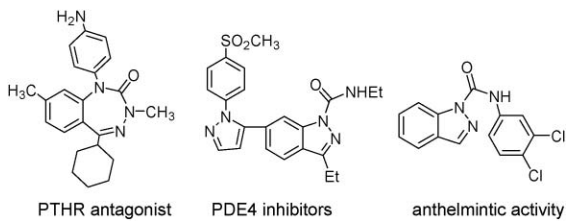
Facile synthesis of 1,3,4-benzotriazepines and 1-arylamide-1*H*-indazoles *via* palladium-catalyzed cyclization of aryl isocyanates and aryl hydrazones under microwave irradiation†

Chune Dong,* Lingli Xie, Xiaohong Mou, Yashan Zhong and Wei Su

Received 20th April 2010, Accepted 19th August 2010
DOI: 10.1039/c0ob00021c

A strategy involving palladium-catalyzed cyclization of halophenyl hydrazones and aryl isocyanates provides a convenient approach to the synthesis of 1,3,4-benzotriazepines (4) or 1-arylamide-1*H*-indazoles (5) in good isolated yields. Microwave irradiation was found to afford high reaction efficiency, while the choice of halophenyl hydrazone had an effect on the pathway of the reaction.

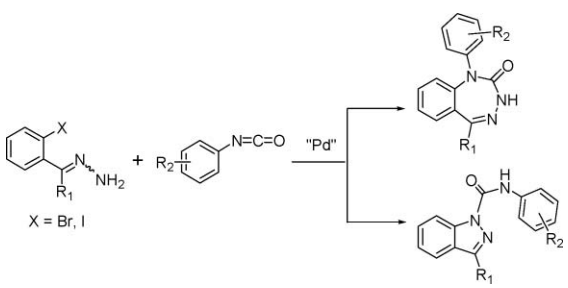
The chemistry of functionalized N-heterocycles, in particular 1,3,4-benzotriazepines and indazoles, continues to be of interest because of the industrial use and biological importance of these classes of compounds.[1] They are known to exhibit a wide range of biological and pharmaceutical properties, including antitumor, anti-inflammatory, and anti-HIV activities; they also act as parathyroid hormone-1 related protein receptor ligands (PTH_1R), phosphodiesterase 4 (PDE4) inhibitors and estrogen receptor ligands *etc* (Scheme 1).[2] Thus, functionalized 1,3,4-benzotriazepines have been used as key building blocks for the preparation of a variety of novel bioactive agents.[3] However, the synthesis of these compounds in a modular fashion is not straightforward. For example, 1,3,4-benzotriazepines are generally prepared by routes involving multiple steps; the products are usually obtained in quite low yields, and toxic reagents are also used,[4] all of which limits the full potential use of these heterocycles in drug discovery. Thus far, in particular, there are no practical and efficient methods for the preparation of 1,3,4-benzotriazepines in one step.



Scheme 1 Pharmaceutically important benzotriazepine and indazoles.

Numerous approaches have been reported for the construction of the indazole skeleton, many of which employ transition metal catalysts and those of palladium in particular.[5] For example, Pd-catalyzed amination reactions have been utilized for indazole synthesis.[6] The Cho group recently described a one-pot synthesis of indazoles from 2-bromobenzaldehydes and aryl hydrazines.[7] More recently, Voskoboynikov and coworkers reported that indazoles can also be obtained by the cyclization of aryl hydrazones.[8] Obviously, these newer methods provide improved results over the classical indazole syntheses. However, the poor availability of certain phosphine ligands as well as the generally drastic reaction conditions (*e.g.*, high temperature, long reaction time) required for these transformations are limitations that preclude the straightforward approach to indazole synthesis. Therefore, the development of efficient methods for the preparation of such compounds from easily available precursors is highly desirable. To our knowledge, however, there are no reports of the facile synthesis of 1-arylamide-1*H*-indazoles under mild conditions by a Pd-catalyzed cyclization reaction approach.

Transition metal-catalyzed cyclization reactions are very attractive methods for organic synthesis that often provide very convenient and effective one-step procedures for ring homologation and give rise to heterocyclic derivatives that are either unavailable or poorly accessible through conventional approaches.[9] Palladium-catalyzed cyclization, in particular, is one of the most powerful methods for forming carbon–carbon and carbon–heteroatom bonds.[10] For the past several years, we have successfully developed some efficient metal catalyst systems for use in cyclocarbonylation[11] and cycloaddition[12] reactions to form five- and six-membered ring heterocycles. In a continuation of our interest in developing new methodology for synthesis of N-heterocycles that are of potential in the pharmaceutical sector, we envisioned that we would be able to direct the metal-catalyzed cyclization reaction pathways so as to form either 1,3,4-benzotriazepines (**4**) or 1-arylamide-1*H*-indazoles (**5**) (Scheme 2). Our hypothesis was that the higher reactivity of C–I bonds compared to C–Br bonds in terms of the rate of Pd(0) oxidative addition, with aryl iodides usually being the most reactive aryl halides in this regard,[13] could be used to effect a divergence of the pathway of cyclization of halophenyl hydrazones (**1** or **2**) with aryl isocyanates **3**.



Scheme 2 One-step synthesis of two different sets of N-heterocycles.

College of Pharmacy, State Key Laboratory of Virology, Wuhan University, Wuhan, 430071, China. E-mail: cdong@whu.edu.cn; Fax: +86-27-68759850; Tel: +86-27-68759586

† Electronic supplementary information (ESI) available: Experimental details. CCDC reference number 773012. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00021c

A divergent synthesis of these two heterocycles from aryl hydrazones and aryl isocyanates was indeed achieved, and we also observed that the structure of the halophenyl hydrazone controlled the reaction manifold. Thus, heating 2-bromophenyl hydrazones (**1**) and isocyanates (**3**) in MeCN at 80 °C under microwave irradiation in the presence of $Pd(OAc)_2$ (0.05 equiv) and PPh_3 (0.2 equiv), using K_2CO_3 as the base, afforded 1,3,4-benzotriazepines (**4**) in moderate to good isolated yields. By contrast, when 2-iodophenyl hydrazones (**2**) were used under otherwise identical reaction conditions, 1-arylamide-1*H*-indazoles (**5**) were obtained smoothly and in good yields.

Synthesis of 1,3,4-benzotriazepines

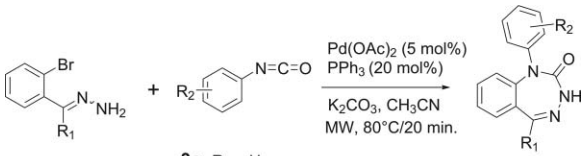
Our studies were initiated by the reaction of 1-(2-bromophenyl)ethanone hydrazone[14] **1a** and *p*-chlorophenyl isocyanate **3d**. After a brief survey of reaction conditions, we found that the solvent, the catalyst and the ligand are critical determinants of the reaction efficiency (see Supporting Information, Table S1†). Ultimately, we found that CH_3CN was the solvent of choice, and $Pd(OAc)_2$ and PPh_3 was the preferred catalyst system for achieving good yields and higher regioselectivity in the reaction of **1a** (1 equiv.) and **3d** (1.2 equiv.) (Table S1, entry 3), and gave the cyclized product **4d** and ring-opened product **6d** in a ratio of 1/1.3 and in 51% overall yield.

Microwave-enhanced organic synthesis has established itself as being superior in many instances when compared to reactions carried out using conventional heating. The use of microwave irradiation often helps to reduce reaction time, increase yields, and improve selectivity.[15] Thus, we next carried out the reaction of halophenyl hydrazones with aryl isocyanates **3** under microwave irradiation. We were pleased to find that under microwave irradiation, for example, the reaction of 1-(2-bromophenyl)ethanone hydrazone **1a** and *p*-chlorophenyl isocyanate **3d** proceeded in a much shorter time (20 min) and with improved yield (93% overall yield) and selectivity (1/1.1 ratio of **4d**/**6d**) when compared to that obtained under the optimized conventional reaction conditions above (Table S1, entry 17 *vs.* entry 3†). As in the majority of cases where microwave irradiation has been found to enhance reactivity and improve yields and selectivity, the improvement we observed in our work may also be attributed to a heating effect, especially when using acetonitrile as solvent, presumably because the heating process in this solvent with a large tan δ value is very fast.

With optimized reaction conditions in hand, we investigated the scope and limitation of this reaction using various aryl hydrazones and aryl isocyanates; representative results are shown in Table 1.

In all the reactions investigated, hydrazones **1** with different substituents at R_1 position exhibited different reactivity toward aryl isocyanates **3**. For example, when less bulky hydrazone **1a** was used, ring-opened side-products were isolated in addition to the desired products, (Table 1, entries 1–5). For example, reaction of **1a** with **3d** gave **4d** in 51% isolated yield, with the side product being obtained in 42% yield (Table 1, entry 4). When *n*-pentyl substituted hydrazone **1b** was reacted with isocyanate **3**, the products were obtained in 35–80% isolated yields along with only trace amounts of ring-opened products (Table 1, entries 6–11). When using hydrazone **1b** with phenyl isocyanate **3a**, the desired product **4f** was obtained in 35% yield together with an unknown compound isolated in *ca.* 28% yield. Unfortunately, we failed in all of our attempts to identify this product (entry 6). In most cases, higher conversions were observed in the reactions of **3** with hydrazone **1c**, which has a bulky phenyl group. The desired products **4** were obtained as the major components, and no ring-opened products were observed (Table 1, entries 12–16).

Table 1 Cyclization reaction of hydrazones with isocyanates catalyzed by palladium under microwave irradiation[a]



1a: R_1 = CH_3
1b: R_1 = n-C_5H_{11}
1c: R_1 = Ph

3a: R_2 = H
3b: R_2 = CH_3-*p*
3c: R_2 = Br-*p*
3d: R_2 = Cl-*p*
3e: R_2 = Cl-*m*

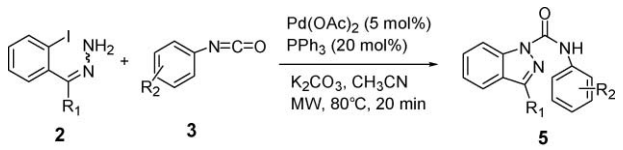
4

Entry	1	3	Conv. (%)[b]	% Yield of 4
1	**1a**	**3a**	48	14 (**4a**)[c]
2	**1a**	**3b**	58	20 (**4b**)[d]
3	**1a**	**3c**	50	24 (**4c**)[e]
4	**1a**	**3d**	93	51 (**4d**)[f]
5	**1a**	**3e**	66	30 (**4e**)[g]
6	**1b**	**3a**	78	35 (**4f**)
7	**1b**	**3b**	75	43 (**4g**)
8	**1b** (*trans*)	**3c**	83	56 (**4h**)
9	**1b** (*cis*)	**3c**	80	56 (**4h**)
10	**1b**	**3d**	95	80 (**4i**)
11	**1b**	**3e**	82	68 (**4j**)
12	**1c**	**3a**	82	43 (**4k**)
13	**1c**	**3b**	88	37 (**4l**)
14	**1c**	**3c**	89	70 (**4m**)
15	**1c**	**3d**	> 98	82 (**4n**)
16	**1c**	**3e**	93	75 (**4o**)

[a] Reaction conditions: 1 mmol of **1**, 1.2 mmol of **3**, 0.05 mmol of $Pd(OAc)_2$, 0.2 mmol of PPh_3, 1.5 mmol of K_2CO_3, in CH_3CN, MW(500 W, 80 °C), 20 min. The temperature in the MW experiments was measured by an internal IR sensor. [b] Conversion was calculated based on the crude ^1H NMR. [c] The ring-opened product was isolated in 12%, [d] 18%, [e] 20%, [f] 42%, [g] 29% yields, respectively.

It should be noted that the substituent on the aryl isocyanates significantly affects the nature of the product. Aryl isocyanates with an electron-donating group or without an aryl substituent gave lower yields. When aryl isocyanates containing electron-withdrawing substituents on the aromatic ring (*i.e.* **3c–e**) were used, the reactions proceeded smoothly in most cases, resulting in the formation of seven-membered ring products **4** in good to excellent conversions and high yields. For example, reaction of **1b** with phenyl isocyanate **3a** formed **4f** in only 35% yield (Table 1, entry 6). Significantly, under the same reaction conditions, *p*-chlorophenyl isocyanate **3d** and *m*-chlorophenyl isocyanate **3e** afforded the products **4i** and **4j** in 80% and 68% isolated yields, respectively (Table 1, entries 10 and 11). In both reactions of **1c** with **3a** and **3b**, good conversions were obtained, but the desired product was isolated in lower yield due to the formation of unknown side products (Table 1, entries 12 and 13). While when **1c** was used for the reaction with aryl isocyanates **3c**–**3e**, the reactions proceeded smoothly, resulting in the formation of **4m**–**4o** in excellent conversions (93–100%) and good isolated yields (70–82%) (Table 1, entries 14–16).

Table 2 One-step synthesis of 1-arylamide-1*H*-indazoles[a]



2a: R_1 = CH_3
2b: R_1 = *n*-C_5H_{11}
2c: R_1 = Ph

3a: R_2 = H
3b: R_2 = CH_3-*p*
3c: R_2 = Br-*p*
3d: R_2 = Cl-*p*
3e: R_2 = Cl-*m*

Entry	2	3	Conv. (%)[b]	% Yield of 5
1	**2a**	**3a**	83	68 (**5a**)
2	**2a**	**3b**	61	46 (**5b**)
3	**2a**	**3c**	51	35 (**5c**)
4	**2a**	**3d**	61	50 (**5d**)
5	**2a**	**3e**	58	43 (**5e**)
6	**2b**	**3a**	88	68 (**5f**)
7	**2b**	**3b**	90	72 (**5g**)
8	**2b**	**3c**	98	84 (**5h**)
9	**2b**	**3d**	> 98	89 (**5i**)
10	**2b**	**3e**	96	75 (**5j**)
11	**2c**	**3a**	78	25 (**5k**)[c]
12	**2c**	**3b**	42	20 (**5l**)[d]
13	**2c**	**3c**	82	12 (**5m**)[e]
14	**2c**	**3d**	52	9 (**5n**)[f]
15	**2c**	**3e**	74	15 (**5o**)[g]

[a] Reaction conditions: 1 mmol of **2**, 1.2 mmol of **3**, 0.05 mmol of $Pd(OAc)_2$, 0.2 mmol of PPh_3, 1.5 mmol of K_2CO_3, in CH_3CN, MW (500 W, 80 °C), 20 min. [b] Conversion was calculated based on the crude ^1H NMR. [c] **4k** was isolated in 48%. [d] **4l** (22%). [e] **4m** (60%). [f] **4n** (33%). [g] **4o** (59%).

Interestingly, the pure *trans* and *cis* isomers of hydrazone **1b** reacted with **3c**, giving the same amount of cyclized product **4h** (Table 1, entries 8 and 9), implying that the hydrazone is undergoing geometric isomerization during the reaction.

Synthesis of the 1-arylamide-1*H*-indazoles

We next attempted to apply the conditions developed for the 2-bromohydrazones to other more reactive 2-iodophenyl hydrazones **2**. We expected that the 1*H*-indazole derivatives would likely be formed from the competitive palladium-catalyzed cyclization of **2** with aryl isocyanates **3** under microwave irradiation. Further experiments revealed the optimal conditions developed above were also generally applicable to the synthesis of the 1-arylamide substituted 1*H*-indazoles **5** (Table 2). It should be noted that the substituent on the aryl hydrazones and aryl isocyanates also has significant effects on the reaction selectivity. Compared to the formation of seven-membered ring products, however, the less bulky hydrazones showed higher reactivity in terms of five-membered ring product formation. When **2a–b** was employed in the reaction, the desired products **5** were obtained in higher conversions and good yields. For example, when the hydrazone **2a** was mixed with aryl isocyanates **3a** and **3d**, the reaction generated **5a** and **5d** in moderate yields (entries 1 and 4), respectively. In the reaction of **2a** with **3e**, **5e** was isolated in 43% yield (entry 5). Almost full conversion and high selectivity were obtained by employing the arylhydrazone **2b** in the above conditions, affording the indazoles in good yields. The reaction of **2b** with **3b** gave the corresponding indazole **5g** in 72% yield (entry 7). Similarly, **2b** reacted smoothly with **3c**, producing **5h** in 84% yield (entry 8). In the case of **3d** and **3e**, **5i** and **5j** were formed in 89% and 75% yields, respectively (entries 9 and 10). However, when phenyl substituted hydrazone **2c** was reacted with **3**, we were surprised to find that the desired products were isolated in quite low yields, along with 1,3,4-benzotriazepines **4**. For example, the reaction of **2c** with **3a** gave the expected product **5k** in 25%, along with **4k** (48%) (entry 11). When **3c** was employed in the reaction, **5m** was isolated in 12% yield, due to the formation of **4m** (60%) (entry 13). These results strongly suggest that the reaction is inherently sensitive to the steric hindrance of the hydrazone and the presence of the substituent at the R_1 position is critical for enforcing this selectivity. The structure of 1-arylamide-1*H*-indazoles was confirmed by the X-ray crystallography of **5d** (Fig. 1).

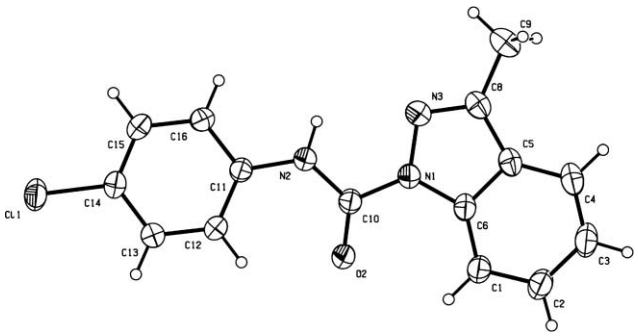
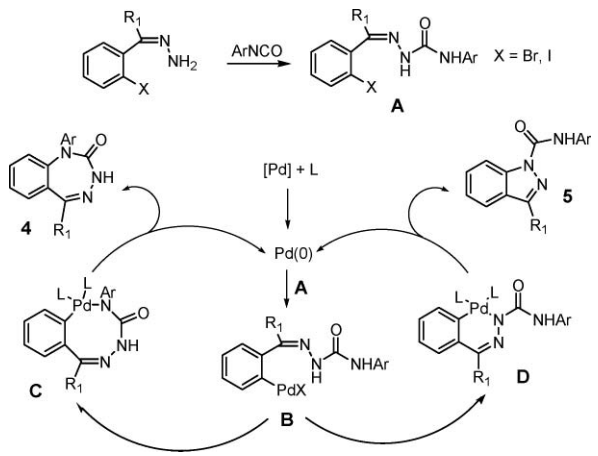


Fig. 1 X-Ray crystal structure of **5d**.

Mechanistic hypothesis

While a precise description of the reaction pathways of the present Pd-catalyzed cyclization reaction still requires comprehensive mechanistic study, we offer a proposal that is presented in Scheme 3. The reaction is initiated by addition of the hydrazone to the isocyanate to afford intermediate **A**, which is observed in all cases. Subsequently, coordination of **A** with the palladium(0) complex leads to the formation of intermediate **B**. Alternatively, intramolecular palladation of **B** generates **C** or **D**. Then reductive elimination affords the desired products **4** or **5**. It is assumed that complex **C** was formed when **1** was used as starting material, while complex **D** was formed when **2** was used in the reaction. This can be explained based on the fact that with sterically hindered



Scheme 3 Mechanistic hypothesis.

hydrazones, the cyclization reaction slower, providing **5** in poor yields with additional formation of **4**.

In conclusion, we have developed a facile, efficient route to 1,3,4-benzotriazepine and 1*H*-indazole derivatives by the palladium-catalyzed cyclization reaction of readily available aryl hydrazones and aryl isocyanates under microwave irradiation. These conditions are applicable to the cyclization of a wide variety of aryl hydrazones and aryl isocyanates, and enable the rapid construction of diverse arrays of 1,3,4-benzotriazepines and 1-arylamide-1*H*-indazoles in a library-like fashion. Notably, these heterocycles are core synthons for many pharmaceutical products. Efforts to study their biological activity further are under way.

Acknowledgements

This work is supported by National Nature Science Foundation of China (20972121, 20872116), the Science Foundation of Ministry of Education for the New Teacher at the University of China (20090141120058), the Important National Science & Technology Specific Projects (No. 2009ZX09301-14), and the startup fund from Wuhan University (Grant 306276315). Prof. John A. Katzenellenbogen is thanked for critical reading of this manuscript. Professor Haibing Zhou is acknowledged for helpful discussions. We also thank Prof. Guofu Qiu for the measurement of NMR.

Notes and references

1 (*a*) M. D. Burke, E. M. Berger and S. L. Schreiber, *Science*, 2003, **302**, 613–618; (*b*) J. Bonjoch and D. Sole, *Chem. Rev.*, 2000, **100**, 3455–3482; (*c*) M. Bradley and L. Weber, *Curr. Opin. Chem. Biol.*, 2000, **4**, 255–256; (*d*) H. L. Fu, C. Dennis, Shala L. Thomas and James P. Snyder, *PCT Int. Appl.*, 2008, 122pp; (*e*) O. Morgenstern, *Pharmazie*, 2000, **55**, 871–891.

2 (*a*) I. M. McDonald, C. Austin, I. M. Buck, D. J. Dunstone, E. Griffin, E. A. Harper, R. A. D. Hull, S. B. Kalindjian, I. D. Linney, C. M. R. Low, M. J. Pether, J. Spencer, P. T. Wright, T. Adatia and A. Bashall, *J. Med. Chem.*, 2006, **49**, 2253–2261; (*b*) I. M. McDonald, C. Austin, I. M. Buck, D. J. Dunstone, J. Gaffen, E. Griffin, E. A. Harper, R. A. D. Hull, S. B. Kalindjian, I. D. Linney, C. M. R. Low, D. Patel, M. J. Pether, M. Raynor, S. P. Roberts, M. E. Shaxted, J. Spencer, K. I. M. Steel, D. A. Sykes, P. T. Wright and W. Xun, *J. Med. Chem.*, 2007, **50**, 4789–4792; (*c*) H. Cerecetto, A. Gerpe, M. Gonzalez, V. J. Aran and C. O. de Ocariz, *Mini-Rev. Med. Chem.*, 2005, **5**, 869–878; (*d*) M. De Angelis, F. Stossi, K. A. Carlson, B. S. Katzenellenbogen and J. A. Katzenellenbogen, *J. Med. Chem.*, 2005, **48**, 1132–1144.

3 L. V. Popova, S. V. Vlasyuk, V. I. Pavlovs'kii and T. L. Karas'ova, *Farmatsevtichnii Zhurnal*, 2002, **2**, 89–92.

4 (*a*) F. R. Alexandre, A. Berecibar, R. Wrigglesworth, L. Perreux, J. Guillon, J. M. Leger, V. Thiery and T. Besson, *Tetrahedron*, 2005, **61**, 8288–8294; (*b*) Z. Jalal A., E. Mustafa M., A. T. Bassam A., L. Stefan and B. Roland, *Heterocycles*, 2008, **75**, 2989–3004; (*c*) G. I. K. S. E. Ivanova, *Zh. Org. Khim.*, 1995, **31**, 1601–1616.

5 (*a*) A. Schmidt, A. Beutler and B. Snovvdovych, *Eur. J. Org. Chem.*, 2008, 4073–4095; (*b*) N. F. Sandra, F. Joan-Carles, F. Pilar, E. Paul and A. Fernando, *QSAR Comb. Sci.*, 2008, **27**, 1267–1273; (*c*) N. Haddad and J. Baron, *Tetrahedron Lett.*, 2002, **43**, 2171–2173; (*d*) M. Y. Watanabe Toshihide and Nishiyama Masakazu., *Angew. Chem., Int. Ed.*, 2000, **39**, 2501–2504.

6 (*a*) J. J. Song and N. K. Yee, *Org. Lett.*, 2000, **2**, 519–521; (*b*) K. Inamoto, M. Katsuno, T. Yoshino, Y. Arai, K. Hiroya and T. Sakamoto, *Tetrahedron*, 2007, **63**, 2695–2711; (*c*) S. P. McClintock, N. Forster, R. Herges and M. M. Haley, *J. Org. Chem.*, 2009, **74**, 6631–6636; (*d*) G. L. Dou and D. Q. Shi, *J. Comb. Chem.*, 2009, **11**, 1073–1077.

7 C. S. L. Cho, K. Dong, N. H. Heo, T. J. Kim and S. C. Shim, *Chem. Commun.*, 2004, 104–105.

8 A. Y. Lebedev, A. S. Khartulyari and A. Z. Voskoboynikov, *J. Org. Chem.*, 2005, **70**, 596–602.

9 (*a*) D. M. D'Souza and T. J. J. Muller, *Chem. Soc. Rev.*, 2007, **36**, 1095–1108; (*b*) F. Bellina and R. Rossi, *Chem. Rev.*, 2010, **110**, 1082–1146.

10 (*a*) S. Diez-Gonzalez, N. Marion and S. P. Nolan, *Chem. Rev.*, 2009, **109**, 3612–3676; (*b*) O. Daugulis, H. Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074–1086; (*c*) K. C. Majumdar and B. Chattopadhyay, *Curr. Org. Chem.*, 2009, **13**, 731–757; (*d*) R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461–1473.

11 (*a*) C. Dong and H. Alper, *Org. Lett.*, 2004, **6**, 3489–3492; (*b*) C. Dong and H. Alper, *J. Org. Chem.*, 2004, **69**, 5011–5014; (*c*) C. Dong and H. Alper, *Tetrahedron: Asymmetry*, 2004, **15**, 35–40.

12 C. Dong and H. Alper, *Tetrahedron: Asymmetry*, 2004, **15**, 1537–1540.

13 (*a*) A. de Meijere and F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, 2nd edn, Wiley-VCH, New York, 2004; (*b*) M. Beller and C. Bolm, *Transition Metals for Organic Synthesis*, Wiley-VCH, New York, 1998; (*c*) J. Tsuji, *Palladium Reagents and Catalysis*, Wiley, New York, 1995.

14 (*a*) A. Shiozawa, K. Narita, G. Izumi, S. Kurashige, K. Sakitama and M. Ishikawa, *Eur. J. Med. Chem.*, 1995, **30**, 85–94; (*b*) S. R. Stauffer, Y. Huang, C. J. Coletta, R. Tedesco and J. A. Katzenellenbogen, *Bioorg. Med. Chem.*, 2001, **9**, 141–150.

15 (*a*) C. O. Kappe, *Angew. Chem., Int. Ed.*, 2004, **43**, 6250 and references therein; (*b*) F. Mavandadi and P. Lidstrom, *Curr. Top. Med. Chem.*, 2004, **4**, 773; (*c*) M. Larhed, C. Moberg and A. Hallberg, *Acc. Chem. Res.*, 2002, **35**, 717; (*d*) B. Wathey, J. Tierney, P. Lidstrom and J. Westman, *Drug Discovery Today*, 2002, **7**, 373; (*e*) S. Caddick and R. Fitzmaurice, *Tetrahedron*, 2009, **65**, 3325–3355.

