JOC*Note*

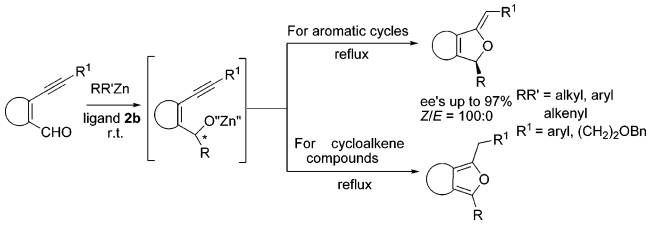
Tandem Addition/Cyclization Reaction of Organozinc Reagents to 2-Alkynyl Aldehydes: Highly Efficient Regio- and Enantioselective Synthesis of 1,3-Dihydroisobenzofurans and Tetrasubstituted Furans

Zhuo Chai,[†] Zheng-Feng Xie,[‡] Xin-Yuan Liu,[†] Gang Zhao,*[,†] and Ji-De Wang*[,‡]

Laboratory of Modern Synthetic Organic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China, and Education Ministry Key Laboratory of Oil and Gas Fine Chemicals, XinJiang University, 14 Shengli Lu, Urumqi 830046, China

zhaog@mail.sioc.ac.cn; awangjdl@xju.edu.cn

Received January 5, 2008



The enantioselective addition of organozinc reagents to some 2-alkynyl benzaldehydes and the subsequent regioselective cyclization step was performed in one pot to form chiral 1,3-dihydroisobenzofurans with good product yields and excellent regio- and enantioselectivities. In the case of 2-alkynylcycloalkene aldehydes, tetrasubstituted furans were obtained in good product yields through a 1, 5-hydride shift of the preformed cyclization product.

Annulation processes involving the addition of heteroatoms to multiple C−C bonds represent an important method for the synthesis of heterocyclic compounds.[1] Usually, such processes are advantageous in terms of atom-economy, operational simplicity, and variability for the design of tandem processes.[1] In the synthesis of 1,3-dihydroisobenzofurans, the cyclization reactions of 2-alkynylbenzyl alcohols which are usually prepared from the corresponding 2-alkynylbenzaldehydes have been realized utilizing a series of metal catalysts[2] or various bases.[3] Such cyclization reactions are particularly challenging because both the 6-*endo-dig* and the 5-*exo-dig* cyclization of 2-alkynylbenzyl alcohols must be well-controlled to avoid formation of intractable mixtures of regioisomeric five- and six-membered rings; *anti*- and *syn*-addition to the triple bond should also be controlled to avoid formation of a mixture of *Z*- and *E*-isomeric isobenzofurans in the case of the 5-*exo-dig* process.[2,3] Meanwhile, to the best of our knowledge, there has been no report concerning the enantioselective formation of chiral 1,3-dihydroisobenzofurans.

Recently, Nakamura and co-workers[4] have pioneered the use of diethylzinc for the cyclization reactions of 2-alkynylphenols. Inspired by this work, our group[5] has also realized the Et_2Zn-catalyzed intramolecular hydroamination reaction of alkynyl sulfonamides to form indole derivatives. On the other hand, the enantioselective addition reactions of organozinc reagents to aldehydes are well developed.[6] On the basis of these studies, we conceived a one-pot procedure involving a tandem addition/cyclization process of organozinc reagents to 2-alkynylbenzaldehydes for the regio- and enantioselective synthesis of 1,3-dihydroisobenzofurans. Thus, the present work presented a novel tandem addition/cyclization of 2-alkynylbenzaldehydes with organozinc reagents in the presence of chiral 2-pyrrolidinylmethanol derivatives to exclusively afford optically active (*S*,*Z*)-1, 3-dihydroisobenzofurans in good yields and excellent enantioselectivities with virtually complete *Z*-selectivities via a highly regiospecific 5-*exo-dig* process involving stereoselective *anti* addition to the triple bond (Scheme 1). Herein, we report our results with this strategy.

Our study began with the use of 2-phenylethynylbenzaldehyde (**1a**) as the probe substrate. In the presence of DPMPM (**2a**) or the dendritic ligand (**2b**) developed by us previously,[7a] we were pleased to find that the asymmetric addition of Et_2Zn to **1a** and the subsequent regiospecific 5-*exo-dig* cyclization to form **3a** could be done in a one-pot fashion in toluene (Table 1). The addition step was performed at room temperature; after disappearance of the aldehyde monitored by TLC on silica gel plates,

* Corresponding author. Fax: 0086-21-64166128.
[†] Shanghai Institute of Organic Chemistry.
[‡] XinJiang University.

(1) For recent reviews, see: (a) Chemler, S. R.; Fuller, P. H. *Chem. Soc. Rev.* **2007**, *36*, 1153. (b) Molteni, V.; Ellis, D. A. *Curr. Org. Synth.* **2005**, *2*, 333. (c) Wolfe, J. P.; Thomas, J. S. *Curr. Org. Chem.* **2005**, *9*, 625. For recent examples, see: (d) Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 9643. (e) Gao, K.; Wu, J. *J. Org. Chem.* **2007**, *72*, 8611. (f) Arimitsu, S.; Hammond, G. *J. Org. Chem.* **2007**, *72*, 8559. (g) Barange, D. K.; Nishad, T. C.; Swamy, N. K.; Bandameedi, V.; Kumar, D.; Sreekanth, B. R.; Vyas, K.; Pal, M. *J. Org. Chem.* **2007**, *72*, 8547. (h) Ding, Q.; Wu, J. *Org. Lett.* **2007**, *9*, 4959. (i) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Org. Lett.* **2006**, *8*, 2803. (j) Tsuji, H.; Mitsui, C.; Llies, L.; Sato, Y.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 11902. (k) Liang, Z.; Ma, S.; Yu, J.; Xu, R. *Tetrahedron* **2007**, *63*, 12877. (l) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5132.

(2) (a) Gabriele, B.; Salerno, G.; Fazio, A. *Tetrahedron* **2003**, *59*, 6251. (b) Hashmi, A. S. K.; Schäfer, S.; Wölfle, M.; Gil, C. D.; Fischer, P.; Laguna, A.; Blanco, M. C.; Gimeno, M. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6184.

(3) (a) Padwa, A.; Krumpe, K. E.; Weingarten, M. D. *J. Org. Chem.* **1995**, *60*, 5595. (b) Hiroya, K.; Jouka, R.; Kameda, M.; Yasuhara, A.; Sakamoto, T. *Tetrahedron* **2001**, *57*, 9697.

(4) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 944.

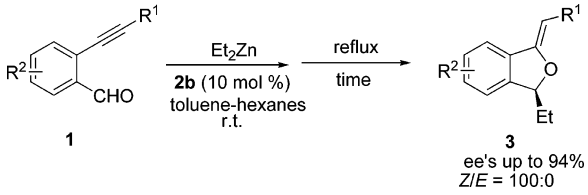
(5) Yin, Y.; Ma, W.-Y.; Chai, Z.; Zhao, G. *J. Org. Chem.* **2007**, *72*, 5731.

(6) For reviews, see: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49−69. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856. (c) Soai, K.; Shibata, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, pp 911−922. (d) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757−824. (e) Pu, L. *Tetrahedron* **2003**, *59*, 9873−9886. For works from our group in this field, see: (f) Zhao, G.; Li, X.-G.; Wang, X.-R. *Tetrahedron: Asymmetry* **2001**, *12*, 399−403. (g) Wu, X.-Y.; Liu, X.-Y.; Zhao, G. *Tetrahedron: Asymmetry* **2005**, *16*, 2299−2305. (h) Chai, Z.; Liu, X.-Y.; Wu, X.-Y.; Zhao, G. *Tetrahedron: Asymmetry* **2006**, *17*, 2442−2447 and ref. 7.

(7) (a) Liu, X.-Y.; Wu, X.-Y.; Chai, Z.; Wu, Y.-Y.; Zhao, G.; Zhu, S.-Z. *J. Org. Chem.* **2005**, *70*, 7432. (b) Chai, Z.; Liu, X.-Y.; Zhang, J.-K.; Zhao, G. *Tetrahedron: Asymmetry* **2007**, *18*, 724.

10.1021/jo800029m CCC: $40.75
Published on Web 03/04/2008

SCHEME 1. Addition and Cyclization Reaction of Organozinc Reagents to 2-Alkynyl Benzaldehydes

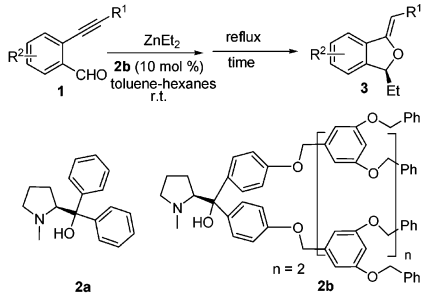


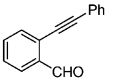
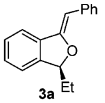
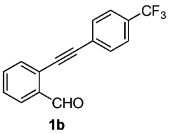
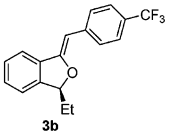
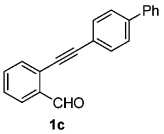
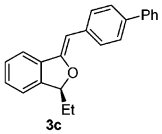
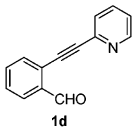
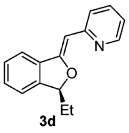
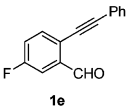
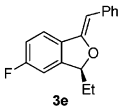
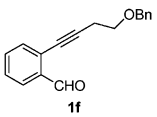
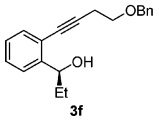
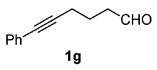
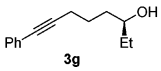
the reaction system was brought to reflux for the next cyclization step. The geometry of the double bond of **3a** was proved to be *Z* by NOE experiments (see the Supporting Information). Both ligands provided similar product yields, while a slightly higher ee value was obtained with the dendritic ligand **2b** (Table 1, entries 1−3).[8] Changing the solvent to Et_2O, CH_2Cl_2, or THF all only led to the ethylation product (*S*)-1-(2-(phenylethynyl)-phenyl)propan-1-ol **3a′** rather than the desired cyclization product, which may be due to the low boiling points of these solvents that fail to effect the cyclization step (Table 1, entries 4−6). Moreover, the dendritic ligand **2b** could be recovered almost quantitatively with the precipitation method by addition of methanol and could be reused at least twice without considerable loss of catalytic activity (Table 1, entries 7 and 8). Subsequent investigation of the scope of this reaction revealed that the reaction could proceed smoothly with a decreased cyclization reaction time when **1b** with the electron-withdrawing group CF_3 was used (Table 1, entry 9). With compounds **1c** and **1d**, slightly less successful results were observed (Table 1, entries 10, 11). Unfortunately, when R^1 was an aliphatic group **1f**, only the ethylation product was isolated (Table 1, entry 13). In addition, a linear substrate **1g** was also prepared and tested under the same reaction conditions, but again only the ethyl adduct was isolated (Table 1, entry 14).

The absolute configuration of the product **3a** was determined to be *S* by conversion into the known (*S*)-3-ethylisobenzofuran-1(3*H*)-one (Scheme 2), which belongs to an important class of compounds with good biological and pharmaceutical activities,[11] followed by comparison of the specific rotation value with literature data (see Experimental Section for details).

We next turned our attention to the scope of several other organozinc reagents. They were reacted with **1a** under similar reaction conditions, and the results are summarized in Table 2. Both the aryl and alkenyl organozinc reagents gave the cyclization products with good yields and high regio- and

TABLE 1. Eantioselective Addition and Cyclization Reaction of Et_2Zn to 2-Alkynylbenzaldehydes[a]



entry	substrate	product	time (h)[b]	yield (%)[c]	ee (%)[d]
1			10	70	94
2[e]			10	71	92
3[f]			10	52	92
4[g]			12	70[g]	90[g]
5[h]			12	75[h]	83[h]
6[i]			12	73[i]	72[i]
7[j]	 1a	 3a	10	72	93
8[k]			10	72	93
9	 1b	 3b	8	75	89
10	 1c	 3c	12	67	83
11	 1d	 3d	10	62	80[l]
12	 1e	 3e	12	83	79
13[m]	 1f	 3f	24	80	82
14[m]	 1g	 3g	24	72	55

[a] Et_2Zn/**1** = 2:1, 10 mol % of **2b**, toluene/hexane = 7:1. [b] Reaction time for the cyclization step. [c] Isolated yields. [d] Determined by chiral HPLC, see text for the determination of the absolute configuration of **3a**. For the other compounds **3b**−**e**, that determination was done by assuming that a similar catalytic mechanism was taken. [e] Ligand **2a** (10 mol %) was used. [f] 5 mol % of **2b** was used. [g] Et_2O used as the cosolvent, and only the ethyl adduct **3a′** was isolated. [h] CH_2Cl_2 used as the cosolvent, and only the ethyl adduct **3a′** was isolated. [i] THF used as the cosolvent, and only the ethyl adduct **3a′** was isolated. [j] Second use of **2b** (10 mol %). [k] Third use of **2b** (10 mol %). [l] The ee value was determined by converting **3d** into the known corresponding phthalide compound **3d′**[11]followed by chiral HPLC analysis. [m] Only the ethyl adduct was isolated.

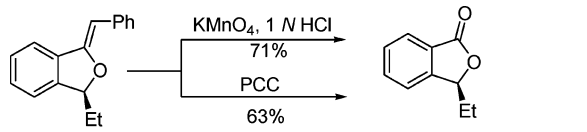
(8) An equilibrium has been proposed between a compound of **3a**'s type and its tautomer 2-benzylisobenzofuran; see: Smith, J. G.; Wikman, R. T. *J. Org. Chem.* **1974**, *39*, 3648. However, in view of the enantioselectivity's retention during the cyclization step, such an equilibrium may be ruled out in our case.

(9) Treatment of the isolated intermediate alkynyl alcohol with Et_2Zn in toluene at 60 °C or with NaOH in THF at room temperature led to its decomposition.

(10) For a recent review on the synthesis and uses of polysubstituted furans, see: (a) Kirsch, S. F. *Org. Biomol. Chem.* **2006**, *4*, 2076; For very recent examples see: (b) Badudri, F.; Cicco, S. R.; Farinola, G. M.; Lopez, L. C.; Naso, F.; Pinto, V. *Chem. Commun.* **2007**, 3756. (c) Liu, Z.; Yu, W.; Yang, L.; Liu, Z.-L. *Tetrahedron Lett.* **2007**, *48*, 5321. (d) William, D. R.; Lee, M.-R.; Song, Y.-A.; Ko, S.-K.; Kim, G.-H.; Shin, I. *J. Am. Chem. Soc.* **2007**, *129*, 9258. (e) Zhan, Z.-P.; Cai, X.-B.; Wang, S.-P.; Yu, J.-L.; Liu, H.-J.; Cui, Y.-Y. *J. Org. Chem.* **2007**, *72*, 9838.

(11) (a) Takahashi, H.; Tsubuki, T.; Higashiyama, K. *Chem. Pharm. Bull.* **1991**, *39*, 3136. (b) Watanabe, M.; Hashimoto, N.; Araki, S.; Butsugan, Y. *J. Org. Chem.* **1992**, *57*, 742. (c) Ramachandran, P. V.; Chen, G.-M.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 2205. (d) Yang, H.; Hu, G.-Y.; Chen, J.; Wang, Y.; Wang, Z.-H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5210.

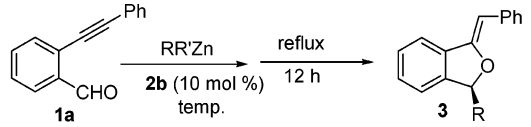
SCHEME 2. Conversion and Determination of the Absolute Configuration of 3a

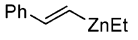
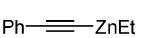


$[\alpha]^{D}_{26}$ = -68.7 (*c* 1.20, $CHCl_3$)

lit.[11a] $[\alpha]^{D}$ = -73.5 (*c* 3.60, $CHCl_3$) for 96% ee (*S*)

TABLE 2. Reaction of Several Different Organozinc Reagents with 1a



entry	RR'Zn[a]	temp (℃)[b]	product (R)	yield (%)[c]	ee (%)[d]
1	Me_2Zn	rt	**3h** (Me)	68	36
2[e,f]	PhZnEt	-15	**3i** (Ph)	59	97
3[e]		0	**3j** (Styryl)	60	91
4[e]		0	complicated	-	-

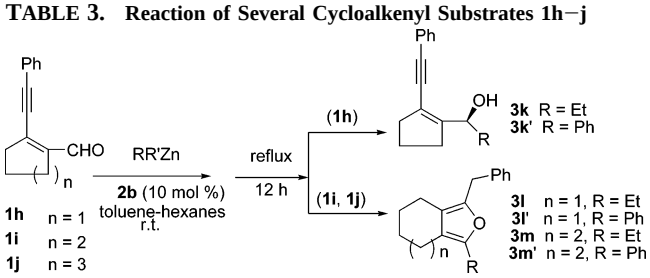
[a] RR′Zn/**1** = 2:1, 10 mol % of **2b**. [b] Reaction temperature for the addition step. [c] Isolated yields. [d] Determined by chiral HPLC. The absolute configuration of the products **3h**−**j** was assigned by assuming that the catalytic mechanism was similar to the one when Et_2Zn was used. [e] See the Supporting Information for experimental details. [f] 15 mol % of **2b** was used.

enantioselectivities (Table 2, entries 2 and 3). However, enantioselectivity was poor when Me_2Zn was used (Table 2, entry 1). The alkynylzinc reagent obtained via treatment of phenylacetylene with Et_2Zn failed to give the corresponding product (Table 2, entry 4), which results could be attributed to the instability of the intermediate product alkynyl alcohol under basic conditions at high temperatures. Control experiments on the separately isolated intermediate alkynyl alcohol revealed that this compound would decompose under basic conditions even at room temperature.[9]

Subsequently, several 2-alkynylcycloalkene aldehydes were prepared and reacted with organozinc reagents to expand the scope of this reaction (Table 3). Unlike their aromatic counterparts, it was found that the products of this reaction were highly dependent on the size of the alkyl cycles of the substrates: for the five-membered cycle, only the intermediate alcohol adduct was isolated; for six- and seven-membered ones, only the tetrasubstituted furan compounds[10] were obtained as a single product, which may result from the 1,5-hydride shift of the corresponding cyclization products.

In conclusion, we have reported a novel tandem addition/cyclization reaction of organozinc reagents to 2-alkynyl aromatic and cycloalkene aldehydes. Using this method, chiral 1,3-dihydroisobenzofurans could be obtained in high ee values and moderate to good yields with virtually complete *Z*-selectivities from aromatic substrates and some tetrasubstitued furan compounds could also be obtained in good yields from cycloalkene substrates.

TABLE 3. Reaction of Several Cycloalkenyl Substrates 1h−j



entry	substrate	RR′Zn[a]	product	yield[b] (%)	ee[c] (%)
1	**1h**	Et_2Zn	**3k**	53	85
2	**1h**	PhZnEt	**3k′**	65	39
3	**1i**	Et_2Zn	**3l**	75	
4	**1i**	PhZnEt	**3l′**	70	
5	**1j**	Et_2Zn	**3m**	70	
6	**1j**	PhZnEt	**3m′**	72	

[a] RR′Zn/**1** = 2:1. [b] Isolated yields. [c] Determined by chiral HPLC. The absolute configuration of **3k** and **3k′** was assigned by assuming that a catalytic mechanism similar to that of the aromatic substrates was taken.

Experimental Section

General Procedure for the Tandem Addition/Cyclization Reaction of Organozinc Reagents with 2-Alkynylbenzaldehydes (Tables 1−3). A Schlenk tube was charged with ligand **2b**[7] (0.025 mmol, 10 mol %), and the system was purged three times with argon. Then 2.5 mL of freshly distilled toluene was added followed by diethylzinc (0.5 mmol, 1.0 M in hexanes); after being stirred for 10 min at room temperature, the substrate aldehyde (0.25 mmol in 1 mL of toluene) was added in one portion. After disappearance of the substrate aldehyde (monitored by TLC on silica gel plates), the system was brought to reflux for the indicated times before being quenched with 8 mL of dry methanol, thus precipitating the dendritic ligand **2b**. After filtration, the filtrate was concentrated, and the residue was purified by chromatography to give the desired products. The dendritic ligand was recovered by extraction of the filtering cake with CH_2Cl_2 followed by removal of the solvent.

(*S*,*Z*)-1-Benzylidene-3-ethyl-1,3-dihydroisobenzofuran (3a, Table 1, Entry 1). Compound **3a** was prepared from 2-(phenylethynyl)benzaldehyde according to the general procedure as a colorless oil (50 mg, 70% yield; 94% ee) after chromatography (silica gel, 2.5% ether in petroleum): $[\alpha]^{26}_{D}$ = 98.2 (*c* 1.25, $CHCl_3$) for 94% ee; IR (CH_2Cl_2, film) 2967, 2926, 1655, 1464, 1052, 961, 762, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 7.5 Hz, 2H), 7.55 (m, 1H), 7.36−7.16 (m, 5H), 7.11(m, 1H), 5.90 (s, 1H), 5.63 (m, 1H), 2.07 (m, 1H), 1.84 (m, 1H), 1.06 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 155.5, 142.3, 136.6, 135.1, 128.5, 128.2, 128.0, 127.7, 125.0, 121.1, 119.8, 95.6, 86.9, 28.8, 8.9; MS (EI) (*m*/*z*) 236 (M^+), 207 (base); HRMS calcd for $C_{17}H_{16}O$ 236.1201, found 236.1194; HPLC Daicel CHIRALCEL OJ column, hexane/IPA = 9:1, 0.75 mL/min, λ 254 nm, $t_R(R)$ = 26.2 min, $t_R(S)$ = 28.5 min. The absolute configuration of **3a** was determined by converting it into the known compound 3-ethylisobenzofuran-1(3*H*)-one. Procedure with $KMnO_4$: To a solution of **3a** (47.2 mg, 0.2 mmol) in 5 mL of acetone were added solid $KMnO_4$ (1.1 equiv) and 0.5 mL of 1 N HCl; after being stirred for 1 h at room temperature, the mixture was filtered through Celite and concentrated, and column chromatography (silica gel, 5% ether in petroleum) gave the desired product as colorless oil. Procedure with PCC: To a solution of **3a** (47.2 mg, 0.2 mmol) in 4 mL of CH_2Cl_2 was added PCC (1.2 equiv), and after being stirred for 2 h at room temperature, the mixture was filtered through Celite and concentrated. Column chromatography (silica gel, 5% ether in petroleum) gave the desired product as a colorless oil. The spectrocopic values were in good agreement with those reported in literature:[11a] IR (neat) 2972, 2937, 1762, 1466, 1059, 960, 738, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 8.0 Hz, 1H), 7.67 (m, 1H), 7.53 (m,

1H), 7.44(d, J = 7.6 Hz, 1H), 5.46 (m, 1H), 2.10 (m, 1H), 1.84 (m, 1H), 1.01 (t, J = 7.0 Hz, 3H); $[\alpha]^{26}_{D} = -68.7$ (c 1.20, $CHCl_3$) [lit.[11a] $[\alpha]_D = -73.5$ (c 3.60, $CHCl_3$) for 96% ee (S)].

1-Benzyl-3-ethyl-4,5,6,7-tetrahydroisobenzofuran (3l, Table 3, Entry 3). This compound was prepared according to the general procedure as a colorless oil (45 mg, 75% yield) after chromatography (silica gel, 2.5% ether in petroleum): IR (CH_2Cl_2, film) 2931, 2856, 1593, 1494, 1453, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.18 (m, 5H), 3.85 (s, 2H), 2.50 (q, J = 7.6 Hz, 2H), 2.39 (m, 4H), 1.64 (m, 4H), 1.15 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 148.9, 144.7, 139.2, 128.5, 128.3, 126.0, 117.2, 115.4, 32.8, 23.5, 20.6, 20.5, 19.8, 12.7; MS (EI) (m/z) 240 (M^+), 225 (base); HRMS calcd for $C_{17}H_{20}O$ 240.1514, found 240.1512.

Acknowledgment. The generous financial support from the National Natural Science Foundation of China, QT Program, Shanghai Natural Science Council, and Excellent Young Scholars Foundation of NNSF is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data for all new compounds and copies of ^1H NMR, ^{13}C NMR, and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800029M