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Chemoselective Synthesis of Naphthylamides and Isoquinolinones *via* Rhodium-Catalyzed Oxidative Dehydrogenative Annulation of Benzamides with Alkynes

Zhuangzhi Shi,[a,c] Conghui Tang,[a,c] and Ning Jiao[a,b,*]

[a] State Key Laboratory of Natural and Biomimetic Drugs, Peking University, School of Pharmaceutical Sciences, Peking University, Xue Yuan Rd. 38, Beijing 100191, People's Pepublic of China
Fax: (+86)-010-8280-5297; e-mail: jiaoning@bjmu.edu.cn
[b] State Key Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai 200032, People's Republic of China
[c] These two authors contributed equally to this work

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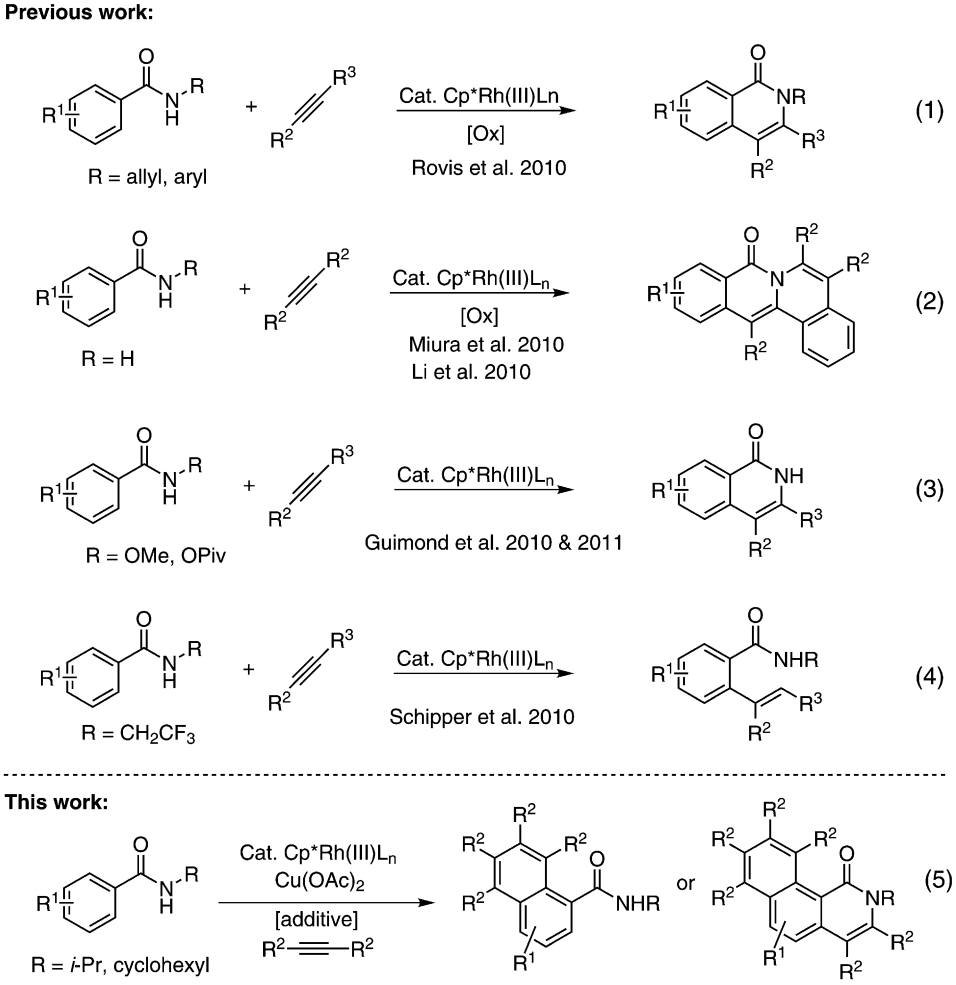
Abstract: A rhodium(III)-catalyzed direct dehydrogenative annulation of benzamides with alkynes through chelating-assisted C–H activation has been developed. Naphthylamide and isoquinolinone derivatives can be chemoselectively obtained by this protocol.

Keywords: alkynes; annulation; benzamides; C–H activation; rhodium

Polyarylated aromatic and heteroaromatic compounds with condensed aromatic cores have attracted considerable attention in the electrochemical, photochemical and functional materials fields because of their stability, their enhanced ability to transport charge, and their fluorescent properties in the solid-state that are brought about by the aryl groups.[1] Transition metal-catalyzed C–H functionalization has been proved to be a powerful method for the construction of heterocycles in organic synthesis.[2] Alkynes as important building blocks and synthons have been widely employed for the construction of multiple arylated compounds.[3,4] Recently, Rh(III)-catalyzed oxidative coupling reactions of acetanilides, benzoic acid, amides, imines, ketones through C–H activation have been developed by Fagnou,[5] Miura,[6] Jones,[7] Glorius,[8] Bergman and Ellman,[9] Shi,[10] Li,[11] Cheng[12] and others.[13] In 2010, Rovis and Hyster developed the oxidative annulation of benzamides and alkynes in the presence of Cu(II) oxidants, and both secondary *N*-alkyl- and *N*-arylbenzamides can be applied as effective substrates [Eq. (1), Scheme 1].[14] The reaction of *N*-unsubstituted benzamides with diarylacetylenes to construct a tetracyclic dibenzoquinolizinone framework was developed by the groups of Miura and Li, respectively [Eq. (2), Scheme 1].[15] Guimond and co-workers found an external oxidant-free process to afford the isoquinolone motif *via* Rh(III)-catalyzed annulation of benzhydroxamic acids with alkynes in which the N–O bond on the directing-group acts as an instrument for C–N bond formation and catalyst release [Eq. (3), Scheme 1].[16] Schipper et al. reported an intermolecular cationic rhodium(III)-catalyzed hydroarylation of alkynes with *N*-mono- or *N,N*-disubstituted benzamides [Eq. (4), Scheme 1).[17] Herein, we want to report a different process that affords the naphthylamide and/or isoquinolinone motifs chemoselectively *via* Rh(III)-catalyzed dehydrogenative annulation of benzamide with alkynes [Eq. (5), Scheme 1].

Our attention was initially drawn to the naphthylamide synthesis from *N*-isopropylbenzamide **1a** with 1,2-diphenylethyne **2a** *via* C–H activation in the presence of $[(RhCp^*Cl_2)_2]$ in toluene under 1 atm O_2. Under these conditions, no desired product **3aa** was observed (entry 1, Table 1). To our delight, 35% of **3aa** and 8% of **4aa** were achieved when $Cu(OAc)_2$ was employed as oxidant (entry 2, Table 1). When dioxane and CH_3CN were evaluated, the reactions only gave low yields (entries 3 and 4, Table 1). It was noted that 73% yield of total products was achieved by using DMF as solvent with a 3:1 ratio of major product **3aa** to **4aa** (entry 5, Table 1). Other oxidants such as AgOAc were less effective than $Cu(OAc)_2$ (entry 6, Table 1). Further studies indicated that the addition of Ag salt in this catalytic system could decrease the yield of **3aa** and increase that of **4aa** (entry 7, Table 1). When the loading of $Cu(OAc)_2$ was increased to 4.1 equiv., 15% of **3aa** and 60% of **4aa**



Scheme 1. Rh(III)-catalyzed reactions of benzamide and alkynes.

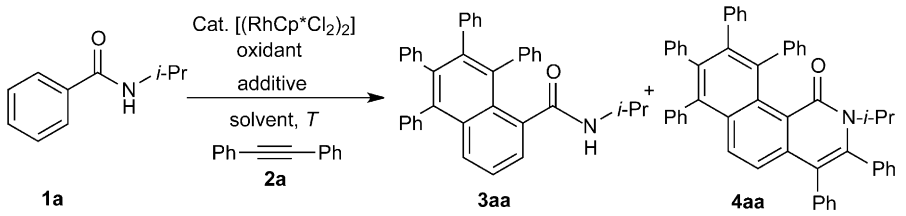
were obtained (entry 8, Table 1). However, other additives such as $AgBF_4$ would decrease the ratio of **4aa** in the total products (entry 9, Table 1).

With this set of conditions in hand, the scope of this amide **3** formation by benzannulation was demonstrated with a variety of substituted *N*-isopropylbenzamides. *N*-Isopropylbenzamide was successfully transformed into the desired product **3aa** in 55% yield with a little **4aa** which could be separated easily *via* column chromatography on silica gel (entry 1, Table 2). The halogen-containing motifs such as **1b** and **1c** worked well in this transformation, giving 1:2 oxidative coupling products **3** under these conditions in moderate to good yields with only trace of 1:3 coupling products **4** (entries 2 and 3, Table 2). The structure of **3ba** was further determined by X-ray (see the Supporting Information).[18] The *meta*- and *ortho*-substituted *N*-isopropylbenzamides could be smoothly converted into the desired products (entries 4 and 5, Table 2). The scope of the intermolecular cyclization reaction was further expanded to other internal alkynes such as **2b**, which produced the desired product **3ab** in 35% yield (entry 6, Table 2). Unfortunately, the terminal alkynes did not work under these conditions.

We next attempted synthesis of isoquinolones under the optimized reaction conditions of **4aa**. The substrate *N*-isopropyl-4-methylbenzamide (**1f)** reacted with diphenylethyne (**2a**) to give the desired product **4fa** in 81% yield (Table 3). Moreover, *tert*-butyl, *n*-pentyl and phenyl groups can also be incorporated in the benzannulated isoquinolone units in this transformation (**4ga**–**4ia**, Table 3). Besides the *N*-isopropyl substrate, *N*-cyclohexyl-4-methylbenzamide (**1j)** can also be converted into the desired compound in 69% yield (**4ja**, Table 3). The scope of the internal alkynes was then investigated with **2b** as the partner. The reactions of **1f** or **1g** with internal alkyne **2b** also proceeded well to afford **4fb** and **4gb** in moderate yields, respectively (Table 3).

On the basis of the known Rh(III)-catalyzed, directing-group assisted C–H bond activation reactions,[5–17,19] a possible mechanism is proposed to account for the present catalytic reaction (Scheme 2). In

Table 1. Rh(III)-catalyzed 1:2 and 1:3 coupling of **1a** with **2a**.[a]



Entry	Oxidation (equiv.)	Solvent	Additive (mol %)	*T* [°C]	Ratio of **3aa** : **4aa**	Yield of **3aa** + **4aa** [%]
1	O_2 (1 atm)	Toluene	no	100		trace
2	$Cu(OAc)_2$ (2.1)	Toluene	no	100	4 : 1	43
3	$Cu(OAc)_2$ (2.1)	Dioxane	no	80	1 : 0	28
4	$Cu(OAc)_2$ (2.1)	CH_3CN	no	80	3 : 1	43
5	**$Cu(OAc)_2$ (2.1)**	**DMF**	**no**	**100**	**3 : 1**	**73**
6	AgOAc (2.1)	DMF	no	100	5 : 1	46
7[b]	$Cu(OAc)_2$ (2.1)	DMF	$AgSbF_6$ (10)	100	1 : 2	67
8[b]	**$Cu(OAc)_2$ (4.1)**	**DMF**	**$AgSbF_6$ (10)**	**120**	**1 : 4**	**75**
9[b]	$Cu(OAc)_2$ (4.1)	DMF	$AgBF_4$ (10)	120	1 : 3	74

[a] **1a** (0.2 mmol), **2a** (0.5 mmol), $[(RhCp^*Cl_2)_2]$ (0.005 mmol), in solvent (1.0 mL), 1 atm of N_2. We did not observe any isoquinolone products like Rovis' work in these reactions

[b] **2a** (0.7 mmol) was used.

the first step, coordination of the nitrogen atom of **1a** to an $Rh(III)L_n$ species and subsequent *ortho* C–H bond activation form a five-membered rhodacycle **A**. Subsequent alkyne insertion generates intermediate **B**. Then the second C–H bond activation on its phenyl ring may occur affording the cyclorhodation intermediate **C**. Subsequently, another alkyne insertion and reductive elimination can generate the naphthylamide **3** and an Rh(I) complex, which is then re-oxidized to $Rh(III)L_n$ species by two atoms of Cu(II) (catalytic cycle a, Scheme 2). Coordination of the formed naphthylamides **3** to $Rh(III)L_n$ species again appears to be the key for the third C–H bond cleavage, this step should be more difficult than the first one, and it is able to be promoted by more reactive $Rh(III)L_n$ species in the presence of $AgSbF_6$. Chemoselective insertion of the third alkyne into the five-membered rhodacycle **E** gives seven-membered rhodacycle **F**. Subsequent reductive elimination takes place to produce the isoquinolone **4** and Rh(I) species. In the presence of another 2 equiv. of $Cu(OAc)_2$, the resulting Rh(I) species can transfer to the catalytically active $Rh(III)L_n$ (catalytic cycle b, Scheme 2).

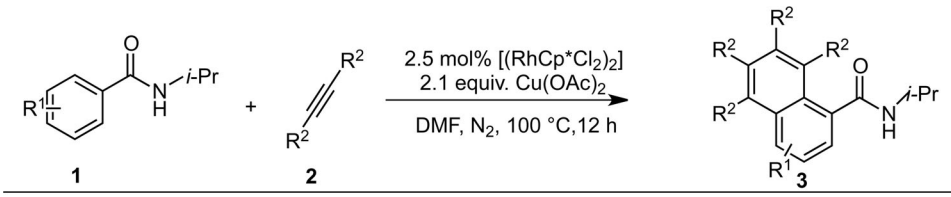
In conclusion, we have developed an rhodium(III)-catalyzed, direct dehydrogenative annulation of benzamides with alkynes through chelating-assisted C–H activation. Naphthylamide and isoquinolinone derivatives can be chemoselectively obtained by this protocol. Multiple C–H bond cleavages are involved in this transformation, which provides a straightforward route to polyarylated heteroaromatic compounds with condensed aromatic cores. Further studies to clearly understand the reaction mechanism and the synthetic applications are ongoing in our laboratory.

Experimental Section

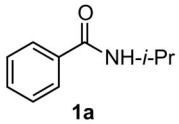
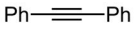
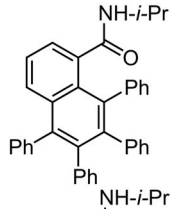
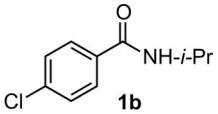
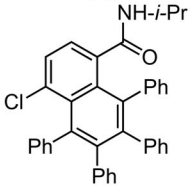
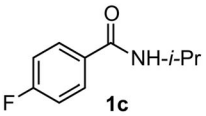
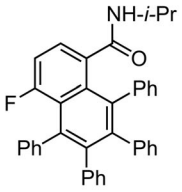
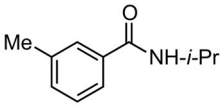
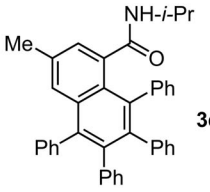
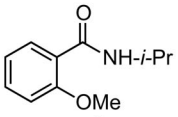
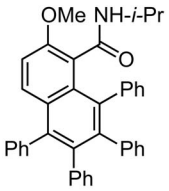
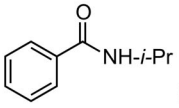
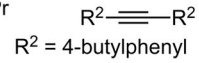
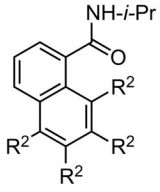
General Procedure for Table 2

To a 20-mL Schlenk tube were added *N*-isopropylbenzamide **1a** (0.2 mmol, 32.6 mg), 1,2-diphenylethyne **2a** (0.5 mmol, 89.0 mg), $[(RhCp^*Cl_2)_2]$ (3.1 mg, 2.5 mol%), $Cu(OAc)_2$ (76.0 mg, 0.42 mmol), followed by addition of DMF (1.0 mL) under N_2. The mixture was heated at 100 °C and stirred overnight under N_2 (1 atm) as monitored by TLC. The solution was then cooled to room temperature, diluted

Table 2. Rh(III)-catalyzed synthesis of naphthylamides *via* cyclization of alkynes with different *N*-isopropylbenzamides.[a]

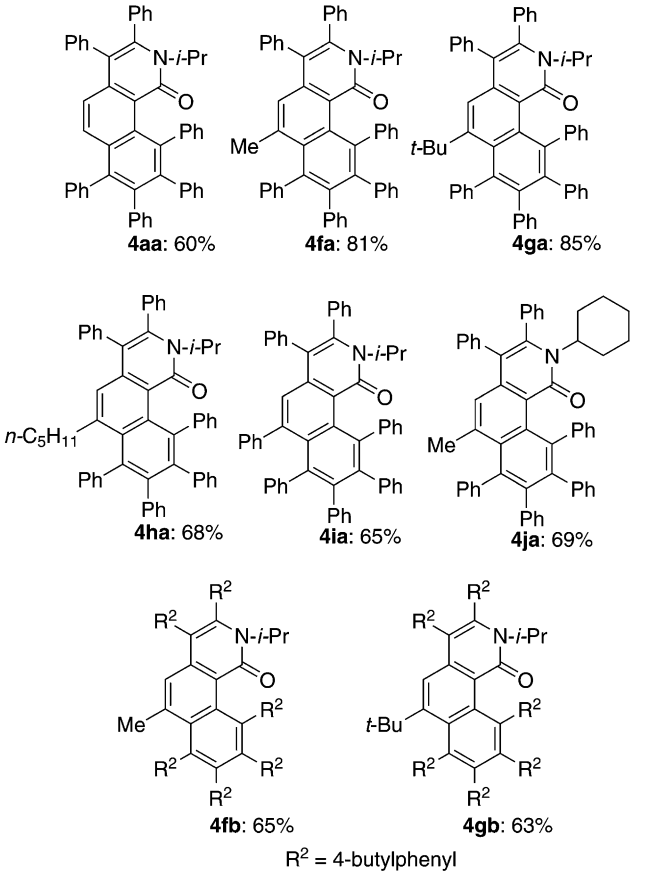


1 **2** **3**

Entry	1	2	Product	Yield [%]
1	 **1a**	 **2a**		**3aa**	55
2	 **1b**	 **2a**		**3ba**	56
3	 **1c**	 **2a**		**3ca**	76
4	 **1d**	 **2a**		**3da**	48
5	 **1e**	 **2a**		**3ea**	56
6	 **1a**	 R^2 = 4-butylphenyl **2b**		**3ab**	35

[a] **1** (0.20 mmol), **2a** (0.50 mmol), [(RhCp*Cl_2)$_2$] (0.005 mmol) and $Cu(OAc)_2$ (0.42 mmol), in DMF (1.0 mL), 1 atm of N_2, 100 °C, overnight; isolated yield; Traces of products **4** were also obtained in some cases as minor products.

Table 3. Rh(III)-catalyzed synthesis of isoquinolones *via* cyclization of alkynes with different *N*-isopropylbenzamides.[a,b]



[a] **1** (0.20 mmol), **2a** (0.70 mmol), $[(RhCp^*Cl_2)_2]$ (0.005 mmol), $AgSbF_6$ (0.02 mmol), and $Cu(OAc)_2$ (0.82 mmol), in DMF (1.0 mL), 1 atm of N_2, 120 °C, overnight; products **3** were also obtained in some cases as minor products.

[b] Isolated yield.

with ethyl acetate (30 mL), washed with H_2O (3 × 10 mL), dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude product was purified by column chromatography on silica gel.

General Procedure for Table 3

To a 20-mL Schlenk tube were added 0.2 mmol *N*-isopropylbenzamide (**1a**), 0.7 mmol 1,2-diphenylethyne (**2a**), $[(RhCp^*Cl_2)_2]$ (3.1 mg, 2.5 mol%), $AgSbF_6$ (6.8 mg, 10 mol%), $Cu(OAc)_2$ (148.0 mg, 0.82 mmol), and the tube was purged with N_2 for three times, followed by addition of DMF (1.0 mL). The mixture was heated at 120 °C under N_2 (1 atm) and stirred overnight as monitored by TLC. The processing procedure was the same as described above

Acknowledgements

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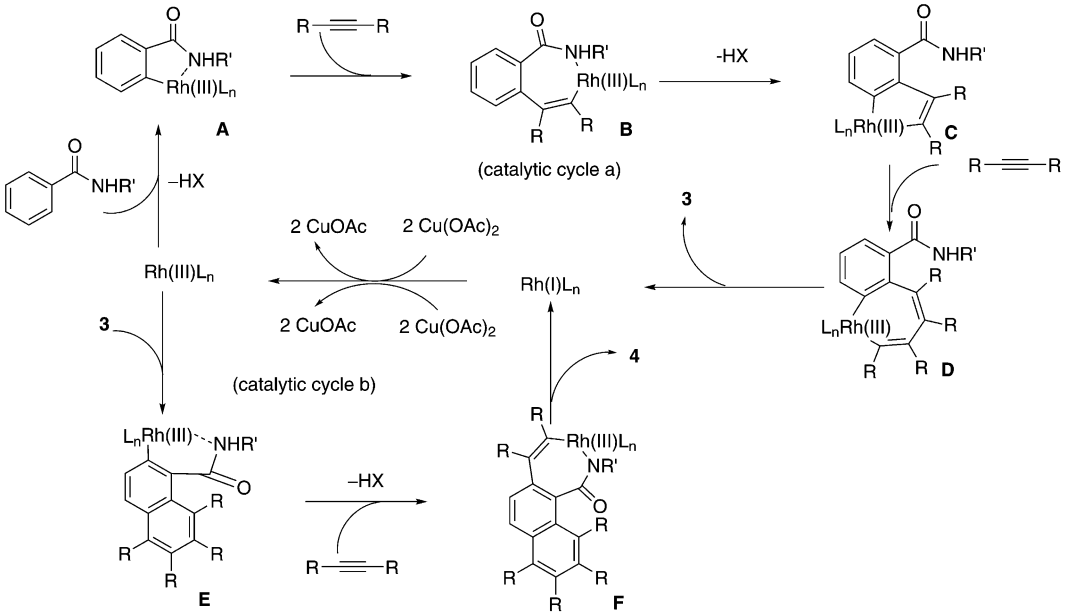
References

[1] a) J. R. Lakowicz, *Principles of Fluorescence Spectroscopy*, Plenum Press, New York, **1999**; b) U. Mitschke, P. J. Bäuerle, *Mater. Chem.* **2000**, *10*, 1471; c) M. D. Watson, A. Fechtenkotter, K. Mullen, *Chem. Rev.* **2001**, *101*,1267; d) J. E. Anthony, *Angew. Chem.* **2008**, *120*, 460; *Angew. Chem. Int. Ed.* **2008**, *47*, 452; e) M. Mazur, P. Krysinski, G. J. Blanchard, *Langmuir* **2005**, *21*, 8802; f) W. Pisula, Z. Tomovic, M. Stepputat, U. Kolb, T.



Scheme 2. Proposed mechanism for the transformation.

Pakula, K. Muellen, *Chem. Mater.* **2005**, *17*, 2641; g) S. Debnath, Q. Cheng, T. G. Hedderman, H. J. Byrne, *J. Phys. Chem. C* **2008**, *112*, 10418; h) T. Okazaki, K. K. Laali, *Adv. Org. Synth.* **2006**, *2*, 353; i) J. N. Moorthy, P. Natarajan, P. Venkatakrishnan, D.-F. Huang, T. J. Chow, *Org. Lett.* **2007**, *9*, 5215.

[2] For recent reviews on C–H activation, see: a) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890; b) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Rev.* **2011**, *111*, 1293; c) C. Copéret, *Chem. Rev.* **2010**, *110*, 656; d) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082; e) M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704; f) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; g) J. L. Bras, J. Muzart, *Chem. Rev.* **2011**, *111*, 1170; h) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315; i) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681; j) R. G. Bergman, *Nature* **2007**, *446*, 391; k) J. F. Hartwig, *Nature* **2008**, *455*, 314; l) S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, *366*, 529.

[3] a) *Acetylene Chemistry: Chemistry, Biology, and Material Science*, (Eds.: P. J. Stang, R. R. Tykwinski, F. Diederich), Wiley-VCH, Weinheim, **2005**; b) R. G. Harvey, *Polycyclic Aromatic Hydrocarbons*, Wiley-VCH, New York, **1997**.

[4] For some annulations of alkynes in our group, see: a) Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui, N. Jiao, *Angew. Chem.* **2009**, *121*, 4642; *Angew. Chem. Int. Ed.* **2009**, *48*, 4572; b) Z. Shi, S. Ding, Y. Cui, N. Jiao, *Angew. Chem.* **2009**, *121*, 8035; *Angew. Chem. Int. Ed.* **2009**, *48*, 7895; c) S. Ding, Z. Shi, Y. Cui, N. Jiao, *Org. Lett.* **2010**, *12*, 1540; d) Z. Shi, Y. Cui, N. Jiao, *Org. Lett.* **2010**, *12*, 1540; e) Z. Shi, B. Zhang, Y. Cui, N. Jiao, *Angew. Chem.* **2010**, *122*, 4130; *Angew. Chem. Int. Ed.* **2010**, *49*, 4036.

[5] a) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474; b) N. Guimond, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 12050.

[6] a) K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2007**, *9*, 1407; b) N. Umeda, H. Tsurugi, T. Satoh, M, Miura, *Angew. Chem.* **2008**, *120*, 4083; *Angew. Chem. Int. Ed.* **2008**, *47*, 4019; c) K. Morimoto, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 2068.

[7] L. Li, W. W. Brennessel, W. D. Jones, *J. Am. Chem. Soc.* **2008**, *130*, 12414.

[8] a) F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9982; b) S. Rakshit, F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9585.

[9] a) K. D. Hesp, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2011**, *133*, 11430; b) A. S. Tsai, M. E. Tauchert, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2011**, *133*, 1248.

[10] a) Y. Li, B.-J. Li, W.-H. Wang, W.-P. Huang, X.-S. Zhang, K. Chen, Z.-J. Shi, *Angew. Chem.* **2011**, *123*, 2163; *Angew. Chem. Int. Ed.* **2011**, *50*, 2115; b) B.-J. Li, H.-Y. Wang, Q.-L. Zhu, Z.-J. Shi, *Angew. Chem.* **2012**, *124*. 4014; *Angew. Chem. Int. Ed.* **2012**, *51*, 3948.

[11] a) F. Wang, G. Song, X. Li, *Org. Lett.* **2010**, *12*, 5430; b) X. Wei, M. Zhao, Z. Du, X. Li, *Org. Lett.* **2011**, *13*, 4636; c) J. Chen, G. Song, C.-L. Pan, X. Li, *Org. Lett.* **2010**, *12*, 5426.

[12] K. Muralirajan, K. Parthasarathy, C.-H. Cheng, *Angew. Chem.* **2011**, *123*, 4255; *Angew. Chem. Int. Ed.* **2011**, *50*, 4169.

[13] For a review, see: T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212.

[14] T. K. Hyster, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 10565.

[15] a) S. Mochida, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Lett.* **2010**, *39*, 744; b) G. Song, D. Chen, C.-L. Pan, R. H. Crabtree, X. Li, *J. Org. Chem.* **2010**, *75*, 7487.

[16] a) N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908; b) N. Guimond, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2011**, *133*, 6449.

[17] D. J. Schipper, M. Hutchinson, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6910.

[18] CCDC 892831 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[19] a) C.-H. Jun, C. W. Moon, D.-Y. Lee, *Chem. Eur. J.* **2002**, *8*, 2422; b) Y. J. Park, C.-H. Jun, *Bull. Korean Chem. Soc.* **2005**, *26*, 877; c) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; d) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147.

