Iron-catalyzed aryl–aryl cross-coupling reaction tolerating amides and unprotected quinolinones†

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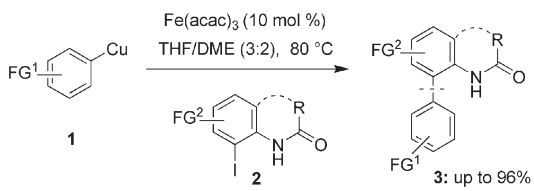
The iron(III)-catalyzed cross-coupling reaction between functionalized arylcopper reagents and aromatic iodides bearing an amide function or an unprotected quinolinone leads smoothly to polyfunctionalized biphenyls in excellent yields due to an intramolecular chelating effect of the amide group.

Transition-metal catalyzed cross-coupling reactions are powerful tools for the formation of new carbon–carbon bonds between C(sp^2)-centers.[1] Most catalytic systems used are based on palladium or nickel.[2,3] These metals are costly or toxic and often require expensive and sophisticated ligands.[4] There is a great need for cheap and environmentally friendly catalysts which do not require complicated ligands. Based on the pioneering work of Kochi,[5] several reports were published using iron salts as catalysts to perform a cross-coupling reaction between a Grignard reagent and an alkyl or alkenyl halide.[6,7] Recently, we have reported an iron-catalyzed aryl–aryl cross-coupling reaction using polyfunctionalized copper reagents for the preparation of highly functionalized biphenyls.[8]

Herein, we wish to report an iron-catalyzed cross-coupling reaction of arylcopper reagents with aryl iodides bearing amide functions or with unprotected iodo-quinolinones. Copper organometallics of type **1** are prepared *via* an iodine–magnesium exchange or a direct Mg-insertion, followed by transmetalation with CuCN·2LiCl. These copper derivatives are treated with a 2-iodophenyl amide or quinolinones of type **2** and $Fe(acac)_3$ (10 mol%). The reaction takes place in THF–DME (3 : 2) at 80 °C and leads to highly functionalized biphenyls of type **3** (Scheme 1).

To delineate the synthetic scope of our method, we have synthesized several heterocyclic compounds and found that



Scheme 1 Iron-catalyzed cross-coupling between arylcopper reagents of type **1** and 2-iodoamides or quinolinones of type **2** leading to functionalized biphenyls of type **3**.

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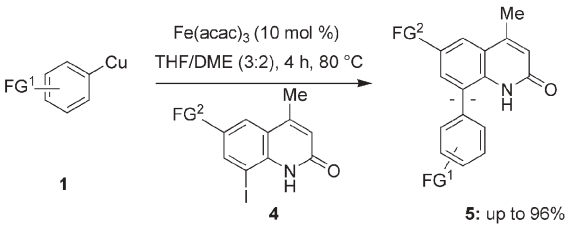
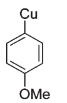
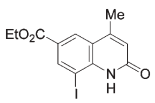
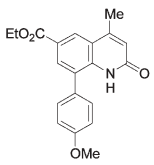
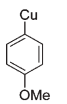
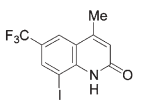
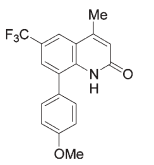
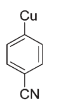
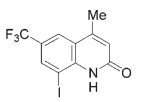
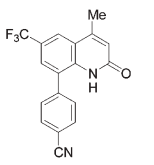
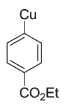
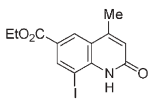
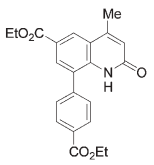
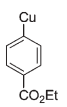
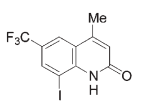
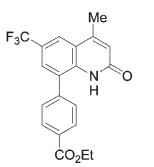
† Electronic supplementary information (ESI) available: Experimental procedures and full characterization of all new compounds. See DOI: 10.1039/b618617c



Scheme 2 Preparation of highly functionalized quinolinones of type **5**.

Table 1 Iron-catalyzed cross-coupling of unprotected quinolinones of type **4** using arylcopper reagents of type **1** leading to highly functionalized quinolinones of type **5**

Entry	ArCu[a]	Electrophile	Product	Yield[b] (%)
1	 **1a**	 **4a**	 **5a**	91
2	 **1a**	 **4b**	 **5b**	84
3	 **1b**	 **4b**	 **5c**	74
4	 **1c**	 **4a**	 **5d**	96
5	 **1c**	 **4b**	 **5e**	88

[a] ArCu(CN)MgBr or ArCu(CN)MgCl. [b] Isolated yield of analytically pure product.

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functionalized quinolinones[9] of type **4** are excellent electrophiles. This method proved to be very efficient for the preparation of highly functionalized quinolinone derivatives of type **5** (Scheme 2 and Table 1).

Both, arylcuprates with electron-rich substituents, such as a methoxy group, as well as arylcuprates bearing electron-withdrawing substituents, undergo this iron-catalyzed cross-coupling reaction in excellent yields. The reaction of the electron-rich 4-methoxyphenylcopper **1a** with quinolinone derivatives **4a** and **4b** leads to the desired products **5a** and **5b** in 91 and 84% yield, respectively (entries 1 and 2, Table 1). Furthermore, Grignard reagents bearing electron-withdrawing groups such as nitrile **1b** or an ester **1c** can be used, to perform this cross-coupling reaction with different quinolinone derivatives **4a** and **4b**. The functionalized quinolinones **5c–5e** can be obtained in yields up to 96% (74–96%, entries 3–5, Table 1).

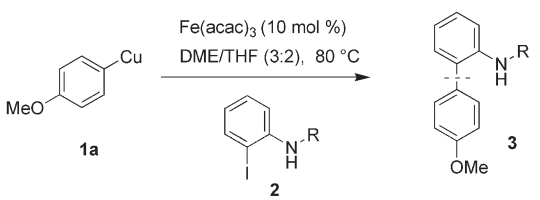
We then examined the use of secondary amides as electrophiles under these reaction conditions. Therefore, we screened several benzamides of type **2** in the reaction with 4-methoxyphenylcopper **1a** in order to investigate the influence of various amides on the formation of products of type **3** (Scheme 3, Table 2).

We observed that the nature of the acyl group has a strong influence on the reactivity (Table 2).

We found that electron-donating substituents led to the highest isolated yield of the products of type **3**. Also, by comparing a tosyl or triflyl protecting group, we observed that the more electron-donating tosylate leads to higher yields (68–84%, entries 5 and 6, Table 2). Other protecting groups such as an acetyl, trifluoroacetyl or benzoyl group gave less satisfactory yields (55–85%, entries 1–3, Table 2).

The 4-methoxybenzoyl group gave the best protection, with the strongest intramolecular chelating effect, and led to the highest isolated yields (92%, entry 4, Table 2). Therefore, functionalized benzanilides of type **6** were used for further cross-coupling reactions leading to highly functionalized biphenyls of type **7**, as shown in Table 3.

The iron-catalyzed cross-coupling of various functionalized amides showed surprising results. Amides with electron-donating substituents yielded the products in 10–20% higher yields than with electron-withdrawing substituents, which is unusual. This may be best explained by assuming that donor-substituents influence the



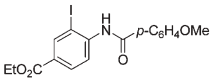
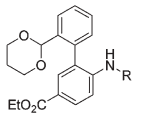
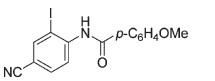
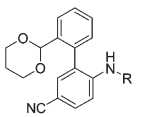
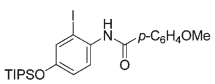
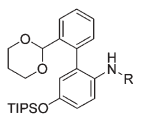
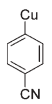
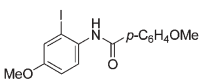
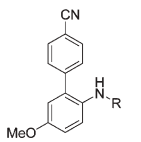
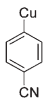
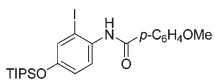
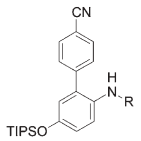
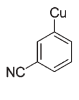
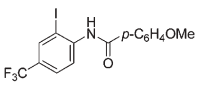
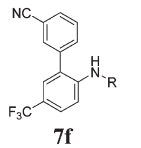
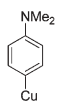
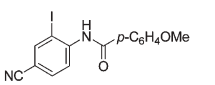
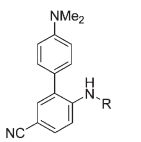
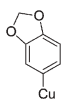
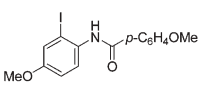
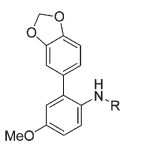
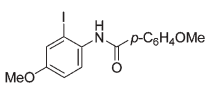
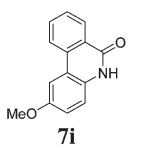
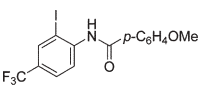
Scheme 3 Fe(III)-catalyzed cross-coupling with benzanilides.

Table 2 Screening of different protecting groups **R** on derivatives of type **2**

Entry	Protecting group **R**	Derivative **3** yield[a] (%)
1	**2a**: CF_3CO	**3a**: 55
2	**2b**: MeCO	**3b**: 74
3	**2c**: PhCO	**3c**: 85
4	**2d**: *p*-$MeOC_6H_4CO$	**3d**: 92
5	**2e**: CF_3SO_2	**3e**: 68
6	**2f**: $TolSO_2$	**3f**: 84

[a] Isolated yield of analytically pure product.

Table 3 Preparation of highly functionalized biphenyls of type **7**

Entry	ArCu[a]	Electrophile	Product[b]	Yield[c] (%)
1	 **1d**	 **6a**	 **7a**	75
2	 **1d**	 **6b**	 **7b**	70
3	 **1d**	 **6c**	 **7c**	82
4	 **1e**	 **6d**	 **7d**	84
5	 **1e**	 **6c**	 **7e**	96
6	 **1f**	 **6e**	 **7f**	70
7	 **1g**	 **6b**	 **7g**	71
8	 **1h**	 **6d**	 **7h**	74
9	 **1i**	 **6d**	 **7i**	92
10	 **1i**	 **6e**	 **7j**	78

[a] ArCu(CN)MgBr or ArCu(CN)MgCl. [b] R = $CO(C_6H_4OMe)$. [c] Isolated yield of analytically pure product.

chelating effect of the amide function. The reaction of the protected aldehyde **1d** with the ester- and nitrile-substituted amides gave compounds **7a** and **7b** in 70–75% yield. The TIPS-protected phenol **6c** led to the sterically hindered compound **7c** in 82% yield (entries 1–3, Table 3). Using 4-cyanophenylcopper **1e** and amides **6d** and **6c** the desired products **7d** and **7e** could be prepared in excellent yields (84–96%, entries 4 and 5, Table 3). The reaction of 3-cyanophenylcopper **1f** gave the derivative **7f** in 70% yield (entry 6, Table 3). Furthermore, electron-rich arylcopper species such as compounds **1g** or **1h** could be reacted with various amides **6b** and **6d** leading to the products **7g** and **7h** in good yields (71–74%, entries 7 and 8, Table 3). Using an *ortho*-carbethoxyphenylcopper **1i** as nucleophile, an intramolecular cyclization with the amide took place and led *in situ* to the phenanthridinone derivatives **7i** and **7j** in 92 and 78% yields, respectively (entries 9 and 10, Table 3).

In summary, we have found a very efficient iron-catalyzed cross-coupling reaction for the preparation of polyfunctionalized biphenyls bearing secondary amide functions. Furthermore, this iron-catalyzed protocol provides an straightforward synthesis of functionalized phenanthridinones, which are intensively studied as potential therapeutic agents, due to their properties as poly(ADP-ribose)polymerase-1 (PARP-1) inhibitors.[10] In addition, this method offers an easy access to highly functionalized unprotected quinolinone derivatives. Further extensions of this iron-catalyzed reaction are underway in our laboratories.

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Notes and references

1 A. de Meijere and F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, 2004; J. Tsuji, *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, Chichester, 1995; N. Miyaura, *Top. Curr. Chem.*, 2002, **219.**

2 E. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley-Intersience, New York, 2002.

3 M. Kumada, *Pure Appl. Chem.*, 1980, **52**, 257; T.-Y. Luh, *Acc. Chem. Res.*, 1991, **24**, 257; S. Sengupta, M. Leite, D. S. Raslan, C. Quesnelle and V. Snieckus, *J. Org. Chem.*, 1992, **57**, 4066; E. Shirakawa, K. Yamasaki and T. Hiyama, *Synthesis*, 1998, 1544; R. Giovannini and P. Knochel, *J. Am. Chem. Soc.*, 1998, **120**, 11186; B. H. Lipshutz, G. Bulwo, F. Fernandez-Lazaro, S.-K. Kim, R. Lowe, P. Mollard and K. L. Stevens, *J. Am. Chem. Soc.*, 1999, **121**, 11664; A. Sophia, E. Karlström, K. Itami and J.-E. Bäckvall, *J. Am. Chem. Soc.*, 2000, **122**, 6950; J. Montgomery, *Acc. Chem. Res.*, 2000, **33**, 467; B. H. Lipshutz, *Adv. Synth. Catal.*, 2001, **343**, 313.

4 C. Dai and G. C. Fu, *J. Am. Chem. Soc.*, 2001, **123**, 2719; A. F. Littke and G. C. Fu, *J. Am. Chem. Soc.*, 2001, **123**, 6989; A. F. Littke and G. C. Fu, *Angew. Chem.*, 2002, **114**, 4350; I. D. Hills, M. R. Netherton and G. C. Fu, *Angew. Chem.*, 2003, **115**, 5927; A. C. Frisch, A. Zapf, O. Briel, B. Kayser, N. Shaikh and M. Beller, *J. Mol. Catal. A: Chem.*, 2004, **214**, 231; A. Tewari, M. Hein, A. Zapf and M. Beller, *Synthesis*, 2004, 935; F. Rataboul, A. Zapf, R. Jackstell, S. Harkal, T. Riermeier, A. Monsees, U. Dingerdissen and M. Beller, *Chem. Eur. J.*, 2004, **10**, 2983.

5 (*a*) M. Tamura and J. K. Kochi, *J. Am. Chem. Soc.*, 1971, **93**, 1487; (*b*) M. Tamura and J. K. Kochi, *Synthesis*, 1971, **93**, 303; M. Tamura and J. K. Kochi, *J. Organomet. Chem.*, 1971, **31**, 289; M. Tamura and J. K. Kochi, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 3063; M. Tamura and J. K. Kochi, *Synthesis*, 1971, 303; J. K. Kochi, *Acc. Chem. Res.*, 1974, **7**, 351; S. Neumann and J. K. Kochi, *J. Org. Chem.*, 1975, **40**, 599; R. S. Smith and J. K. Kochi, *J. Org. Chem.*, 1976, **41**, 502; G. Molander, B. Rahn, D. C. Shubert and S. E. Bonde, *Tetrahedron Lett.*, 1983, **24**, 5449.

6 G. Cahiez and S. Marquais, *Pure Appl. Chem.*, 1996, **68**, 669; G. Cahiez and S. Marquais, *Tetrahedron Lett.*, 1996, **37**, 1773; G. Cahiez and H. Avedissian, *Synthesis*, 1998, 1199; K. Shinokubo and K. Oshima, *Eur. J. Org. Chem.*, 2004, 2081; M. A. Fakhfakh, X. Franck, R. Hocquemiller and B. Figadère, *J. Organomet. Chem.*, 2001, **624**, 131; M. Hocek and H. Dvoráková, *J. Org. Chem.*, 2003, **68**, 5773; B. Hölzer and R. W. Hoffmann, *Chem. Commun.*, 2003, 732; W. Dohle, F. Kopp, G. Cahiez and P. Knochel, *Synlett*, 2001, 1901; M. Hojo, Y. Murakami, H. Aihara, R. Sakuragi, Y. Baba and A. Hosomi, *Angew. Chem.*, 2001, **113**, 641; M. Nakamura, A. Hirai and E. Nakamura, *J. Am. Chem. Soc.*, 2001, **122**, 978; E. Alvarez, T. Cuvigny, C. H. du Penhoat and M. Julia, *Tetrahedron*, 1998, **44**, 119; V. Finandanese, G. Marchese, V. Martina and L. Ronzini, *Tetrahedron Lett.*, 1984, **25**, 4805.

7 K. L. Rollick and J. K. Kochi, *Organometallics*, 1982, **1**, 725; A. Fürstner, A. Leitner, M. Méndez and H. Krause, *J. Am. Chem. Soc.*, 2002, **124**, 13856; A. Fürstner and A. Leitner, *Angew. Chem.*, 2002, **114**, 632; A. Fürstner and A. Leitner, *Angew. Chem.*, 2003, **115**, 320; G. Seidel, D. Laurich and A. Fürstner, *J. Org. Chem.*, 2004, **69**, 3950; B. Scheiper, M. Bonnekessel, H. Krause and A. Fürstner, *J. Org. Chem.*, 2004, **69**, 3943; A. Fürstner, D. de Souza, L. Parra-Rapado and J. T. Jensen, *Angew. Chem.*, 2003, **115**, 5516; M. Nakamura, K. Matsuo, S. Ito and E. Nakamura, *J. Am. Chem. Soc.*, 2004, **126**, 3686; T. Nagano and T. Hayashi, *Org. Lett.*, 2004, **6**, 1297; R. Martin and A. Fürstner, *Angew. Chem.*, 2004, **116**, 4045; R. B. Bedford, D. W. Bruce, R. M. Frost, J. W. Goodby and M. Hird, *Chem. Commun.*, 2004, 2822; R. B. Bedford, D. W. Bruce, R. M. Frost and M. Hird, *Chem. Commun.*, 2005, 4161; R. B. Bedford, M. Betham, D. W. Bruce, A. A. Danopoulos, R. M. Frost and M. Hird, *J. Org. Chem.*, 2006, **71**, 1104.

8 I. Sapountzis, W. Lin, C. Kofink, C. Despotopoulou and P. Knochel, *Angew. Chem.*, 2005, **117**, 1682; P. Knochel, I. Sapountzis, T. Korn, W. Lin and C. Kofink, *Ger. Offen.*, 2006, DE102004049508.

9 A. Staubitz, W. Dohle and P. Knochel, *Synthesis*, 2003, 233–242.

10 G. Constantino, A. Macchiarulo, E. Camaioni and R. Pellicciari, *J. Med. Chem.*, 2001, **44**, 3786; J.-H. Li, L. Sedyuk, D. V. Ferraris, G. Xiao, K. L. Tays, P. W. Kletzly, W. Li, S. Lautar, J. Zhang and V. J. Kalish, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1687.

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