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Efficient Synthesis of Biaryls through the Kumada Reaction Catalyzed by Carbene Adducts of Cyclopalladated Ferrocenylimine

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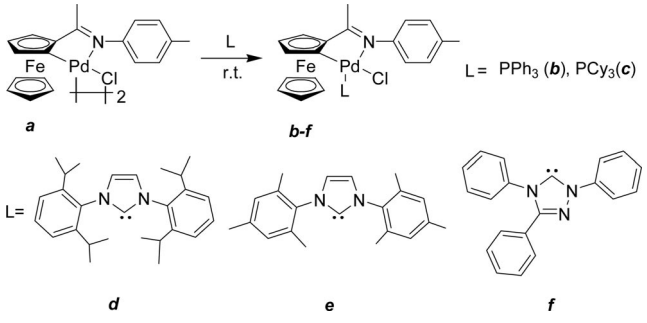
Keywords: Biaryls / Carbene ligands / Palladium / Ferrocene / Cross-coupling

A series of carbene adducts of cyclopalladated ferrocenylimine were prepared and evaluated in the cross-coupling reaction of aryl halides with Grignard reagents (the Kumada reaction). Complex **d** exhibited high catalytic activity for the coupling of aryl chlorides with sterically hindered Grignard reagents and the reaction tolerated various functional groups. A wide range of biaryls were efficiently obtained in good to excellent yields in the presence of 0.5 mol-% catalyst under mild reaction conditions.

Introduction

Unsymmetrical biaryls are important building blocks for the synthesis of functional materials,[1] natural products,[2] and pharmaceuticals.[3] The Kumada reaction[4] is one of the most powerful and versatile methods with which to assemble such fragments. However, only modest progress in the development of this reaction has been made in recent years[5] compared to other cross-coupling reactions, such as the Suzuki,[6] Still,[7] and Negishi reactions,[8] due to the inherently inferior functional group tolerance. On the other hand, the Kumada reaction could offer a more direct approach to the synthesis of biaryls because aryl boronic acids (Suzuki coupling), stannanes (Stille coupling), and zinc compounds (Negishi coupling) are usually prepared from either Grignard or organolithium precursors.[9] Direct use of Grignard reagents in coupling reactions could efficiently shorten the synthetic procedure and reduce the cost. However, there are some challenges that still exist for this reaction, such as limitations in the use of the less expensive and more available aryl chlorides as substrates, inferior tolerance of functional groups, less efficient synthesis of sterically hindered biaryls and requirement for high loading of catalyst (1–5 mol-%). Nolan's group[5b] reported the coupling of aryl chlorides with aryl Grignard reagents at elevated reaction temperature (80 °C) in the presence of 1 mol-% N-heterocyclic carbene-Pd complex. However, this protocol was less tolerant of functional groups. Organ et al.[5r] described a successful application of the Kumada reaction using PEPPSI as catalyst with a higher catalyst loading (2 mol-%). For these reasons, use of the Kumada coupling protocol remains an attractive and potentially highly efficient alternative route to unsymmetrical biaryls.

Over the past decade, part of our research effort has focused on the synthesis and application of cyclopalladated ferrocenylimines.[10] We found that they were highly versatile in coupling reactions, such as the Suzuki and the Heck reactions. Moreover, carbene adducts (Scheme 1) exhibited high activity with sterically hindered aryl chlorides as substrates in the Suzuki coupling.[10d] This has prompted us to explore the potential applications of such palladacycles in the Kumada reaction. Herein, we disclose our results on the application of carbene adducts of cyclopalladated ferrocenylimine as efficient catalysts for the coupling of a wide range of aryl halides with Grignard reagents, especially *ortho*-substituted Grignard reagents, with low catalyst loading (0.5 mol-%) under mild reaction conditions.



Scheme 1. Cyclopalladated ferrocenylimine and its adducts.

Results and Discussion

Palladacycles **a**–**f** were prepared according to the previously reported procedures.[10,11] At the outset of our stud-

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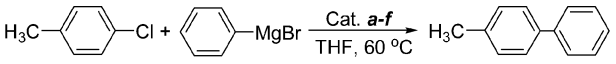
ies, the coupling of 4-chlorotoluene with phenylmagnesium bromide was chosen as a model reaction to evaluate the catalytic activity of complexes **a**–**f**. As shown in Table 1, complexes **c** and **d** showed higher catalytic activity; in the presence of 1.0 mol-% catalyst loading, these complexes provided the desired products in 90 and 94% yields, respectively (Entries 3 vs. 4). However, when catalyst loading was reduced to 0.5 mol-%, use of complex **c** only gave 80% yield, whereas complex **d** remained highly efficient (Entries 4 vs. 7).

Table 1. Screening of catalysts for the Kumada coupling.



Entry[a]	Cat.	Cat. [mol-%]	Yield [%][b]
1	**a**	1.0	trace amounts
2	**b**	1.0	trace amounts
3	**c**	1.0	90
4	**d**	1.0	94
5	**e**	1.0	78
6	**f**	1.0	25
7	**d**	**0.5**	**94**
8	**c**	**0.5**	**80**

[a] *Reaction conditions:* 4-chlorotoluene (1.0 mmol), PhMgBr (3.0 equiv.) in THF (2.0 mL), LiCl (2 equiv.), THF (2.0 mL), 24 h. [b] Yields based on 4-chlorotoluene and assessed by GC.

To further compare the catalytic activity of complexes **c** and **d**, first, the coupling of 4-chlorotoluene with phenylmagnesium bromide was performed at room temperature (Figure 1); this coupling was affected by the depressed temperature in two cases, however, the yield decreased dramatically when complex **c** was used as catalyst. Secondly, when the coupling of sterically hindered substrates 2-chloroanisole with (2-methylphenyl)magnesium bromide was assessed, complex **d** was found to be significantly superior to complex **c** (Figure 2). A catalyst loading of 0.5 mol-% complex **d** was therefore established for the following studies. We believe that the enhancement of "steric-bulk" in relation to the topography of the metal center is critical to the success of the palladacycle-catalyzed Kumada reactions, although the exact reason for the superiority of complex **d** is not clear.

We then investigated the influence of solvents, additives, and reaction temperature on the Kumada reaction. The reaction of 4-chlorotoluene with phenylmagnesium bromide was again chosen as a model reaction. As shown in Table 2, the cross-coupling product was obtained in 73% yield when tetrahydrofuran (THF) was used as solvent (Entry 1). The use of mixed solvents, such as THF/toluene, THF/dioxane, THF/*N*,*N*-dimethylformamide (DMF), only gave the product in 52, 60, and 31% yields, respectively (Entries 2–4); the homocoupling product of the Grignard reagent was observed in all cases. The yields of cross-coupling product increased significantly in the presence of two equivalents of LiCl (Entries 1 vs. 5) and decreased when the reaction was carried out at room temperature (Entries 5 vs. 7). Moreover,

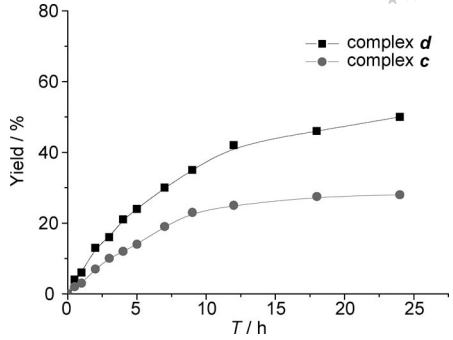


Figure 1. The Kumada reaction catalyzed by complexes **c** and **d** at room temperature. *Reaction conditions:* 4-Chlorotoluene (1.0 mmol), PhMgBr (3.0 equiv.) in THF (2.0 mL), cat. (0.5 mol-%), LiCl (2.0 equiv.), THF (2.0 mL), 24 h; yields based on 4-chlorotoluene and assessed by GC.

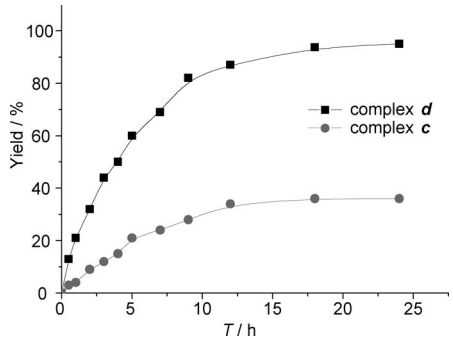


Figure 2. The Kumada reaction of 2-chloroanisole with (2-methylphenyl)magnesium bromide catalyzed by complexes **c** and **d**. *Reaction conditions:* 2-Chloroanisole (1.0 mmol), (2-methylphenyl) magnesium bromide (3.0 equiv.) in THF (2.0 mL), cat. (0.5 mol-%), LiCl (2.0 equiv.), THF (2.0 mL), 24 h; yields based on 2-chloroanisole and assessed by GC.

shortening the reaction time from 24 to 12 h did not affect the yields (Entries 5 vs. 10), and 96% yield was obtained using 4-bromotoluene and phenylmagnesium bromide as substrates at room temperature (Entry 11).

The range of substrates was then extended under the optimized conditions. The major disadvantage of the Kumada reaction is the low tolerance of functional groups. Therefore, our preliminary study was focused on aryl bromides with either functional groups or heteroatoms as substrates at room temperature (Table 3). The reaction of 2-bromobenzonitrile with *p*-tolylMgBr afforded the desired *o*-(*p*-tolyl)benzonitrile in 80% yield (Entry 1), which is a key intermediate in the synthesis of antihypertensive drugs.[12] Gratifyingly, the Boc protecting group was also tolerated to give the product **2**, which is also an important drug intermediate (Entry 2).[13] Unactivated vinyl bromides were also applied to the Kumada coupling to provide the desired products. 1-(2-Bromovinyl)benzene and 2-bromo-1,1-diphenylethene substrates gave the corresponding products in 95 and 90% yields, respectively (Entries 4 and 5). So far, coupling reactions of vinyl halides with Grignard reagents

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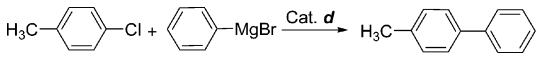
Table 2. Coupling reaction of 4-chlorotoluene with phenylmagnesium bromide.

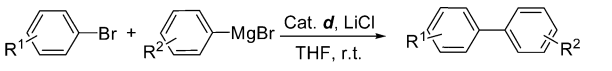


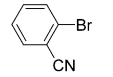
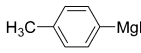
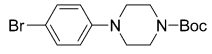
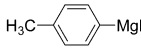
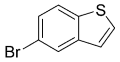
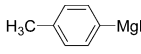
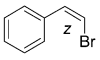
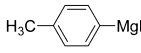
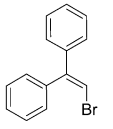
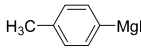
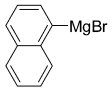
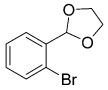
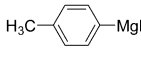
Entry[a]	Solvent	Additive	*T* [°C]	Time [h]	Yield [%][b]
1	THF	–	60	24	73
2	THF/toluene (1:1)	–	60	24	52
3	THF/dioxane (1:1)	–	60	24	60
4	THF/DMF (1:1)	–	60	24	31
5	THF	LiCl (2 equiv.)	60	24	94
6	THF	–	r.t.	24	20
7	THF	LiCl (2 equiv.)	r.t.	24	50
8	THF	LiCl (2 equiv.)	60	4	69
9	THF	LiCl (3 equiv.)	60	4	30
10	THF	LiCl (2 equiv.)	60	12	93
11[c]	THF	LiCl (2 equiv.)	r.t.	12	96

[a] *Reaction conditions:* 4-chlorotoluene (1.0 mmol), PhMgBr (3.0 equiv.) in THF (2.0 mL), cat. **d** (0.5 mol-%), solvent (2.0 mL). [b] Yields are based on aryl halides, and assessed by GC. [c] *Reaction conditions:* 4-bromotoluene (1.0 mmol), PhMgBr (3.0 equiv.) in THF (2.0 mL), cat. **d** (0.5 mol-%), solvent (2.0 mL).

have rarely been reported.[5p,5u] Furthermore, the coupling of aryl Grignard reagents proceed smoothly with benzothiophene, thiophene, and aldehyde-derived halides (Entries 3, 6, and 7).

Table 3. Coupling of aryl bromides with arylmagnesium halides at room temperature.

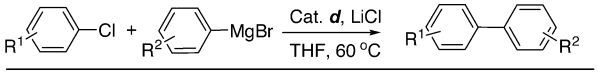


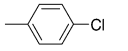
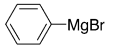
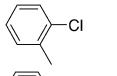
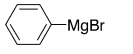
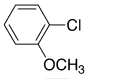
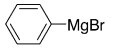
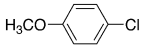
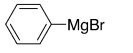
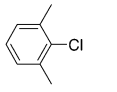
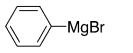
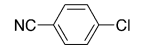
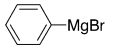
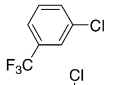
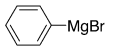
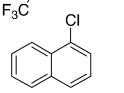
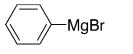
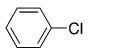
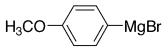
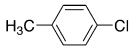
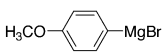
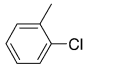
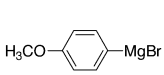
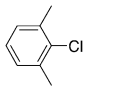
Entry[a]	Ar^1Br	Ar^2MgBr	Product	Yield/%[b]
1			**1**	80
2			**2**	63
3			**3**	87
4			**4**	95
5			**5**	90
6			**6**	69
7			**7**	89

[a] *Reaction conditions:* aryl bromide (1.0 mmol), ArMgBr (3.0 equiv.) in THF (2.0 mL), cat. **d** (0.5 mol-%), LiCl (2.0 equiv.), THF (2.0 mL), r.t., 12 h. [b] Isolated yields based on aryl bromides after two runs.

We then investigated the Kumada coupling of aryl chlorides (Table 4). In all cases, aryl chlorides with both electron-withdrawing (such as CN and CF_3) and electron-do-

Table 4. Coupling of aryl chlorides with arylmagnesium halides.



Entry[a]	Ar^1Cl	Ar^2MgBr	Product	Yield/%[b]
1			**8**	93
2			**9**	93
3			**10**	95
4			**11**	97
5			**12**	89
6			**13**	93
7			**14**	96
8			**15**	98
9			**11**	95
10			**16**	96
11			**17**	92
12			**18**	91
13			**19**	94
14			**20**	94

[a] *Reaction conditions:* Aryl chloride (1.0 mmol), ArMgBr (3.0 equiv.) in THF (2.0 mL), cat. **d** (0.5 mol-%), LiCl (2.0 equiv.), THF (2.0 mL), 60 °C, 12 h. [b] Isolated yields based on aryl chorides after two runs.

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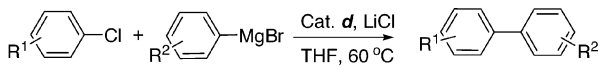
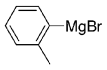
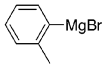
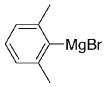
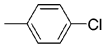
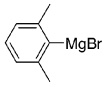
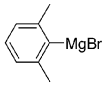
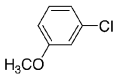
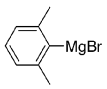
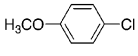
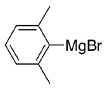
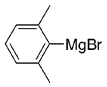
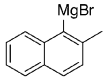
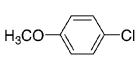
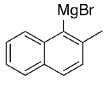
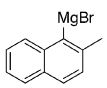
nating (such as CH_3 and CH_3O) groups gave excellent yields (89–97%, Entries 1–7 and 9–13). Chloronaphthalene coupled with both phenylmagnesium bromide and (4-methoxyphenyl)magnesium bromide to afford the desired products in 98 and 94% yields, respectively (Entries 8 and 14). Moreover, increased steric bulk in the aryl chloride did not significantly affect the yields; for example, 2-chloro-*m*-xylene gave excellent yields (Entries 5 and 12). These results prompted us to investigate the synthesis of more sterically hindered C–C biaryl compounds catalyzed by complex **d**.

As shown in Table 5, this reaction system is capable of efficiently synthesizing di- and tri-*ortho*-substituted biaryls, even when electron-rich chlorides that are generally reluctant to undergo oxidative addition under mild conditions, were used as substrates. Coupling of 2-chloroanisole with 2-tolylmagnesium bromide gave the corresponding biaryl **21**

Table 5. Coupling of sterically hindered substrates.



Entry[a]	Ar^1Cl	Ar^2MgBr	Product	Yield/%[b]
1[c]			**21**	87
2			**21**	95
3			**12**	93
4			**22**	93
5			**23**	88
6			**24**	90
7			**18**	94
8			**25**	83
9			**26**	88
10			**27**	91
11			**28**	79

[a] *Reaction conditions:* Aryl chloride (1.0 mmol), ArMgBr (3.0 equiv.) in THF (2.0 mL), cat. **d** (0.5 mol-%), LiCl (2.0 equiv.), THF (2.0 mL), 60 °C, 24 h. [b] Isolated yields based on aryl chloride after two runs. [c] Reaction time: 12 h.

in 95% yield (Entry 2). (2,6-Dimethylphenyl)magnesium bromide coupled with chlorobenzene, 4-chlorotoluene, 2-chlorotoluene, 3-chloroanisole, 4-chloroanisole, and chloronaphthalene, to provide the desired products in 83–94% yields (Entries 3–8). Biaryls **26** and **27** were obtained in 88 and 91% yields from the coupling of (2-methylnaphthyl)-magnesium bromide with chlorobenzene and 4-chloroanisole, respectively (Entries 9 and 10). Moreover, tri-*ortho*-substituted biaryls **23**, **25**, and **28** were obtained in good yields from 2-chlorotoluene and chloronaphthalene upon reaction with *ortho*-substituted Grignard reagents (Entries 5, 8, and 11).

Conclusions

In summary, we have found that complex **d**, which bears a strongly electron-donating and sterically hindered carbene moiety, is highly efficient for the cross-coupling of aryl halides with Grignard reagents in the presence of 0.5 mol-% catalyst and two equivalents of LiCl under mild reaction conditions. This reaction system tolerates various functional groups, and could be efficiently applied to the synthesis of di- and tri-*ortho*-substituted biaryls.

Experimental Section

General: Melting points were measured with a XT-5 microscopic apparatus. GC analyses were performed with an Agilent 4890D gas chromatograph. ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker DPX 400 instrument using $CDCl_3$ as the solvent and TMS as the internal standard. Elemental analyses were conducted with a Carlo Erba 1160 elemental analyzer. All chemicals were reagent grade and used without further purification.

General Procedure for the Kumada Coupling Reaction: Aryl halide (1.0 mmol), ArMgBr (3.0 mmol) in THF (2.0 mL), complex **d** (0.5 mol-%), LiCl (2.0 mmol), and anhydrous THF (2.0 mL) were added to an oven-dried flask under an N_2 atmosphere. The reaction was stirred at either r.t. or 60 °C. The reaction mixture was cooled to r.t., quenched with HCl (1.0 M), and extracted three times with dichloromethane. The combined organic phase was washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. After purification by flash chromatography (petroleum ether/ethyl acetate) the yields were assessed based on the amount of aryl halide. The products were characterized by ^1H NMR and ^{13}C NMR analyses and the data were consistent with those reported in the literature. The identities of the new compounds were further confirmed by elemental analysis.

***o*-(*p*-Tolyl)benzonitrile (1):**[14] White solid; m.p. 47–49 °C (ref.[14] 49–51 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, J = 7.7 Hz, 1 H), 7.76–7.60 (m, 1 H), 7.50–7.39 (m, 4 H), 7.30–7.25 (m, 2 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.4, 138.6, 135.2, 133.6, 132.7, 129.9, 129.4, 128.59, 128.55, 127.2, 118.8, 111.1, 21.2 ppm.

***tert*-Butyl 4-(4′-Methylbiphenyl-4-yl)piperazine-1-carboxylate (2):** White solid; m.p. 189–191 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, J = 8.6 Hz, 2 H), 7.45 (d, J = 8.1 Hz, 2 H), 7.21 (d, J = 7.9 Hz, 2 H), 6.97 (d, J = 8.7 Hz, 2 H), 3.60–3.58 (m, 4 H), 3.18–3.15 (m, 4 H), 2.37 (s, 3 H), 1.48 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.7, 150.2, 137.8, 136.2, 132.9, 129.4,

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127.6, 126.4, 116.7, 79.9, 49.3, 28.4, 21.0 ppm. $C_{22}H_{28}N_2O_2$: calcd. C 74.97, H 8.01, N 7.95; found C 74.93, H 8.09, N 7.90.

3-(4-Methylphenyl)benzothiophene (3): White solid; m.p. 120–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (s, 1 H), 7.92 (d, J = 8.4 Hz, 1 H), 7.59–7.55 (m, 3 H), 7.47 (d, J = 5.4 Hz, 1 H), 7.38 (d, J = 5.4 Hz, 1 H), 7.28 (d, J = 7.9 Hz, 2 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.2, 138.5, 138.4, 137.6, 136.9, 129.5, 127.2, 126.9, 124.0, 123.8, 122.6, 121.7, 21.1 ppm. $C_{15}H_{12}S$: calcd. C 80.31, H 5.39, S 14.29; found C 79.96, H 5.35, S 14.37.

(*Z*)-1-(4-Methylphenyl)-2-phenylethene (4):[15] Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.24 (m, 2 H), 7.21–7.15 (m, 3 H), 7.13 (d, J = 8.1 Hz, 2 H), 7.00 (d, J = 7.9 Hz, 2 H), 6.53 (s, 2 H), 2.28 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.4, 136.8, 134.2, 130.1, 129.5, 128.9, 128.84, 128.83, 128.80, 128.7, 128.14, 128.13, 126.9, 21.2 ppm.

2-(4-Methylphenyl)-1,1-diphenylethene (5):[16] Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.19 (m, 10 H), 6.93–6.91 (m, 5 H), 2.24 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 141.7, 140.6, 136.6, 134.5, 130.4, 129.5, 128.79, 128.76, 128.7, 128.22, 128.18, 128.15, 127.6, 127.39, 127.36, 21.2 ppm.

2-(1-Naphthyl)thiophene (6):[17] Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23–8.21 (m, 1 H), 7.89–7.83 (m, 2 H), 7.56 (d, J = 6.9 Hz, 1 H), 7.51–7.46 (m, 3 H), 7.42–7.40 (m, 1 H), 7.245–7.236 (m, 1 H), 7.18–7.16 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.7, 133.8, 132.4, 131.8, 128.4, 128.3, 128.2, 127.4, 127.2, 126.4, 126.0, 125.7, 125.6, 125.2 ppm.

2-[4′-Methyl(1,1′-biphenyl)-2-yl]-1,3-dioxolane (7):[18] Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.70 (m, 1 H), 7.40–7.38 (m, 2 H), 7.33 (d, J = 7.8 Hz, 2 H), 7.28–7.21 (m, 3 H), 5.68 (s, 1 H), 4.18–4.15 (m, 2 H), 3.95–3.91 (m, 2 H), 2.40 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.1, 137.0, 136.9, 134.5, 130.0, 129.5, 129.0, 128.7, 127.4, 126.5, 101.2, 65.4, 21.2 ppm.

4-Methylbiphenyl (8):[5q] White solid; m.p. 44–45 °C (ref.[5q] 43–45 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, J = 7.4 Hz, 2 H), 7.49 (d, J = 8.0 Hz, 2 H), 7.41 (t, J = 7.5 Hz, 2 H), 7.31 (t, J = 7.3 Hz, 1 H), 7.24 (d, J = 8.0 Hz, 2 H), 2.39 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 138.3, 137.0, 129.4, 128.7, 127.0, 21.1 ppm.

2-Methylbiphenyl (9):[19] Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.36 (m, 2 H), 7.32–7.29 (m, 3 H), 7.25–7.21 (m, 4 H), 2.25 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.0, 135.4, 130.4, 129.9, 129.3, 128.8, 128.1, 127.3, 126.8, 125.8, 20.5 ppm.

2-Methoxybiphenyl (10):[5q] Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, J = 7.7 Hz, 2 H), 7.41–7.38 (m, 2 H), 7.32–7.29 (m, 3 H), 7.04–6.96 (m, 2 H), 3.78 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4, 138.5, 130.8, 130.7, 129.5, 128.6, 127.9, 126.9, 120.8, 111.2, 55.5 ppm.

4-Methoxybiphenyl (11):[5q] White solid; m.p. 84–86 °C (ref.[5q] 85–87 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.52 (m, 4 H), 7.43–7.39 (m, 2 H), 7.30–7.25 (m, 1 H), 6.99–6.97 (m, 2 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 140.8, 133.8, 128.7, 128.1, 126.7, 126.6, 114.2, 55.3 ppm.

2,6-Dimethylbiphenyl (12):[5b] Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.38 (m, 2 H), 7.32–7.29 (m, 1 H), 7.16–7.08 (m, 5 H), 2.02 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.9, 141.2, 136.1, 129.1, 128.5, 127.3, 127.1, 126.7, 20.9 ppm.

4-Cyanobiphenyl (13):[5n] White solid; m.p. 84–86 °C (ref.[5n] 85–87 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.67 (m, 4 H), 7.60–7.58 (m, 2 H), 7.50–7.40 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 139.2, 132.6, 129.1, 128.6, 127.7, 127.2, 118.9, 110.9 ppm.

3-(Trifluoromethyl)biphenyl (14):[20] Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (s, 1 H), 7.72 (d, J = 7.6 Hz, 1 H), 7.59–7.55 (m, 3 H), 7.50 (t, J = 7.7 Hz, 1 H), 7.46–7.42 (m, 2 H), 7.38–7.35 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.0, 139.8, 131.0 (q, J = 32 Hz), 130.4, 129.3, 129.0, 128.8, 128.0, 127.2, 124.2 (q, J = 275.2 Hz), 122.9, 120.2 ppm.

1-Phenylnaphthalene (15):[19] Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.83 (m, 2 H), 7.81–7.78 (m, 1 H), 7.48–7.44 (m, 6 H), 7.43–7.14 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.8, 140.3, 133.8, 131.7, 130.1 128.3, 127.7, 127.3, 127.0, 126.1, 125.8, 125.4 ppm.

4-Methoxy-4′-methylbiphenyl (16):[5n] Colorless solid; m.p. 117–118 °C (ref.[5n] 107.9–108.1 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, J = 8.7 Hz, 2 H), 7.45 (d, J = 8.0 Hz, 2 H), 7.23 (md, J = 8.0 Hz, 2 H), 6.96 (d, J = 8.7 Hz, 2 H), 3.84 (s, 3 H), 2.38 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 138.0, 136.3, 133.7, 129.4, 127.9, 126.6, 114.1, 55.3, 21.0 ppm.

4-Methoxy-2′-methylbiphenyl (17):[5n] Light-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.19 (m, 6 H), 6.94 (d, J = 8.8 Hz, 2 H), 3.83 (s, 3 H), 2.27 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 141.6, 135.5, 134.4, 130.3, 130.2, 129.9, 127.0, 125.8, 113.5, 55.3, 20.6 ppm.

4′-Methoxy-2,6-dimethylbiphenyl (18):[21] White solid; m.p. 49–50 °C (ref.[21] 52–53 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14–7.04 (m, 5 H), 6.96 (d, J = 8.5 Hz, 2 H), 3.85 (s, 3 H), 2.04 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 141.5, 136.5, 133.3, 130.0, 127.2, 126.9, 113.8, 55.2, 20.9 ppm.

4′-Methoxy-3-(trifluoromethyl)biphenyl (19):[5n] Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (s, 1 H), 7.70–7.68 (m, 1 H), 7.54–7.47 (m, 4 H), 7.00–6.96 (m, 2 H), 3.84 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 141.6, 132.2, 131.1 (d, J = 31.8 Hz), 129.9, 129.2, 128.9, 128.2 (q, J = 272.2 Hz), 123.4 (q, J = 3.8 Hz), 123.3 (q, J = 3.8 Hz), 114.4, 55.3 ppm.

1-(4-Methoxyphenyl)naphthalene (20):[24] Solid; m.p. 115–117 °C (ref.[24] 116–117 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.88 (m, 2 H), 7.83 (d, J = 8.2 Hz, 1 H), 7.52–7.45 (m, 2 H), 7.44–7.39 (m, 4 H), 7.04–7.01 (m, 2 H), 3.14 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 139.9, 133.8, 133.1, 131.8, 131.1, 128.2, 127.3, 126.9, 126.1, 125.9, 125.7, 125.4, 113.7, 55.3 ppm.

2-Methoxy-2′-methylbiphenyl (21):[5t] Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–6.94 (m, 8 H), 3.74 (s, 3 H), 2.14 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 138.7, 136.8, 131.0, 130.9, 130.0, 129.6, 128.6, 127.3, 125.4, 120.5, 110.7, 55.4, 19.9 ppm.

2,6,4′-Trimethylbiphenyl (22):[22] Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, J = 7.8 Hz, 2 H), 7.14–7.12 (m, 1 H), 7.09–7.08 (m, 2 H), 7.02 (d, J = 8.0 Hz, 2 H), 2.39 (s, 3 H), 2.03 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.9, 138.1, 136.3, 136.2, 136.1, 129.2, 129.0, 127.3, 126.9, 21.3, 20.9 ppm.

2,6,2′-Trimethylbiphenyl (23):[5t] Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.02 (m, 7 H), 1.96 (s, 3 H), 1.94 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 140.5, 135.8, 135.6, 129.9, 129.8, 129.3, 128.8, 127.2, 127.0, 126.9, 126.0, 125.5, 20.3, 19.4 ppm.

3′-Methoxy-2,6-dimethylbiphenyl (24):[22] Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.27 (m, 1 H), 7.13–7.09 (m, 1

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H), 7.05 (d, J = 7.2 Hz, 2 H), 6.85–6.82 (m, 1 H), 6.70–6.65 (m, 2 H), 3.76 (s, 3 H), 2.00 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6, 142.5, 141.7, 136.0, 129.4, 127.2, 127.0, 121.4, 114.5, 112.1, 55.2, 20.7 ppm.

1-(2,6-Dimethylphenyl)naphthalene (25):[23] White solid; m.p. 70–71 °C (ref.[23] 71–72 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.84 (m, 2 H), 7.55–7.51 (m, 1 H), 7.48–7.44 (m, 1 H), 7.33 (d, J = 3.6 Hz, 2 H), 7.27–7.22 (m, 2 H), 7.17 (d, J = 7.5 Hz, 2 H), 1.90 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.6, 138.8, 137.0, 133.8, 131.8, 128.3, 127.33, 127.27, 127.2, 126.4, 126.0, 125.8, 125.7, 125.4, 20.4 ppm.

2-Methyl-1-phenylnaphthalene (26):[25] Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, J = 7.6 Hz, 1 H), 7.77 (d, J = 8.4 Hz, 1 H), 7.49–7.26 (m, 9 H), 2.23 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8, 138.2, 133.1, 133.0, 131.9, 130.1, 128.6, 128.4, 128.3, 128.2, 127.7, 127.2, 127.0, 126.1, 125.8, 124.7 ppm.

1-(4-Methoxyphenyl)-2-methylnaphthalene (27):[26] White solid; m.p. 95–97 °C (lit.[26] 96–98 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.0 Hz, 1 H), 7.75 (d, J = 8.4 Hz, 1 H), 7.45–7.19 (m, 4 H), 7.17 (d, J = 1.9 Hz, 1 H), 7.02 (d, J = 8.6 Hz, 1 H), 3.88 (s, 3 H), 2.24 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6, 137.8, 133.5, 133.3, 132.0, 131.9, 131.2, 128.6, 127.7, 127.1, 126.2, 125.7, 124.7, 113.8, 55.3, 20.9 ppm.

2-Methyl-1,1′-binaphthyl (28):[27] Colorless solid; m.p. 131–134 °C (lit.[27] 132–134 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.82 (m, 5 H), 7.56–7.15 (m, 8 H), 2.08 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.6, 134.4, 133.8, 128.7, 128.4, 127.9, 127.8, 127.7, 127.6, 126.3, 126.2, 126.08, 126.06, 125.98, 125.95, 128.9, 125.7, 125.4, 124.9, 20.6 ppm.

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[1] a) L. Pu, *Chem. Rev.* **1998**, *98*, 2405–2494; b) X. Mei, C. Wolf, *Chem. Commun.* **2004**, 2078–2079; c) G. E. Tumambac, X. Mei, C. Wolf, *Eur. J. Org. Chem.* **2004**, 3850–3856; d) X. Mei, C. Wolf, *J. Am. Chem. Soc.* **2004**, *126*, 14736–14737; e) G. E. Tumambac, C. Wolf, *Org. Lett.* **2005**, *7*, 4045–4048; f) C. Wolf, S. Liu, B. C. Reinhardt, *Chem. Commun.* **2006**, 4242–4444; g) X. Mei, C. Wolf, *Tetrahedron: Asymmetry* **2006**, *47*, 7901–7904; h) X. Mei, C. Wolf, *J. Am. Chem. Soc.* **2006**, *128*, 13326–13327.

[2] O. Baudoin, F. Gueritte, *Stud. Nat. Prod. Chem.* **2003**, *29*, 355–417.

[3] a) A. V. R. Rao, M. K. Gurjar, K. L. Reddy, A. S. Rao, *Chem. Rev.* **1995**, *95*, 2135–2167; b) K. C. Nicolaou, C. N. C. Boddy, S. Bräse, N. Winssinger, *Angew. Chem. Int. Ed.* **1999**, *38*, 2096–2152; c) G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427.

[4] K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376.

[5] a) T. Kamikawa, T. Hayashi, *J. Org. Chem.* **1998**, *63*, 8922–8925; b) J. K. Huang, S. P. Nolan, *J. Am. Chem. Soc.* **1999**, *121*, 9889–9890; c) V. Bonnet, F. Mongin, F. Trecourt, G. Queguiner, P. Knochel, *Tetrahedron Lett.* **2001**, *42*, 5717–5719; d) J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc.* **2002**, *124*, 4222–4223; e) A. C. Frisch, N. Shaikh, A. Zapf, M. Beller, *Angew. Chem.* **2002**, *114*, 4218–4221; f) T. J. Korn, G. Cahiez, P. Knochel, *Synlett* **2003**, 1892–1894; g) A. C. Frisch, F. Rataboul, A. Zapf, M. Beller, *J. Organomet. Chem.* **2003**, *687*, 403–409; h) M. Nakamura, K. Matsuo, S. Ito, B. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 3686–3687; i) T. Nagano, T. Hayashi, *Org. Lett.* **2004**, *6*, 1297–1299; j) L. M. Yang, L. F. Huang, T. Y. Luh, *Org. Lett.* **2004**, *6*, 1461–1463; k) A. C. Frisch, A. Zapf, O. Briel, B. Kayser, N. Shaikh, M. Beller, *J. Mol. Catal. A* **2004**, *214*, 231–239; l) M. E. Limmert, A. H. Roy, J. F. Hartwig, *J. Org. Chem.* **2005**, *70*, 9364–9370; m) T. J. Korn, M. A. Schade, M. N. Cheemala, S. Wirth, S. A. Guevara, G. Cahiez, P. Knochel, *Synthesis* **2006**, 3547–3574; n) L. Ackermann, A. Althammer, *Org. Lett.* **2006**, *8*, 3457–3460; o) N. Roques, L. Saint-Jalmes, *Tetrahedron Lett.* **2006**, *47*, 3375–3378; p) L. Ackermann, C. J. Gschrei, A. Althammer, M. Riederer, *Chem. Commun.* **2006**, 1419; q) F. Y. Tsai, B. N. Lin, M. J. Chen, C. Y. Mou, S. T. Liub, *Tetrahedron* **2007**, *63*, 4304–4309; r) G. M. Organ, M. Abdel-Hadi, S. Avola, N. Hadei, J. Nasielski, J. C. O'Brien, C. Valente, *Chem. Eur. J.* **2007**, *13*, 150–157; s) R. Martin, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3844–3845; t) C. Wolf, H.-H. Xu, *J. Org. Chem.* **2008**, *73*, 162–167; u) Z.-X. Xi, B. Liu, W.-Z. Chen, *J. Org. Chem.* **2008**, *73*, 3954–3957; v) C. E. Hartmann, S. P. Nolan, S. J. C. Cazin, *Organometallics* **2009**, *28*, 2915–2919.

[6] For Suzuki cross-couplings, see: a) N. Miyaura, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437–3440; b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; c) A. Suzuki, *J. Organomet. Chem.* **2002**, *653*, 83–90; d) J. Yin, M. P. Rainka, X.-X. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1162–1163; e) J. F. Jensen, M. Johannsen, *Org. Lett.* **2003**, *5*, 3025–3028; f) O. Navarro, R. A. Kelly, S. P. Nolan, *J. Am. Chem. Soc.* **2003**, *125*, 16194–16195; g) G. Altenhoff, R. Goddard, C. Lehmann, F. Glorius, *J. Am. Chem. Soc.* **2004**, *126*, 15195–15201; h) R. Singh, M. S. Viciu, N. Kramareva, O. Navarro, S. P. Nolan, *Org. Lett.* **2005**, *7*, 1829–1832; i) N. Marion, O. Navarro, J. Mei, E. D. Stevens, N. M. Scott, S. P. Nolan, *J. Am. Chem. Soc.* **2006**, *128*, 4101–4111.

[7] For Stille cross-couplings, see: a) M. Kosugi, S. Sasazama, Y. Shimizu, T. Migita, *Chem. Lett.* **1977**, 301–302; b) D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638; c) J. K. Stille, *Angew. Chem.* **1986**, *98*, 504–519; d) C. Wolf, X. Mei, *J. Am. Chem. Soc.* **2003**, *125*, 10651–10658; e) G. E. Tumambac, C. Wolf, *J. Org. Chem.* **2004**, *69*, 2048–2055; f) W. Su, S. Urgaonkar, P. A. McLaughlin, J. G. Verkade, *J. Am. Chem. Soc.* **2004**, *126*, 16433–16439; g) G. E. Tumambac, C. Wolf, *J. Org. Chem.* **2005**, *70*, 2930–2938; h) X. Mei, R. M. Martin, C. Wolf, *J. Org. Chem.* **2006**, *71*, 2854–2861.

[8] For Negishi cross-couplings, see: a) A. O. King, N. Okukado, E. Negishi, *J. Chem. Soc., Chem. Commun.* **1977**, 683–684; b) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821–1823; c) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340–348; d) J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028–13032; e) M. Genov, B. Fuentes, P. Espinet, B. Pelaz, *Tetrahedron: Asymmetry* **2006**, *17*, 2593–2595; f) M. Genov, A. Almorin, P. Espinet, *Tetrahedron: Asymmetry* **2007**, *18*, 625–627.

[9] a) E. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley, New York, **2002**; b) A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., Wiley-VCH, Weinheim, Germany, **2004**; c) G.-H. Fang, Z.-J. Yan, J. Yang, M.-Z. Deng, *Synthesis* **2006**, 1148–1154.

[10] a) C. Xu, J.-F. Gong, S.-F. Yue, Y. Zhu, Y.-J. Wu, *Dalton Trans.* **2006**, 4730–4739; b) J.-Y. Li, A.-J. Yu, Y.-J. Wu, Y. Zhu, C.-X. Du, H.-W. Yang, *Polyhedron* **2007**, *26*, 2629–2637; c) J. Ma, X.-L. Cui, B. Zhang, M.-P. Song, Y.-J. Wu, *Tetrahedron* **2007**, *63*, 5529–5538; d) M.-J. Cui, J.-Y. Li, A.-J. Yu, J.-L. Zhang, Y.-J. Wu, *J. Mol. Catal. A* **2008**, *290*, 67–71.

[11] a) S.-Q. Huo, Y.-J. Wu, C.-X. Du, Y. Zhu, H.-Z. Yuan, X.-A. Mao, *J. Organomet. Chem.* **1994**, *483*, 139–146; b) I. P. Beletskaya, A. V. Cheprakov, *J. Organomet. Chem.* **2004**, *689*, 4045–4082; c) J.-F. Gong, G.-Y. Liu, Y. Zhu, C.-X. Du, M.-P. Song, Y.-J. Wu, *Chem. J. Chin. Univ.* **2006**, *27*, 1266–1271.

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[12] a) H. Kageyama, T. Miyazaki, Y. Kimura, *Synlett* **1994**, 371–372; b) J. A. Miller, R. P. Farrell, *Tetrahedron Lett.* **1998**, *39*, 6441–6444; c) P. Walla, C. O. Kappe, *Chem. Commun.* **2004**, 564–565.
[13] a) L. C. Meurer, R. L. Tolman, E. W. Chapin, R. Saperstein, P. P. Vicario, M. M. Zrada, M. MacCoss, *J. Med. Chem.* **1992**, *35*, 3845–3857; b) C. Tahtaoui, I. Parrot, P. Klotz, F. Guillier, J. L. Galzi, M. Hibert, B. Ilien, *J. Med. Chem.* **2004**, *47*, 4300–4315; c) H.-L. Zheng, M. W. Lev, B. A. Orit, E. Silvina, Z. I. Cabantchik, W. Abraham, B. H. Y. Moussa, F. Mati, *Bioorg. Med. Chem.* **2005**, *13*, 773–783.
[14] M. Lombardo, M. Chiarucci, C. Trombini, *Green Chem.* **2009**, *11*, 574–579.
[15] H. Zhao, Y. Wang, J.-C. Sha, S.-R. Sheng, M.-Z. Cai, *Tetrahedron* **2008**, *64*, 7517–7523.
[16] E. F. Corsico, R. A. Rossi, *J. Org. Chem.* **2004**, *69*, 6427–6432.
[17] S. E. Denmark, J. D. Baird, *Org. Lett.* **2006**, *8*, 793–795.
[18] N. Kokuni, T. Yamane, T. Nakamura, M. Watanabe, *Jpn. Kokai Tokkyo Koho* **1996**, *JP* 08231454, 19960910.
[19] Z.-X. Xi, B. Liu, W.-Z. Chen, *J. Org. Chem.* **2008**, *73*, 3954–3957.
[20] M. A. D. Heiden, H. Plenio, *Chem. Eur. J.* **2004**, *10*, 1789–1797.
[21] D. Stefano, *Synthesis* **2006**, 1117–1123.
[22] R. Singh, M. S. Viciu, N. Kramareva, O. Navarro, S. P. Nolan, *Org. Lett.* **2005**, *7*, 1829–1832.
[23] C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743–4748.
[24] L. Q. Wang, W. J. Lu, *Org. Lett.* **2009**, *11*, 1079–1082.
[25] A. C. Glass, B. B. Morris, L. N. Zakharov, S.-Y. Liu, *Org. Lett.* **2008**, *10*, 4855–4857.
[26] A. N. Cammidge, V. H. M. Goddard, H. Gopee, N. L. Harrison, D. L. Hughes, C. J. Schubert, B. M. Sutton, G. L. Watts, A. J. Whitehead, *Org. Lett.* **2006**, *8*, 4071–4074.
[27] R. P. J. Bronger, P. J. Guiry, *Tetrahedron: Asymmetry* **2007**, *18*, 1094–1102.

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