Journal of Fluorine Chemistry 132 (2011) 71–74

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Short communication

A recyclable fluoroalkylated 1,4-disubstituted [1,2,3]-triazole organocatalyst for aldol condensation of aldehydes and ketones

Yi-Wei Zhu, Wen-Bin Yi *, Chun Cai

School of Chemical Engineering, Nanjing University of Science and Technology, 200 Xiao Ling Wei Street, Nanjing, Jiangsuang 210094, People's Republic of China

ARTICLE INFO

Article history:
Received 17 September 2010
Received in revised form 18 October 2010
Accepted 9 November 2010
Available online 16 November 2010

Keywords:
Fluoroalkylated 1,4-disubstituted triazole
Aldol condensation
Fluorous solid-phase extraction

ABSTRACT

A new fluoroalkylated 1,4-disubstituted [1,2,3]-triazole was prepared and acted as an organocatalyst for aldol condensation of different ketones with various aldehydes. Aldol condensation proceeded efficiently in the presence of catalytic amount of fluoroalkylated [1,2,3]-triazole. The catalyst could be easily recovered by fluorous solid-phase extraction with excellent purity and reused for three runs with slightly decrease in its activity.

1. Introduction

Currently, due to low toxicity, operational simplicity and efficiency, compared to traditional metal-based catalysts, there is much interest in organocatalysts [1]. However, their drawbacks also have been realized. The major limitations using organocatalyst catalyzed reactions are high catalyst loadings (up to 20 mol%) and the difficulty of recovering the catalyst [2]. An alternative strategy is to design recyclable and subsequently reusable versions of organocatalysts [3].

In 1997, Curran's group reported the first example of application of solid–liquid separations based on fluorous silica gel [4]. They found that these separations were operationally convenient and were applicable to substances that contain only relatively few fluorine atoms such as light-fluorous reagent. This is a key finding since light-fluorous reagents and catalysts have chemical and physical properties that are similar to their non-fluorous counterparts. Recently, fluorous organocatalysts have emerged as attractive tools in Michael addition, Diels–Alder reaction as well as 1,3-dipolar cycloaddition with high recyclability [5]. Compared to recyclable heterogeneous organocatalysts, the fluorous organocatalysts are soluble in common reaction solvents, yet they can be easily separated and recovered from the reaction mixture by fluorous solid-phase extraction (F-SPE) [6–8].

In the course of our extensive synthetic and physical investigations involving substituted [1,2,3]-triazole **1** (Fig. 1), also, our group inspired by fluorous tag idea [9] and recent reports on the N-methylimidazole as a Lewis base catalyst for the aldol condensation of trimethylsilyl enolate with aldehyde [10,11]. As in the continuation of our work on the fluorous catalysts for C–C bond formation reaction, we tried to examine whether the substituted [1,2,3]-triazoles could catalyze this type reaction efficiently. So we have applied the fluoroalkylated [1,2,3]-triazole **2** (Fig. 2) organocatalyst to one of the most fundamental and important C–C bondforming reactions—the aldol condensation of ketones with aldehydes, which are usually catalyzed by strong acids or bases, and various Lewis acids [12]. To our delight, the catalyst exhibited excellent catalytic activity in aldol condensation.

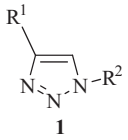
2. Results and discussion

The fluoroalkylated 1,4-disubstituted [1,2,3]-triazoles **2**, **3** and **4** (Fig. 2) were synthesized via the 1,3-dipolar cycloaddition of fluoroalkylated azides with terminal alkynes in the presence of Cu(I) salt as catalyst at room temperature (Scheme 1). Similar article was described by Yong-Ming Wu and co-workers, while we did not obtain what we want in this way [13,14]. The fluorous catalyst is easily separated by fluorous solid-phase extraction (F-SPE) and can be reused for several times without a significant loss of catalytic activity.

We first carried out a model reaction involving benzaldehyde, acetophenone, and fluorous catalysts to optimize the reaction conditions. As could be seen from Table 1, both the structure of

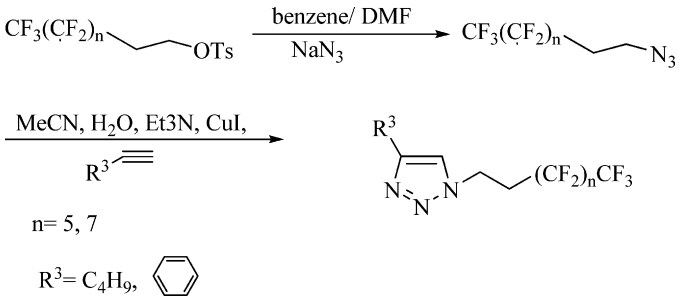
* Corresponding author. Tel.: +86 25 84315514; fax: +86 25 84315030.
E-mail address: yiwenbin@mail.njust.edu.cn (W.-B. Yi).

0022-1139/$ – see front matter. Crown Copyright © 2010 Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2010.11.004



1

Fig. 1. Fluoroalkylated 1,4-disubstituted [1,2,3]-triazole.

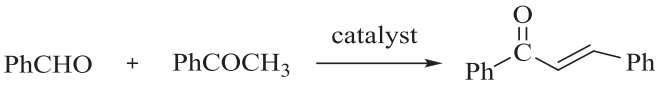


Scheme 1. Preparation of fluoroalkylated 1,4-disubstituted [1,2,3]-triazole organocatalysts 2, 3, 4.

catalyst and the temperature had a pronounced effect on the yield. The catalysts **2**, **3** and **4** were investigated (Table 1, entries 1–3). As a result, **2** was found to be the most effective structure. The effect of catalyst loading was also evaluated (Table 1, entries 4 and 5), When 5 mol% of catalyst **2** was used, the reaction was accelerated and afforded the product in 85% yield, while 10 mol% of catalyst was found to be most efficient. Next, different reaction temperature was studied (Table 1, entries 4–6), the best temperature was found at 100 °C. Thus we selected **2** as the catalyst, 100 °C as the reaction temperature and 10 mol% of catalyst which are the best condition for the aldol condensation.

To demonstrate the scope of the reaction, a series of aldehydes and ketones were used for aldol condensation. As revealed in Table 2, all the reactions proceeded efficiently to furnish the products in good to excellent yields (66–96%). The condensation products were isolated and identified as α,β-unsaturated ketones, and no side-reactions were observed. Based on ^{1}H NMR and GC–MS data, the reaction was found to give the E-stereoisomer as the sole product. Significant structural variation of aldehydes, which possess both electron withdrawing and donating groups could efficiently participate in the process. The condensations of *p*-substituted benzaldehyde with *p*-substituted acetophenones yielded the corresponding chalcones and the product yields were remarkably affected by the substituent groups of either aldehydes or ketones: reactants having electron-withdrawing substituents gave high yields and those having electron-donating ones gave low yields. The cross-condensations of cyclopentanone and cyclohexanone with different aromatic aldehydes were finished within 10–20 h and could give good yields (84–96%). Reactions of acetone with different aromatic aldehydes were also been studied, good yields could be obtained of 74–79%.

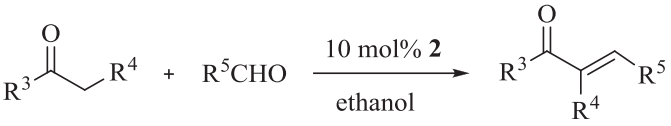
Table 1
Exploration of fluoroalkylated 1,4-disubstituted [1,2,3]-triazole organocatalyst promoted aldol reaction of benzaldehyde with acetophenone[a].



Entry	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield (%)[b]
1	**2**(10)	100	16	91
2	**3**(10)	100	16	87
3	**4**(10)	100	16	82
4	**2**(5)	100	16	85
5	**2**(10)	120	16	90
6	**2**(10)	80	16	84

[a] The reaction condition: benzaldehyde, 4 mmol; acetophenone, 5 mmol; ethanol, 6 mL.
[b] Isolated yield based on benzaldehyde.

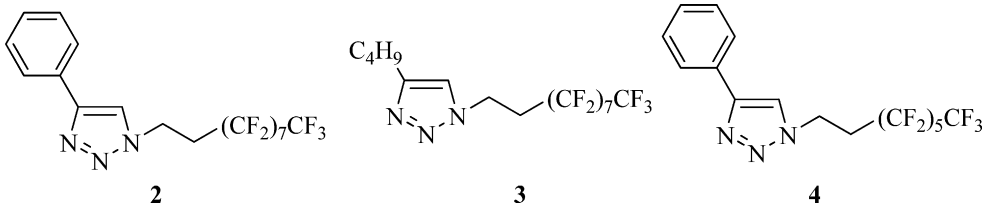
Table 2
Fluoroalkylated 1,4-disubstituted [1,2,3]-triazole **2** catalyzed aldol condensation[a].



Entry	R^3	R^4	R^5	Time (h)	Yield (%)[b]
1	Ph	H	4-Cl-Ph	16	91
2	Ph	H	4-CH_3O-Ph	16	66
3	Ph	H	4-CH_3-Ph	16	74
4	Ph	H	4-NO_2-Ph	16	94
5	$(CH_2)_6$		Ph	20	91
6	$(CH_2)_6$		4-CH_3O-Ph	20	84
7	$(CH_2)_6$		4-NO_2-Ph	20	95
8	$(CH_2)_5$		4-NO_2-Ph	10	96
9	$(CH_2)_5$		4-CH_3O-Ph	10	90
10	4-NO_2-Ph	H	Ph	20	70
11	4-CH_3O-Ph	H	Ph	20	92
12	CH_3	H	Ph	16	79
13	CH_3	H	4-CH_3O-Ph	16	74

[a] The reaction condition: aldehyde, 4 mmol; ketone, 5 mmol; ethanol, 6 mL; 100 °C.
[b] Isolated yield based on the aldehyde.

After 16 h, condensation product was obtained in 91% isolated yield by the reaction of benzaldehyde and acetophenone. As summarized in Fig. 3, good yields could maintaine for 3 cycles. Benzaldehyde and acetophenone were combined in ethanol at room temperature. The sample was then heated to 100 °C and became homogeneous. After stirring for 16 h, the mixture was concentrated and then loaded onto a FluoroFlash® silica gel cartridge (2 g) for F-SPE, eluted by 75% methanol at first for non-fluorous component, methanol was then added onto the fluorous silica gel column continuously for obtaining the elutant of fluoroalkylated triazole organocatalyst **2**. When the bulk of solvent was removed and product was dried in vacuo at 50 °C for 8 h, the



2 **3** **4**

Fig. 2. Fluoroalkylated triazole organocatalysts.

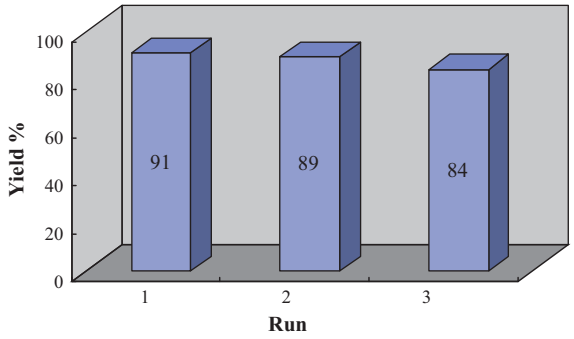


Fig. 3. Recycling and reuse of organocatalyst 2 in promoting the reaction of benzaldehyde and acetophenone.

solid could be reused for the next reaction. As would be expected, the fluorous catalyst can be reused for three times without a significant loss of yield.

3. Conclusions

In summary, a new fluoroalkylated 1,4-disubstituted [1,2,3]-triazole organocatalyst has been developed. The catalyst shows high activity in aldol condensation. Also, the catalyst can be easily recovered by fluorous solid-phase extraction with excellent purity. Application of this catalyst for other reactions is under investigation and will be reported in due course.

4. Experimental

4.1. General remarks

Melting points were obtained with Shimadzu DSC-50 thermal analyzer. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were characterized with a Bruker Advance RX500 spectrometer. IR spectra were recorded in KBr disks with a SHIMADZU IRPrestige-21 FT-IR spectrometer. Mass spectra were recorded on a Saturn 2000GC/MS instrument. All chemicals were reagent grade and used as purchased without further purifications.

4.2. General procedure for the fluoroalkylated 1,4-disubstituted [1,2,3]-triazole organocatalyst

Fluoroalkyl tosylate (**I**, 3.098 g, 5 mmol) was added to a solution of NaN_3 (0.650 g, 10 mmol) in a mixed solvent of DMF (15 mL) and benzene (15 mL) at 70 °C. The mixture was stirred for 20 h, then cooled down to 50 °C, poured into 100 mL ice water, extracted with ether (3× 40 mL). The combined organic layer was washed with saturated brine (2× 50 mL) and dried by magnesium sulfate, after removal of the solvent, the crude product was purified by distillation under atmospheric or reduced pressure. So the fluoroalkylazide (**II**, 2.125 g, 71.3%) was in hand.

To a 25 mL 3-necked round flask, fluoroalkylazide (3 mmol), phenylacetylene (3.3 mmol), triethylamine (3.3 mmol), acetonitrile (4 mL), water (8 mL) and CuI (6 mg, 0.03 mmol) were added successively. The mixture was stirred at room temperature for 20 h. Then 10 mL water was added, the mixture was extracted with ether (3× 10 mL). The combined organic layer was washed with saturated brine and dried with sodium sulfate. After removal of solvent under reduced pressure, the crude product was purified by flash chromatography on a silicon gel column with hexane/ethyl acetate (v/v: 5:1) as eluent to give fluoroalkylated 1,4-disubstituted [1,2,3]-triazole **2** as a white solid (1.099 g, 1.86 mmol, 62%).

4.2.1. 1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)-4-phenyl-1H-1,2,3-triazole

White solid m.p. 147–150 °C; ^{1}H NMR (500 MHz, DMSO) δ 7.84 (d, J = 8 Hz, 2H, Ar-H), 7.82 (s, 1H, Tr-H), 7.42 (t, J = 8 Hz, 2H, Ar-H), 7.35 (t, J = 8 Hz, 1H, Ar-H), 4.71 (t, J = 7 Hz, 2H, Tr.CH_2), 2.88 (m, 2H, CH_2CF_2); ^{13}C NMR (125 MHz, DMSO) 148.2 (C), 130.2 (C), 129.2 (CH), 128.4 (CH), 126.1 (CH), 120.2 (CH), 42.6 (CH_2), 32.2 (CH_2) (t, ^{2}JFC = 21 Hz); IR (KBr) 3123, 3094, 1339, 1206, 1146, 1115, 1098, 986, 970, 768, 706, 693, 678, 663 cm^{-1}; MS (EI, 70 eV) m/z (rel intensity) 591 (M^+, 20), 572 ([M-F]$^+$, 15) 563 ([M-N_2]$^+$, 62), 144 ([M-C_8F_{17} $CH_2.CH_2$]$^+$, 30), 116 ([M-$C_8F_{17}.CH_2.CH_2$-N_2]$^+$, 100).

4.3. Typical procedure for organocatalyst 2 catalyzed the aldol reaction

Acetophenone (5 mmol) and fluoroalkylated 1,4-disubstituted [1,2,3]-triazole organocatalyst **2** (0.236 g, 0.4 mmol) in 6 mL of ethanol was stirred at room temperature for 20 min. Then benzaldehyde (4 mmol) was added and the resulting mixture was stirred at 100 °C for 16 h. The crude product was purified by column chromatography on silica gel, eluted by 75% methanol then methanol to give 0.757 g (91%) of the desired product as a yellowish solid.

4.3.1. Chalcone

A yellowish solid; m.p. 56–58 °C (lit. [15] 57–58 °C). IR (KBr) 3231, 2932, 1830, 1731, 1654, 1286, 752, 681 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.12 (d, J = 16.0 Hz, 1H), 7.24 (d, J = 16.0 Hz, 1H), 7.09–7.31 (m, 5H), 7.39–7.92 (m, 5H). MS (EI) m/z 207 (M^+).

4.3.2. 4-Chlorochalcone

A yellow solid; m.p. 114–115 °C (lit. [15] 114–117 °C). IR (KBr) 3080, 2908, 1780, 1713, 1651, 1205, 913, 748 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (d, J = 16.0 Hz, 1H), 7.12 (d, J = 16.0 Hz, 1H), 6.23 (d, 2H), 7.10–7.34 (m, 4H), 7.36–8.01 (m, 5H). MS (EI) m/z 244 (M^{++2}), 242 (M^+).

4.3.3. 4-Methoxychalcone

A russety solid; m.p. 75–76 °C (lit. [15] 75–77 °C). IR (KBr) 3302, 2979, 1830, 1722, 1661, 1185, 929, 815 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (s, 3H), 5.96 (d, J = 16.0 Hz, 1H), 6.85 (d, J = 16.0 Hz, 1H), 6.92–7.21 (m, 4H), 7.32–7.99 (m, 5H). MS (EI) m/z 238 (M^+).

4.3.4. 4-Methylchalcone

A yellowish solid; m.p. 98 °C (lit. [15] 97–98 °C). IR (KBr) 3210, 2915, 1760, 1696, 1651, 1086, 942, 842, 722 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 3H), 6.01 (d, J = 16.4 Hz, 1H), 7.04 (d, J = 16.4 Hz, 1H), 7.05–7.36 (m, 4H), 7.38–7.82 (m, 5H). MS (EI) m/z 221 (M^+).

4.3.5. 4-Nitrochalcone

A brown solid; m.p. 158–159 °C (lit. [15] 158–160 °C). IR (KBr) 3235, 2908, 1871, 1673, 1660, 1476, 922, 834 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (d, J = 16.1 Hz, 1H), 7.41 (d, J = 16.1 Hz, 1H), 7.36–7.69 (m, 3H), 7.70–8.31 (m, 4H). MS (EI) m/z 252 (M^+).

4.3.6. 2,6-Dibenzylidenecyclohexanone

A yellow solid; m.p. 116 °C (lit. [15] 116–117 °C). IR (KBr) 3020, 2921, 1663, 1612, 1570, 1269, 1139, 768, 689 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74–1.86 (m, 2H), 2.94 (t, J = 6.4 Hz, 4H), 7.26–7.46 (m, 10H), 7.80 (s, 2H). MS (EI) m/z 273 (M^+).

4.3.7. 2,6-Di(p-methoxybenzylidene)cyclohexanone

A yellow solid; m.p. 202–203 °C (lit. [15] 203–204 °C). IR (KBr) 3022, 2920, 1658, 1605, 1568, 1265, 1140, 781, 687 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.80–1.84 (m, 2H), 2.96 (t, J = 6.0 Hz, 4H), 3.84 (s, 6H), 6.92–7.38 (m, 8H), 7.79 (s, 2H). MS (EI) m/z 333 (M^+).

4.3.8. 2,6-Di(p-nitrobenzylidene)cyclohexanone

A russety solid; m.p. 158 °C (lit. [15] 159 °C). IR (KBr) 3086, 2932, 1670, 1612, 1581, 1524, 1340, 805 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.86–1.93 (m, 2H), 2.99 (t, J = 5.6 Hz, 4H), 7.60–8.24 (m, 8H), 8.32 (s, 2H). MS (EI) m/z 363 (M^+).

4.3.9. 2,6-Di(p-nitrobenzylidene)cyclopentanone

A russety solid; m.p. 230–233 °C (lit. [15] 230–231 °C). IR (KBr) 3108, 2850, 1708, 1602, 1525, 1344, 821 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 3.05 (t, 4H), 7.61–8.13 (m, 8H), 8.27 (s, 2H). MS (EI) m/z 349 (M^+).

4.3.10. 2,6-Di(p-methoxybenzylidene)cyclopentanone

A green solid; m.p. 211–212 °C (lit. [15] 210–211 °C). IR (KBr) 2965, 2841, 1649, 1592, 1506, 1247, 1025, 830 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 3.11 (t, 4H), 3.86 (s, 6H), 6.96–7.59 (m, 8H), 7.60 (s, 2H). MS (EI) m/z 319 (M^+).

4.3.11. 4′-Nitrochalcone

A yellow solid; m.p. 150–153 °C (lit. [15] 151–152 °C). IR (KBr) 3010, 2895, 1708, 1681, 1642, 1468, 920, 837 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.33 (d, J = 16.1 Hz, 1H), 7.35 (d, J = 16.1 Hz, 1H), 7.14–7.38 (m, 5H), 7.48–8.24 (m, 4H). MS (EI) m/z 253 (M^+).

4.3.12. 4′-Methoxychalcone

A russety solid; m.p. 109–111 °C (lit. [15] 109–110 °C). IR (KBr) 3210, 2880, 1832, 1725, 1670, 1210, 854, 730 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 3.78 (s, 3H), 6.10 (d, J = 16.0 Hz, 1H), 7.24 (d, J = 16.0 Hz, 1H), 7.08–7.61 (m, 9H). MS (EI) m/z 238 (M^+).

4.3.13. Benzylideneacetone

A yellowish solid; m.p. 40–42 °C (lit. [15] 41–42 °C). IR (KBr) 3108, 2960, 1835, 1720, 1663, 1180, 943, 817 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.38 (s, 3H), 6.65 (d, J = 16.5 Hz, 1H), 7.45 (d, J = 16.5 Hz, 1H), 7.35–7.72 (m, 5H). MS (EI) m/z 147 (M^+).

4.3.14. 4-Methoxybenzylideneacetone

A yellowish solid; m.p. 44–45 °C (lit. [15] 44–46 °C). IR (KBr) 3202, 2946, 1780, 1723, 1588, 1182, 920, 826, 764 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.26 (s, 3H), 3.81 (s, 3H), 6.50 (d, J = 16.0 Hz, 1H), 7.45 (d, J = 16.0 Hz, 1H), 7.09–7.32 (m, 4H). MS (EI) m/z 178 (M^+).

4.4. Procedure for recycling and reusing organocatalyst 2 in the aldol reaction

Acetophenone (5 mmol) and fluoroalkylated 1,4-disubstituted [1,2,3]-triazole organocatalyst **2** (0.236 g, 0.4 mmol) in 6 mL of ethanol was stirred at room temperature for 20 min. Then benzaldehyde (4 mmol) was added and the resulting mixture was stirred at 100 °C for a specified reaction time period. The mixture was concentrated and then loaded onto a FluoroFlash® silica gel cartridge (2 g), eluted by 75% methanol at first for non-fluorous component, methanol was then added onto the fluorous gel column continuously for obtaining the elutant of fluoroalkylated triazole organocatalyst **2**. When the bulk of solvent was removed and product was dried in vacuo at 50 °C for 8 h, the fluoroalkylated triazole organocatalyst **2** could be recycled effectively. Furthermore, the recoverable organocatalyst could be used directly for the next run.

Acknowledgments

The authors gratefully acknowledge the financial support of the project of "NUST Excellence Initiative", NUST Research Funding (2010ZYTS022), the Doctoral Fund of Ministry of Education of China (200802881024), Jiangsu Provincial Natural Science Foundation of China (sbk201040048) and National Natural Science Foundation of China (20902047).

References

[1] (a) P.I. Dalko, L. Moisan, Angew. Chem. Int. Ed. 43 (2004) 5138–5175;
(b) K.N. Houk, B. List, Acc. Chem. Res. 37 (2004) 487–631;
(c) B. List, Chem. Commun. (2006) 819–824;
(d) G. Guillena, D.J. Ramón, Tetrahedron: Asymmetry 17 (2006) 1465–1492.
[2] S.H. Youk, S.H. Oh, H.S. Rho, J.E. Lee, J.W. Lee, C.E. Song, Chem. Commun. (2009) 2220–2222.
[3] (a) L. Zu, H. Li, J. Wang, X. Yu, W. Wang, Tetrahedron Lett. 47 (2006) 5131–5134;
(b) L. Zu, J. Wang, H. Li, W. Wang, Org. Lett. 8 (2006) 3077–3079;
(c) W. Wang, Y. Mei, H. Li, J. Wang, Org. Lett. (2005) 601–604;
(d) T. Miura, K. Imai, M. Ina, N. Tada, N. Imai, A. Itoh, Org. Lett. (2010) 1620–1623.
[4] D.P. Curran, S. Hadida, M. He, J. Org. Chem. 62 (1997) 6714–6715.
[5] W. Zhang, C. Cai, Chem. Commun. (2008) 5686–5694.
[6] W.B. Yi, C. Cai, X. Wang, Eur. J. Org. Chem. (2007) 3445–3448.
[7] W.B. Yi, C. Cai, X. Wang, J. Fluorine Chem. 128 (2007) 919–924.
[8] W. Zhang, D.P. Curran, Tetrahedron 62 (2006) 11837–11865.
[9] H. Nakamura, B. Linclau, D.P. Curran, J. Am. Chem. Soc. 123 (2001) 10119–10120.
[10] R. Srivastava, J. Mol. Catal. A: Chem. 264 (2007) 146–152.
[11] H. Hagiwara, H. Inoguchi, M. Fukushima, T. Hoshi, T. Suzuki, Tetrahedron Lett. 47 (2006) 5371–5373.
[12] R.L. Reeves, in: S. Patai (Ed.), Chemistry of Carbonyl Group, Wiley, New York, 1966, pp. 580–593.
[13] A.W. Mcculloch, A.G. Mclnnes, Can. J. Chem. 52 (1974) 3569–3576.
[14] Y.M. Wu, J. Deng, X. Fang, Q.Y. Chen, J. Fluorine Chem. 125 (2004) 1415–1423.
[15] K. Watanabe, A. Imazawa, Bull. Chem. Soc. Jpn. 55 (1982) 3208–3211.