS spectra. The β-diketones **2a**−**2n** contained the corresponding enol forms as major tautomers with an exception of **2o**, which existed in the keto form.

We next extended the reaction to aliphatic α-bromomethyl ketones and cyclic α-bromo ketones under standard conditions. The results are shown in Table 3. The procedures described above for obtaining β-diketones became invalid when aliphatic α-bromomethyl ketones were submitted to this reaction, but, 1,2-disubstituted cyclopropanols or 2,4-disubstituted furans were obtained with moderate yields according to the steric feature of the substrates. For example, reactions of 1-bromo-4-phenylbutan-2-one and 1-bromoheptan-2-one with 2.0 equiv of Furukawa reagent give rise to the 1,2-disubstituted cyclopropanols **4a** and **4b** in 50% and 48% yields, respectively (entries 1 and 2, Table 3). The relative stereochemistry of alkyl substitutes on the cyclopropane ring was absolutely *cis*, which was firmly established by NOESY studies.[15] On the contrary, the 1,2-disubstituted cyclopropanols obtained from β-diketones by using organozinc reagent were trans.[13]

When aliphatic α-bromomethyl ketones with steric hindrance were submitted to this reaction, the 2,4-disubstituted furan

TABLE 3. Reaction of Aliphatic α-Bromo Ketones with Furukawa Reagent ($EtZnCH_2I$)

Entry	Substrate	Time (h)	Product	Yield %[a]
1		4	 **4a**	50
2		4	 **4b**	48
3[b]		5	 **5a**	56
4[b]		5	 **5b**	45
5		4	NR[c]	-
6		4	 **6a**	75
7		4	 **6b**	50

[a] Isolated yields. [b] Trace amount of 1,2-disubstituted cyclopropanols was detected. [c] NR = no reaction.

products were obtained as major products along with trace amounts of 1,2-disubstituted cyclopropanols. Treatment of 2-bromo-1-cyclohexylethanone and 2-bromo-1-cycloheptylethanone with 2.0 equiv of Furukawa reagent furnished the products 2,4-dicyclohexylfuran **5a** and 2,4-dicycloheptylfuran **5b** in 56% and 45% yields, respectively (entries 3 and 4, Table 3).[16] However, no reaction was observed when a large, bulky alkyl substrate, such as, 1-bromo-3,3-dimethylbutan-2-one, was submitted to this reaction (entry 5, Table 3). Cyclic α-bromo ketones were converted into the corresponding cyclopropanols under the same conditions. The reaction of 2-bromocyclooctanone and 2-bromocyclododecanone with Furukawa reagent afforded the cyclopropanols **6a** and **6b** in 75% and 50% yields, respectively (entries 6 and 7, Table 3).[17]

On the basis of these experiments, the mechanistic pathway for this new Reformatsky-type reaction of α-bromo ketones with Furukawa reagent is proposed as shown in Scheme 2. The first step of the reaction is initiated by the insertion of organozinc into the halogen−carbon bond to form an enol **7**, an analogue of Reformatsky species, derived from α-bromo ketones **1** reacted with Furukawa reagent ($EtZnCH_2I$). Nucleophilic addition of the enol **7** to a second α-bromo ketone **1** gives the self-condensation species **3**, which is the key intermediate of the reaction. When R is an aryl group, the intermediate **3** undergoes

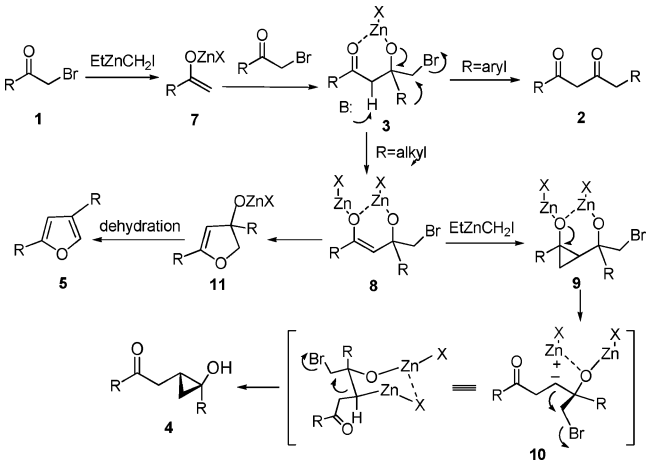
(14) Treatment of 4-bromo-3-hydroxy ketones **3b** with 3.0 equiv of Furukawa reagent in CH_2Cl_2 for 5 h at room temperature gave product **2b** in 32% yield along with recovered 4-bromo-3-hydroxy ketones **3b**.

(15) See the Supporting Information for details.

(16) Treatment of α-bromo ketones with zinc afforded furans; see: Spencer, T. A.; Britton, R. W.; Watt, D. S. *J. Am. Chem. Soc.* **1967**, *89*, 5727.

(17) Ito, S.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1998**, *39*, 5253.

SCHEME 2. Tentative Mechanistic Pathway for the Reaction of α-Bromo Ketones with Furukawa Reagent



an elimination of Br anion and C−C bond sigmatropic rearrangement of the aryl group to provide the desired β-diketones **2**.[18,7f] The experimental results mentioned above indicate that[1,2] sigmatropic migration of the aryl group to form β-diketone is the rate-controlling step in the reaction. The aryl group with electron-donor substituents on its phenyl ring transfers faster than that with electron-withdrawal substituents. The latter does not undergo rearrangement at 0 °C, and the intermediates **3** can be isolated in good yields (Scheme 1). At room temperature, both kind substituents can undergo migration smoothly to form the desired β-diketones.

When R is an alkyl group, the R group has a low migratory aptitude (i.e., contributes little to resonance stabilization of the transition state).[19] Thus, deprotonation of intermediate **3** with a base generates an enol **8** in preference to the C−C bond sigmatropic rearrangement. The species **8** undergoes cyclopropanation with Furukawa reagent to give the intermediate **9**, followed by a ring-opening reaction and intramolecular S_N2 displacement to form *cis*-1,2-disubstituted cyclopropanols **4**. When R is a bulky alkyl group, the intermediate **8** undergoes S_N2 displacement (which is an intramolecular nucleophilic attack of the enol oxygen upon the electrophilic carbon on which Br is attached), and then the Br anion leaves to furnish the intermediates **11**, followed by dehydration to generate 2,4-disubstituted furan **5**. The reaction of cyclic α-bromo ketone with one equivalent of Furukawa reagent afforded zinc enolates, which undergo cyclopropanation with a second equivalent of the zinc species to give the product **6**.

(18) Kohler, E. P.; Tishler, M. *J. Am. Chem. Soc.* **1935**, *57*, 217.
(19) Geissman, T. A.; Akawie, R. I. *J. Am. Chem. Soc.* **1951**, *73*, 1993.

In conclusion, we have developed a new and efficient synthetic methodology for the synthesis of β-diketones from α-bromo ketones. The reaction of aromatic α-bromo ketones with Furukawa reagent ($EtZnCH_2I$) afforded the desired β-diketones in good yields under mild conditions. Although aliphatic α-bromo ketones resulted in diminished efficiency for the synthesis of β-diketones, 2,4-disubstituted furans or *cis*-1,2-disubstituted cyclopropanols were obtained in moderate yields under the same conditions.

Experimental Section

General Procedure for the Reaction of α-Bromo Ketones with Furukawa Reagent. A 25-mL round-bottom flask was equipped with a stir bar and charged with freshly distilled methylene chloride (3 mL), and neat diethylzinc (100 μL, 1.0 mmol) was added via syringe under an atmosphere of nitrogen at 0 °C. Then methylene iodide (80 μL, 1.0 mmol) was added dropwise via syringe under nitrogen, and the resulting white suspension was stirred for additional 10 min α-Bromo ketone (0.5 mmol) was added to the reaction mixture, and then the ice bath was removed. The solution was allowed to stir at room temperature until TLC indicated complete consumption of the starting α-bromo ketones. The reaction mixture was quenched by saturated aqueous ammonium chloride solution and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine and then dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give the crude products, which were purified by column chromatograph packed with silica gel using petroleum ether/ethyl acetate (50:1 to 10:1) as eluent to afford the pure products.

1,4-Diphenylbutane-1,3-dione[20](2a). The title compound was prepared from 2-bromo-1-phenylethanone (99.5 mg, 0.5 mmol) according to the general procedure, and the desired β-diketone (50.0 mg, 84% yield) was obtained as a white solid after flash chromatography on silica gel (50:1 petroleum ether/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 15.95 (s, 1H), 7.73 (d, J = 7.2 Hz, 2H), 7.41 (t, J = 7.2 Hz, 1H), 7.38 (t, J = 7.2 Hz, 2H), 7.20 (m, 5H), 6.04 (s, 1H), 3.65 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 194.9, 183.5, 135.3, 134.9, 132.4, 129.5, 128.9, 128.7, 127.2, 127.1, 96.3, 46.2; IR (neat; cm^{-1}): υ 2962, 1599, 1262, 698. HRMS (EI): calcd for $C_{16}H_{14}O_2$ (M^+), 238.0994; found: 238.0999.

Acknowledgment. We are grateful to the National Natural Science Foundation of China (20572104) and the Program of NCET for financial support.

Supporting Information Available: Detailed experimental procedures and characterization data for all previously unknown products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7013627

(20) Facchetti, A.; Streitwieser, A. *J. Org. Chem.* **2004**, *69*, 8345.