Tetrahedron 68 (2012) 5806–5809

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

NHC–Pd(II)–Im (NHC=*N*-heterocyclic carbene, Im=1-methylimidazole) complex catalyzed coupling reaction of arylboronic acids with carboxylic acid anhydrides in water

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ARTICLE INFO

Article history:
Received 22 February 2012
Received in revised form 13 April 2012
Accepted 4 May 2012
Available online 14 May 2012

Keywords:
N-Heterocyclic carbene
Palladium complex
Coupling reaction
Water
Synthetic method

ABSTRACT

A well-defined *N*-heterocyclic carbene (NHC)–palladium chloride–imidazole complex exhibited high catalytic activity in the coupling reaction of arylboronic acids with carboxylic acid anhydrides in pure water under mild conditions. Under the optimal conditions, all reactions gave the desired coupling products in moderate to high yields.

1. Introduction

Diaryl ketones are fundamental intermediates in the synthesis of natural products and biologically active small molecules.[1] Classical route to synthesize diaryl ketones is the Friedel–Crafts acylation of aromatic compounds in the presence of excess amounts of Lewis acid.[2] During the past years, transition metal-catalyzed reactions had provided many opportunities for the synthesis of these compounds.[3] For instance, the palladium-catalyzed acylation of carbon nucleophiles, such as arylboronic acids with carboxylic acid derivatives is one of the most efficient reactions.[4] However, the above mentioned methods are usually carried out in organic solvents in the presence of phosphine-based ligands. Comparing to toxic, volatile and flammable organic solvents, water, is nontoxic, nonflammable, and environmentally benign and had attracted much attention in synthetic organic chemistry.[5] In addition, comparing to air- and thermal-sensitive phosphine ligands, *N*-heterocyclic carbenes (NHCs), usually with higher air- and thermal-stability, have become a big challenger to phosphine ligands in the metal-catalyzed carbon–carbon and carbon–heteroatom bond formation reactions.[6] However, to the best of our knowledge, applications of NHC–metal complexes in pure water were rarely reported to date.[7] Recently, we have synthesized a well-defined NHC–palladium chloride-1-methylimidazole [NHC–Pd(II)–Im] complex **1** derived from IPr·HCl [1,3-bis(2,6-diisopropylphenyl)–imidazolium chloride], $PdCl_2$ and 1-methylimidazole (Fig. 1), and found it to be an efficient catalyst in the formation of carbon–carbon and carbon–nitrogen bonds.[8] For example, it was reported that complex **1** exhibited high catalytic activity in the Suzuki–Miyaura coupling of aryl chlorides performed in pure water under mild conditions.[8c] These results prompted us to find out more applications of this complex in organic synthesis performed in water. In continuing research, we found that complex **1** was also an efficient catalyst for the coupling reaction of arylboronic acids with carboxylic acid anhydrides in pure water. Herein, we report these results in detail.

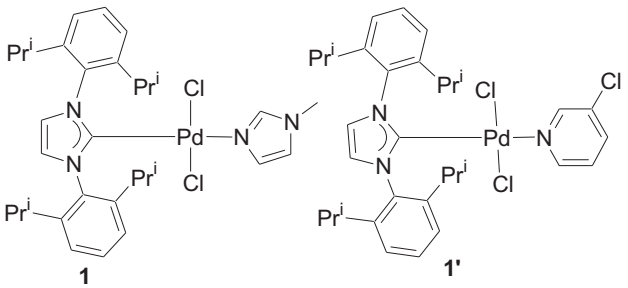

Fig. 1. NHC–Pd(II)–Im complex **1** and PEPPSI **1′**.

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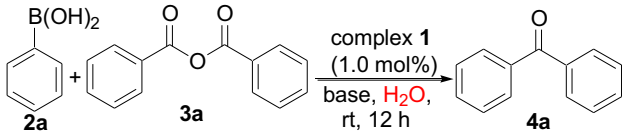
doi:10.1016/j.tet.2012.05.016

2. Results and discussion

Initial studies were carried out using phenylboronic acid **2a** (0.75 mmol) and benzoic anhydride **3a** (1.5 mmol) as the substrates, NHC–Pd(II)–Im complex **1** (1.0 mol %) as the catalyst, H_2O (2.0 mL) as the solvent at room temperature to find out the best base. As can be seen from Table 1, the best similar results can be achieved when K_2CO_3, Na_2CO_3, Cs_2CO_3, and $NaHCO_3$ were used as the base, respectively, (Table 1, entries 1, 2, 4, and 7). For other bases, such as Li_2CO_3, NaOH, and $KHCO_3$, all reactions proceeded smoothly to give product **4a** in lower yields within 12 h (Table 1, entries 3, 5, and 6). A similar complex, such as PEPPSI **1′**[9] (Fig. 1) was also tested in this reaction, and inferior result was obtained (Table 1, entry 8). Owing to the lower molecular mass and lower cost, $NaHCO_3$ was chosen as the best base. So the optimal reaction conditions were established as using NHC–Pd(II)–Im complex **1** (1.0 mol %) as the catalyst, $NaHCO_3$ as the base in water at room temperature.

Table 1
Optimization for the NHC–Pd(II)–Im complex **1**-catalyzed reaction of phenylboronic acid **2a** and benzoic anhydride **3a** in H_2O



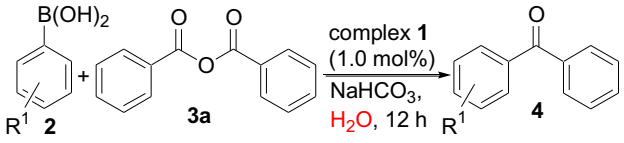
Entry[a]	Base	Yield (%)[b]
1	K_2CO_3	97
2	Na_2CO_3	92
3	Li_2CO_3	53
4	Cs_2CO_3	97
5	NaOH	44
6	$KHCO_3$	62
7	$NaHCO_3$	99
8[c]	$NaHCO_3$	60

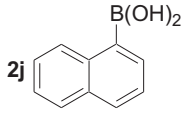
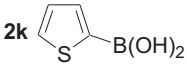
[a] All reactions were carried out using **2a** (0.75 mmol), **3a** (2.0 equiv), **1** (1.0 mol %), base (2.4 mmol) in H_2O (2.0 mL) at rt for 12 h.
[b] Isolated yields.
[c] PEPPSI **1′** as the catalyst.

With the optimal reaction conditions in hand, we then first investigated the reactions of various arylboronic acids **2** with benzoic anhydride **3a** to test the generality. As can be seen from Table 2, all reactions took place smoothly to give the corresponding coupling products **4** in moderate to high yields under suitable temperature. Substituents on the arylboronic acids **2** have some effect on these reactions. For instance, for 4-fluorophenylboronic acid **2b**, 3,5-dimethylphenylboronic acid **2c** and 3-methylphenylboronic acid **2i**, the corresponding ketones **4b**, **4c**, and **4i** were formed in high yields at room temperature (Table 2, entries 1, 2, and 8). For 4-methoxyphenylboronic acid **2d**, 2-methylphenylboronic acid **2f**, 4-methylphenylboronic acid **2h** and 1-naphthylboronic acid **2j**, the ketone products **4d**, **4f**, **4h**, and **4j** were obtained in good yields at 50 °C (Table 2, entries 3, 5, 7, and 9). Only moderate yields of products **4e** and **4g** were obtained when moderately electron-poor 4-chlorophenylboronic acid **2e** and strongly electron-poor 3-nitrophenylboronic acid **2g** were used as the substrates (Table 2, entries 4 and 6).

The reactions between various arylboronic acids **2** and carboxylic acid anhydrides **3** were also investigated under the similar reaction conditions. It is worthy of note here that Na_2CO_3 was found to be the most suitable base in these cases. Most reactions took place smoothly to give the corresponding diaryl ketones **4** in good to high yields at 50 °C within 12 h (Table 3). Substituents on the arylboronic acids **2** almost have no obvious effect on the reactions. On the contrary, substituents on the carboxylic acid anhydrides **3** affected the reactions in some extent. For example, although the reaction was retarded when substrate **3c** having electron-rich *para*-MeO on the phenyl ring was used, good yield can also be obtained when the reaction time was prolonged to 24 h (Table 3, entry 5). Substrate **3f** having electron-poor *para*-Cl group on the phenyl ring was not suitable and no desired product was observed (Table 3, entry 12). Substrate **3d** having an *ortho*-EtO group on the phenyl ring only gave product **4n** in 58% yield presumably due to its steric hindrance (Table 3, entry 6). Heteroarylboronic acid, such as 2-thienylboronic acid **2k** was also tested and only 43% yield of product **4k** was obtained (Table 1, entry 10).

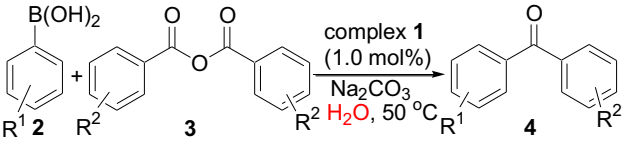
Table 2
NHC–Pd(II)–Im complex **1**-catalyzed reactions of arylboronic acids **2** and benzoic anhydride **3a** in H_2O



Entry[a]	**2** (R^1)	Temp (°C)	Yield (%)[b]
1	**2b** (4-F)	rt	**4b**, 98
2	**2c** (3,5-Me_2)	rt	**4c**, 99
3	**2d** (4-MeO)	50	**4d**, 88
4	**2e** (4-Cl)	rt	**4e**, 52
5	**2f** (2-Me)	50	**4f**, 80
6	**2g** (3-NO_2)	70	**4g**, 70
7	**2h** (4-Me)	50	**4h**, 85
8	**2i** (3-Me)	rt	**4i**, 92
9		50	**4j**, 94
10		50	**4k**, 43

[a] All reactions were carried out using **2** (0.75 mmol), **3a** (2.0 equiv), **1** (1.0 mol %), $NaHCO_3$ (2.4 mmol) in H_2O (2.0 mL) at the listed temperature for 12 h.
[b] Isolated yields.

Table 3
NHC–Pd(II)–Im complex **1**-catalyzed reactions of arylboronic acids **2** and carboxylic acid anhydrides **3** in H_2O



Entry[a]	**2** (R^1)	**3** (R^2)	Yield (%)[b]
1	**2a** (H)	**3b** (4-Me)	**4h**, 91
2	**2b** (4-F)	**3b**	**4l**, 80
3	**2d** (4-MeO)	**3b**	**4m**, 91
4	**2h** (4-Me)	**3b**	**4n**, 82
5[c]	**2h**	**3c** (4-MeO)	**4m**, 86
6	**2h**	**3d** (2-EtO)	**4o**, 58
7	**2a**	**3e** (3-Me)	**4i**, 89
8	**2h**	**3e**	**4p**, 83
9	**2d**	**3e**	**4q**, 89
10	**2i** (3-Me)	**3e**	**4r**, 93
11	**2j** (2-Me)	**3e**	**4s**, 86
12	**2d**	**3f** (4-Cl)	—

[a] Otherwize specified, all reactions were carried out using **2** (0.75 mmol), **3** (2.0 equiv), **1** (1.0 mol %), Na_2CO_3 (2.4 mmol) in H_2O (2.0 mL) at 50 °C for 12 h.
[b] Isolated yields.
[c] The reaction time was 24 h.

3. Conclusion

In conclusion, the well-defined NHC–Pd(II)–Im complex **1** derived from commercially available IPr·HCl, $PdCl_2$, and 1-methylimidazole showed efficient catalytic activity in the coupling reactions of arylboronic acids with carboxylic acid anhydrides in pure water under mild conditions. Under the optimal reaction conditions, all reactions took place smoothly to give the desired diaryl ketones in moderate to high yields. It is worth noting here that the results reported in this paper is the application of NHC–metal complexes in pure water, which are not developed very popularly to date and will open new opportunities for NHC–metal complexes in organic synthesis.

4. Experimental section

4.1. General remarks

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-300 or 500 MHz spectrometer for solution in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard; *J*-values are in Hertz. Commercially obtained reagents were used without further purification. Flash column chromatography was carried out using Huanghai 300–400 mesh silica gel at increased pressure.

4.2. Experimental procedures

Under N_2 atmosphere, $NaHCO_3$ (2.4 mmol), benzoic anhydride **3a** (1.5 mmol), phenylboronic acid **2a** (0.75 mmol), and H_2O were successively added into a Schlenk reaction tube. The mixture was stirred at room temperature for about 10 min. Then NHC–Pd(II)–Im complex **1** (1.0 mol %) was added. The mixture was stirred at room temperature for 12 h and then was diluted with CH_2Cl_2, washed with saturated brine, dried over anhydrous Na_2SO_4. The dried organic phase was then filtered, concentrated under reduced pressure and purified by flash column chromatography on silica gel to give the pure product **4a**.

4.2.1. Compound ***4a***.[10] A white solid. ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 7.47–7.57 (m, 4H, Ar), 7.58–7.61 (m, 2H, Ar), 7.80–7.82 (m, 4H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.2, 130.0, 132.4, 137.6, 196.7.

4.2.2. Compound ***4b***.[10] A white solid. ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 7.03 (t, *J*=8.5 Hz, 2H, Ar), 7.36 (t, *J*=7.5 Hz, 2H, Ar), 7.46 (t, *J*=7.5 Hz, 1H, Ar), 7.65 (d, *J*=7.5 Hz, 2H, Ar), 7.72 (dd, *J*=8.5, 5.5 Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 116.7 (d, J_{C-F}=22.3 Hz), 119.4 (d, J_{C-F}=21.2 Hz), 125.8 (d, J_{C-F}=2.9 Hz), 128.4, 129.9 (d, J_{C-F}=9.0 Hz), 132.7, 137.0, 139.7 (d, J_{C-F}=6.3 Hz), 162.5 (d, J_{C-F}=246.6 Hz), 195.3.

4.2.3. Compound ***4c***.[11] A white solid. ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 2.23 (s, 6H, Me), 7.08 (s, 1H, Ar), 7.25–7.49 (m, 5H, Ar), 7.67 (s, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 127.8, 128.2, 130.0, 132.2, 134.1, 137.7, 137.9, 197.2.

4.2.4. Compound ***4d***.[10] A white solid. ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 3.75 (s, 3H, OMe), 6.84 (d, *J*=9.0 Hz, 2H, Ar), 7.35 (t, *J*=7.5 Hz, 2H, Ar), 7.44 (t, *J*=7.5 Hz, 1H, Ar), 7.64 (d, *J*=7.5 Hz, 2H, Ar), 7.72 (d, *J*=9.0 Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.4, 113.5, 128.1, 129.6, 130.0, 131.8, 132.4, 138.2, 163.1, 195.4.

4.2.5. Compound ***4e***.[10] A white solid. ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 7.46–7.51 (m, 4H, Ar), 7.59–7.62 (m, 1H, Ar), 7.45–7.78 (m, 4H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.4, 128.6, 129.9, 131.5, 132.6, 135.9, 137.3, 138.9, 195.5.

4.2.6. Compound ***4f***.[10] A white solid. ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 2.24 (s, 3H, Me), 7.22–7.29 (m, 3H, Ar), 7.30–7.46 (m, 3H, Ar), 7.57 (t, *J*=7.0 Hz, 1H, Ar), 7.80 (d, 2H, *J*=7.0 Hz, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9, 125.1, 128.40, 128.45, 130.1, 130.2, 130.9, 133.1, 136.7, 137.7, 138.6, 198.6.

4.2.7. Compound ***4g***.[12] A light yellow solid. ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 7.54 (t, *J*=7.5 Hz, 2H, Ar), 7.67 (t, *J*=7.5 Hz, 1H, Ar), 7.71 (t, *J*=8.0 Hz, 1H, Ar), 7.81 (d, *J*=8.0 Hz, 2H, Ar), 8.15 (d, *J*=7.5 Hz, 2H, Ar), 8.45 (d, *J*=8.0 Hz, 1H, Ar), 8.63 (s, 1H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 124.7, 126.7, 128.7, 129.6, 130.0, 133.4, 135.4, 136.2, 139.1, 148.1, 194.2.

4.2.8. Compound ***4h***.[10] A white solid. ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 2.45 (s, 3H, Me), 7.29 (d, *J*=8.5 Hz, 2H, Ar), 7.48 (t, *J*=7.5 Hz, 2H, Ar), 7.58 (t, *J*=7.5 Hz, 1H, Ar), 7.73 (d, *J*=8.5 Hz, 2H, Ar), 7.79 (d, *J*=7.5 Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 128.2, 129.0, 129.9, 130.3, 130.6, 132.2, 134.9, 138.0, 143.2, 196.5.

4.2.9. Compound ***4i***.[10] A white solid. ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 7.23–7.30 (m, 2H, Ar), 7.37 (t, *J*=7.5 Hz, 2H, Ar), 7.46–7.53 (m, 3H, Ar), 7.70 (d, *J*=7.5 Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 127.3, 128.0, 128.2, 129.9, 130.4, 132.2, 133.1, 137.6, 137.7, 138.1, 196.8.

4.2.10. Compound ***4j***.[10] A white solid. ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 7.26–7.60 (m, 7H, Ar), 7.87–8.00 (m, 5H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 124.3, 125.7, 126.4, 127.2, 127.8, 128.36, 128.40, 130.4, 131.0, 131.2, 133.2, 133.7, 136.3, 138.3, 198.0.

4.2.11. Compound ***4k***.[3a] A white solid. ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 7.17 (dd, *J*=6.5, 8.0 Hz, 1H, Ar), 7.47–7.53 (m, 2H, Ar), 7.57–7.63 (m, 1H, Ar), 7.65 (dd, *J*=1.5, 6.5 Hz, 1H, Ar), 7.73 (dd, *J*=1.5, 8.0 Hz, 1H, Ar), 7.85–7.88 (m, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 127.9, 128.4, 129.1, 132.2, 134.2, 134.8, 138.2, 143.6, 188.2.

4.2.12. Compound ***4k***.[10] A white solid. ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 2.45 (s, 3H, Me), 7.16 (t, *J*=8.4 Hz, 2H, Ar), 7.26–7.31 (m, 2H, Ar), 7.69 (d, *J*=8.4 Hz, 2H, Ar), 7.83 (dd, *J*=9.0, 5.4 Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 115.3 (d, J_{C-F}=21.6 Hz), 129.0, 130.1, 132.5 (d, J_{C-F}=9.0 Hz), 134.1 (d, J_{C-F}=3.0 Hz), 134.7, 143.3, 165.2 (d, J_{C-F}=252.1 Hz), 195.0.

4.2.13. Compound ***4l***.[9] A white solid. ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 2.44 (s, 3H, Me), 3.89 (s, 3H, OMe), 6.94 (d, *J*=9.0 Hz, 2H, Ar), 7.28 (d, *J*=8.1 Hz, 2H, Ar), 7.68 (d, *J*=8.1 Hz, 2H, Ar), 7.82 (d, *J*=9.0 Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 55.5, 113.5, 128.9, 130.0, 132.4, 135.5, 142.6, 144.4, 163.0, 195.4.

4.2.14. Compound ***4m***.[10] A white solid. ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 2.44 (s, 6H, Me), 7.27 (d, *J*=8.1 Hz, 4H, Ar), 7.70 (d, *J*=8.1 Hz, 4H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 128.9, 130.2, 135.2, 142.9, 196.2.

4.2.15. Compound ***4n***. A colorless liquid. ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 1.11 (t, *J*=7.2 Hz, 3H, Me), 2.41 (s, 3H, Me), 3.97 (q, *J*=7.2 Hz, 2H), 6.94–7.04 (m, 2H, Ar), 7.22 (d, *J*=7.5 Hz, 2H, Ar), 7.35–7.46 (m, 2H, Ar), 7.70 (d, *J*=7.5 Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 21.7, 64.0, 112.5, 120.4, 128.8, 129.5, 129.8, 131.6, 135.6, 143.5, 156.6, 196.4. IR (neat) ν 1659, 1597, 1447, 1131, 1298, 1239, 1150, 1117, 1041, 931, 916, 835, 752, 731, 682 cm^{-1}. MS (ESI, *m*/*z*): 241 $[M+H]^+$; HRMS (ESI): Calcd for $C_{16}H_{17}O_2$ $[M+H]^+$: 241.1223; Found: 241.1237.

4.2.16. Compound ***4o***.[10] A white solid. ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 2.42 (s, 3H, Me), 2.44 (s, 3H, Me), 7.26–7.37 (m, 4H, Ar),

7.55–7.61 (m, 2H, Ar), 7.72 (d, J=8.1 Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.5, 127.1, 127.9, 128.8, 130.17, 130.24, 132.8, 135.0, 137.91, 137.95, 143.0, 196.6.

4.2.17. Compound ***4p***.[10] A white solid. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 2.42 (s, 3H, Me), 3.89 (s, 3H, OMe), 6.97 (d, J=9.0 Hz, 2H, Ar), 7.32–7.37 (m, 2H, Ar), 7.52–7.58 (m, 2H, Ar), 7.83 (d, J=9.0 Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 55.5, 113.5, 127.0, 128.0, 130.2, 130.3, 132.5, 132.6, 138.0, 138.3, 163.2, 195.8.

4.2.18. Compound ***4q***.[3e] A white solid. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 2.42 (s, 6H, Me), 7.33–7.41 (m, 4H, Ar), 7.55–7.62 (m, 4H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 127.3, 128.0, 130.4, 133.1, 137.7, 138.1, 197.2.

4.2.19. Compound ***4r***.[13] A white solid. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 2.33 (s, 3H, Me), 2.40 (s, 3H, Me), 7.22–7.41 (m, 6H, Ar), 7.56 (d, J=7.5 Hz, 1H, Ar), 7.65 (s, 1H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9, 21.3, 125.1, 127.5, 128.3, 128.4, 130.1, 130.4, 130.9, 133.9, 136.7, 137.7, 138.3, 138.8, 198.8.

Acknowledgements

Financial support from the National Natural Science Foundation of China (No. 21002072) and the Opening Foundation of Zhejiang Provincial Top Key Discipline (No. 1000612001) is greatly acknowledged. Y.L. and S.-Y.L. thank Science and Technology Department of Zhejiang Province (Xinmiao Programme) for financial support (Nos. 2011R424016 and 2010R424016).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.05.016. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

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