# Synthesis of Polysubstituted Naphthalenes by Iron-Catalyzed [2+2+2] Annulation of Grignard Reagents with Alkynes

Laurean Ilies, Arimasa Matsumoto, Motoaki Kobayashi, Naohiko Yoshikai,<sup>1</sup> Eiichi Nakamura\*

Department of Chemistry, School of Science, The University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113-0033, Japan Fax +81(3)58006889; E-mail: nakamura@chem.s.u-tokyo.ac.jp

Received: 26.06.2012; Accepted after revision: 20.07.2012

**Abstract:** Iron catalyzes the oxidative [2+2+2] annulation of an arylmagnesium compound with two molecules of an internal alkyne via C–H bond activation at 0 °C to produce polysubstituted naph-thalene.

**Key words:** alkynes, annulation, C–H bond activation, iron, naph-thalene

Polycyclic aromatic compounds have received much attention in materials science,<sup>2</sup> resulting in considerable interest in the development of new synthetic routes.<sup>3</sup> An attractive strategy to synthesize these compounds is the annulation of simple starting materials<sup>4</sup> to construct molecular complexity in an expeditious manner. For example, the [2+2+2] annulation of a benzene fragment with two molecules of alkyne<sup>5</sup> represents a concise approach to polysubstituted naphthalenes<sup>6</sup> (cf. Scheme 1, conversion of 1 and 2a to 3a); however, it typically relies on expensive and toxic metal catalysts, such as Pd, Rh, or Ir, and harsh reaction conditions. In concomitant work,<sup>7</sup> one of us has demonstrated that an arylindium reagent can be annulated with two molecules of an internal alkyne using an iron catalyst<sup>8</sup> at 60 °C. We report here that iron catalyzes the annulation of organomagnesium reagents with internal alkynes via C-H bond activation at 0 °C in the presence of an organic dihalide as a mild oxidant (Scheme 1).

We previously reported that iron catalyzes the [4+2]benzannulation between a biphenylmagnesium bromide and an alkyne, probably via formation of a biphenyl ferracycle.<sup>9</sup> We conjectured that a similar ferracycle (**B** in Scheme 1) might be formed via iron-catalyzed carbometalation of an alkyne with an arylmagnesium reagent,<sup>10</sup> followed by base-assisted C–H bond activation.<sup>11</sup> The intermediate B could then undergo insertion of another alkyne,<sup>9</sup> followed by oxidatively induced reductive elimination<sup>12</sup> to produce a polysubstituted naphthalene (Scheme 1).<sup>13</sup> After extensive experimentation (see the Supporting Information for optimization studies), we found that the reaction of phenylmagnesium bromide (1, 1.18 M in THF, 1.0 mL, 1.2 mmol) with diphenylacetylene (2a, 72 mg, 0.40 mmol) in the presence of  $Fe(acac)_3$ (0.04 mmol) as a catalyst, 1,10-phenanthroline (phen, 0.04 mmol) as a ligand, and 1,2-dichloroisobutane (DCIB,

Advanced online publication: 03.09.2012

1.2 mmol) as an oxidant in THF at 0 °C for one hour gave 1,2,3,4-tetraphenylnaphthalene (**3a**) in 73% isolated yield, together with a small amount of carbometalated product **4**. Note that one equivalent of PhMgBr was consumed as a base that takes up the *ortho*-hydrogen atom, a fraction was used for reduction of the iron salt to an active iron species, and a fraction was used in a competing iron-catalyzed oxidative homocoupling<sup>14</sup> to produce a small amount of biphenyl.

The choice of ligand was crucial for this reaction (Table 1). In the absence of a ligand (Table 1, entry 2), only a trace of the desired product **3a** was obtained, together with about 20% of carbometalated product **4**. Diphosphine (Table 1, entry 5) and carbene (Table 1, entry 6) ligands gave the same result as when the reaction was performed in the absence of any ligand (Table 1, entry 2), suggesting ineffective coordination of the active iron species. This observation stands in contrast to previous work using arylindium reagents,<sup>7</sup> where diphosphine ligands were the most effective and 1,10-phenanthroline gave only a trace amount of the desired product. A tridentate ligand (Table

Table 1Investigation of the Reaction Conditions for the Annulationof PhMgBr (1) with Diphenylacetylene  $(2a)^a$ 

Entry	Conditions	Yield of <b>3a</b> (%) <sup>b</sup>	Yield of 4 (%) <sup>b</sup>	Yield of <b>2a</b> (%) <sup>b</sup>
1	standard <sup>a</sup>	68	10	6
2°	without ligand	1	21	63
3°	Bipy <sup>d</sup> as ligand	12	19	55
4 <sup>c</sup>	terpyridine <sup>e</sup> as ligand	0	3	43
5°	Dppf <sup>f</sup> as ligand	2	24	61
6 <sup>c</sup>	IPr·HCl <sup>g</sup> as ligand	1	21	60
7	without DCIB	2	9	72
8	$Fe(acac)_3$ (5 mol%)	39	11	38

<sup>a</sup> Standard reaction conditions: diphenylacetylene (**2a**, 0.40 mmol), PhMgBr (**1**, 1.2 mmol) in THF, Fe(acac)<sub>3</sub> (0.04 mmol), 1,10-phenan-throline (0.04 mmol), and 1,2-dichloroisobutane (1.2 mmol) in THF at 0 °C for 1–3 h.

<sup>b</sup> Determined by GC in the presence of *n*-tridecane as an internal standard.

- <sup>c</sup> Conditions: 2 equiv of 1,2-dichloroisobutane was used.
- <sup>d</sup> Bipy = 2,2'-bipyridine.
- <sup>e</sup> Terpyridine = 2,6-bis(2-pyridyl)pyridine.
- <sup>f</sup> Dppf = 1,1'-bis(diphenylphosphino)ferrocene.
- <sup>g</sup> IPr·HCl = 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride.

SYNLETT 2012, 23, 2381–2384

DOI: 10.1055/s-0032-1317077; Art ID: ST-2012-U0548-L

<sup>©</sup> Georg Thieme Verlag Stuttgart · New York



Scheme 1

Table 2 Iron-Catalyzed Annulation of Arylmagnesium Compounds with Internal Alkynes<sup>a</sup>



<sup>&</sup>lt;sup>a</sup> Reaction conditions: alkyne (0.30–0.40 mmol), Grignard reagent (3 equiv), Fe(acac)<sub>3</sub> (10 mol%), 1,10-phenanthroline (10 mol%), and 1,2-dichloroisobutane (3 equiv) in THF at 0 °C for 1 h. See Supporting Information for details.

<sup>b</sup> Isolated yield.

<sup>e</sup> Determined by <sup>1</sup>H NMR spectroscopy.

Synlett 2012, 23, 2381-2384

<sup>&</sup>lt;sup>c</sup> Determined by GC in the presence of *n*-tridecane as an internal standard.

<sup>&</sup>lt;sup>d</sup> p-Anis = 4-methoxyphenyl.



## Scheme 2

1, entry 4) suppressed not only the desired reaction but also the initial carbometalation step, suggesting inactivation of the active species through strong coordination. In the absence of the oxidant (Table 1, entry 7), a stoichiometric amount of carbometalated product 4 was obtained, together with a trace amount of naphthalene **3a**. Attempts to decrease the catalyst loading (Table 1, entry 8) resulted in a sharp decrease in yield.

The electron density of the substrates did not significantly affect the reaction (Table 2, entries 1–3). A chloride group was tolerated well (Table 2, entry 2), and the five chlorine atoms on **3b** can serve as a platform for further functionalization. A dialkylalkyne (Table 2, entry 4) could also be used, albeit in lower yield. This also stands in contrast to the previous work using arylindium reagents,<sup>7</sup> where dialkylalkynes reacted the best and diarylalkynes gave low yields. A limitation of the present reaction is the lack of regioselectivity, which surfaces as a problem when the alkyne and the Grignard reagent possess different aryl groups (Table 2, entry 5). This limitation was found to be a severe obstacle to achieving versatility of this reaction unless the regioisomeric products can be separated readi-

ly, by chromatography, recrystallization, or sublimation. We speculate that the reason for this poor regioselectivity is the iron-catalyzed isomerization of alkene intermediates such as **A** in Scheme 1. We observed similar isomerization during an iron-catalyzed C–H activation reaction, <sup>11c</sup> when THF was found to accelerate the isomerization reaction, whereas aromatic solvents retarded it. The selectivity of the present annulation reaction was also found to depend on the solvent, and changing THF to a mixture of diethyl ether and benzene resulted in an improved regioselectivity, at the expense of lower conversion (Scheme 2).

To evaluate the products for applications to organic electronic materials, we examined the standard physical properties of 3a-c; they are summarized in Table 3. These compounds show absorption maxima in the ultraviolet region, and increased electron density results in a red shift of the absorption. The blue fluorescence of these compounds is also red-shifted upon increased electron density, and the quantum yield of the methoxy-substituted 3c is also significantly higher (Table 3, entry 3). The electron-rich compound 3c showed a pseudoreversible electron-

Entry	Compound		$\lambda_{abs,max}{}^{a}\left(nm\right)$	$\lambda_{em,max}{}^{a,b}(nm)$	$\Phi_{\mathrm{f}}{}^{\mathrm{a,b}}$	$E_{\mathrm{ox}}^{}\mathrm{c}}(\mathrm{V})$
1		<b>3a</b> X = H	296 283 (sh)	354	0.06	1.04
2		<b>3b</b> X = Cl	302 (sh)	362	0.06	_
3		3c X = OMe	341 (sh)	379 <sup>d</sup>	0.34 <sup>d</sup>	0.81° 1.05

Table 3 Physical Properties of Compounds 3a-c

<sup>a</sup> In CH<sub>2</sub>Cl<sub>2</sub>.

<sup>b</sup> Irradiated at  $\lambda = 300$  nm. The absolute quantum yield was determined by a calibrated integrating-sphere system.

<sup>c</sup> Oxidation potential determined by cyclic voltammetry for a  $CH_2Cl_2$  solution (0.5 mmol/L), using tetrabutylammonium perchlorate (0.1 mol/L) as an electrolyte. The scan rate was 100 mV/s, three cycles per measurement. Glassy carbon was used as the working electrode, platinum wire as the counter electrode and Ag<sup>+</sup>/Ag as a standard electrode.  $E_{ox}$  refers to the anode potential for the irreversible reduction wave; its value was determined by differential pulse voltammetry (DPV) and corrected from a ferrocene standard.

<sup>d</sup> Irradiated at  $\lambda = 330$  nm.

<sup>e</sup> Pseudoreversible.

© Georg Thieme Verlag Stuttgart · New York

chemical oxidation wave at 0.81 V, whereas **3a** showed an irreversible wave at 1.04 V, and the electron-deficient compound **3b** was not oxidized within the potential window of dichloromethane, indicating stabilization of the radical cation by the electron-donating methoxy groups.

In conclusion, we have developed an iron-catalyzed [2+2+2] annulation reaction of arylmagnesium compounds with internal alkynes under oxidative conditions, a reaction that proceeds through C–H bond activation at 0 °C to produce polysubstituted naphthalenes. Efforts to control the regioselectivity of this reaction and to expand the reaction scope toward creation of organic semiconductors<sup>15</sup> are under way.

#### Typical Procedure (Scheme 1)

Diphenylacetylene (2a, 72 mg, 0.40 mmol), 1,2-dichloroisobutane (0.14 mL, 1.2 mmol), Fe(acac)<sub>3</sub> (15 mg, 0.04 mmol), 1,10-phenanthroline (8 mg, 0.04 mmol), and THF (2.0 mL) were placed in an oven-dried Schlenk tube, under argon. A THF solution of PhMgBr (1.0 mL, 1.18 mol/L, 1.2 mmol) was added to the mixture over 5 min at 0 °C. The reaction mixture immediately turned from redbrown to purple. After stirring for 1 h, a 1 M aq solution of HCl was added. After extraction with toluene three times, the combined organic layers were concentrated under reduced pressure to obtain a pale-orange solid. The crude material was purified by silica gel column chromatography (eluent: hexane-toluene = 3:2) to afford 1,2,3,4-tetraphenylnaphthalene (3a) as a white solid (63 mg, 73%). The spectral data were in agreement with those reported in the literature.<sup>16</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 7.66-7.62$  (m, 2 H), 7.41– 7.37 (m, 2 H), 7.27–7.17 (m, 10 H), 6.88–6.80 (m, 10 H). <sup>13</sup>C NMR  $(125 \text{ MHz}, \text{CDCl}_3): \delta = 140.2, 139.3, 138.6, 138.1, 131.7, 131.0,$ 127.2, 126.7, 126.3, 126.1, 125.6, 125.0. GC-MS (EI): m/z (%) = 433 (38), 432 (100) [M<sup>+</sup>], 355 (14), 77 (25).

### Acknowledgment

We thank MEXT for financial support [KAKENHI Specially Promoted Research No. 22000008 to E. N., and Grant-in-Aid for Young Scientists (B) No. 23750100 to L.I.]. A.M. thanks the Japan Society for the Promotion of Science for Young Scientists for a Research Fellowship (No. 21-8684).

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

## **References and Notes**

- Current address: Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore.
- (2) (a) Harvey, R. G. *Polycyclic Aromatic Hydrocarbons*; Wiley-VCH: New York, **1997**. (b) Grimsdale, C. G.; Müllen, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 5592.
  (c) Anthony, J. E. *Angew. Chem. Int. Ed.* **2008**, *47*, 452.
- (3) Feng, X.; Pisula, W.; Müllen, K. Pure Appl. Chem. 2009, 81, 2203.
- (4) Saito, S.; Yamamoto, Y. Chem. Rev. 2000, 100, 2901.

- (5) Selected examples: (a) Herwig, W.; Metlesics, W.; Zeiss, H. J. Am. Chem. Soc. 1959, 81, 6203. (b) Sakakibara, T.; Tanaka, Y.; Yamasaki, S.-I. Chem. Lett. 1986, 797. (c) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. Organometallics 1987, 6, 1941. (d) Pena, D.; Pérez, D.; Guitián, E.; Castedo, L. J. Am. Chem. Soc. 1999, 121, 5827. (e) Yasukawa, T.; Satoh, T.; Miura, M.; Nomura, M. J. Am. Chem. Soc. 2002, 124, 12680. (f) Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. J. Org. Chem. 2003, 68, 6836. (g) Ueura, K.; Satoh, T.; Miura, M. J. Org. Chem. 2007, 72, 5362. (h) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. Angew. Chem. Int. Ed. 2008, 47, 4019. (i) Wu, Y.-T.; Huang, K.-H.; Shin, C.-C.; Wu, T.-C. Chem.-Eur. J. 2008, 14, 6697. (j) Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. Org. Lett. 2009, 11, 5198. (k) Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. J. Org. Chem. 2011, 76, 2867.
- (6) de Koning, C. B.; Rousseau, A. L.; van Otterlo, W. A. L. *Tetrahedron* **2003**, *59*, 7.
- (7) Adak, L.; Yoshikai, N. Tetrahedron 2012, 68, 5167.
- (8) (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. Chem. Rev. 2004, 104, 6217. (b) Enthaler, S.; Junge, K.; Beller, M. Angew. Chem. Int. Ed. 2008, 47, 3317. (c) Plietker, B. Iron Catalysis in Organic Chemistry; Wiley-VCH: Weinheim, 2008. (d) Sherry, B. D.; Fürstner, A. Acc. Chem. Res. 2008, 41, 1500. (e) Czaplik, W. M.; Mayer, M.; Cvengros, J.; Jacobi von Wangelin, A. ChemSusChem 2009, 2, 396. (f) Nakamura, E.; Yoshikai, N. J. Org. Chem. 2010, 75, 6061. (g) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. Chem. Rev. 2011, 111, 1293.
- (9) Matsumoto, A.; Ilies, L.; Nakamura, E. J. Am. Chem. Soc. 2011, 133, 6557.
- (10) (a) Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem. Int. Ed.* 2001, *40*, 621.
  (b) Shirakawa, E.; Yamagami, T.; Kimura, T.; Yamaguchi, S.; Hayashi, T. *J. Am. Chem. Soc.* 2005, *127*, 17164.
  (c) Zhang, D.; Ready, J. M. *J. Am. Chem. Soc.* 2006, *128*, 15050. (d) Yamagami, T.; Shintani, R.; Shirakawa, E.; Hayashi, T. *Org. Lett.* 2007, *9*, 1045.
- (11) (a) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. J. Am. Chem. Soc. 2008, 130, 5858. (b) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. Angew. Chem. Int. Ed. 2009, 48, 2925. (c) Ilies, L.; Asako, S.; Nakamura, E. J. Am. Chem. Soc. 2011, 133, 7672. (d) Ilies, L.; Kobayashi, M.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. Adv. Synth. Catal. 2012, 354, 593. (e) Ilies, L.; Konno, E.; Chen, Q.; Nakamura, E. Asian J. Org. Chem. 2012, 7, in press; DOI: 10.1002/ajoc.201200042.
- (12) Yoshikai, N.; Asako, S.; Yamakawa, T.; Ilies, L.; Nakamura, E. *Chem.–Asian J.* **2011**, *6*, 3059.
- (13) A mechanism involving two successive carbometalations to generate a dienyliron species, followed by cyclization through base-assisted C–H bond activation cannot be excluded.
- (14) (a) Cahiez, G.; Chaboche, C.; Mahuteau-Betzer, F.; Ahr, M. Org. Lett. 2005, 7, 1943. (b) Nagano, T.; Hayashi, T. Org. Lett. 2005, 7, 491. (c) Cahiez, G.; Moyeux, A.; Buendia, J.; Duplais, C. J. Am. Chem. Soc. 2007, 129, 13788.
- (15) (a) Tsuji, H.; Mitsui, C.; Ilies, L.; Sato, Y.; Nakamura, E. J. Am. Chem. Soc. 2007, 129, 11902. (b) Ilies, L.; Tsuji, H.; Sato, Y.; Nakamura, E. J. Am. Chem. Soc. 2008, 130, 4240. (c) Zhu, X.; Mitsui, C.; Tsuji, H.; Nakamura, E. J. Am. Chem. Soc. 2009, 131, 13596.
- (16) Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. Org. Lett. 2009, 11, 5198.