

Iron-catalyzed Benzannulation Reactions of 2-Alkylbenzaldehydes and Alkynes Leading to Naphthalene Derivatives

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Received January 6, 2013

ABSTRACT



An efficient and practical method for the synthesis of naphthalene derivatives via Fe(III)-catalyzed benzannulation of 2-(2-oxoethyl)-benzaldehydes and alkynes has been developed. The system holds the advantages of cheap catalysts, wide substrate scope, and mild reaction conditions.

Aromatic compounds are one of the most widely distributed classes of organic compounds in nature.¹ Many applications can be found in the fields of coal chemical industry, medicinal chemistry, and material science.² Among different aromatic compounds, naphthalene derivatives have attracted much attention in the design of chiral

catalysts³ and advanced functional materials.^{2e,f} Therefore, methods for the synthesis of naphthalene derivatives, especially the polysubstituted ones, is of great importance.

Lewis acid-catalyzed benzannulations of enynals with unsaturated compounds (alkynes, alkenes, and enols) have been proven to be one of the most powerful and reliable approaches to naphthalene derivatives. For example, Yamamoto and co-workers had developed a variety of transition metal-catalyzed benzannulations of enynals with alkynes or enols leading to naphthalenes.^{4a–d} Recently, we reported an efficient route to polysubstituted tetrahydronaphthols via silver-catalyzed [4 + 2] cyclization of 2-alkylbenzaldehydes and alkenes⁵ (Scheme 1, eq 1). It is supposed that the reaction proceeded via Diels–Alder reactions of alkenes with benzo-1,3-butadienols (also called hydroxy-*o*-quinodimethanes or *o*-QDMs), which was generated from the enolization of 2-(2-oxoethyl)-benzaldehydes. Inspired by these results, also as part of our continuous efforts to

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(1) (a) Carmona, M.; Zamarró, M. T.; Blázquez, B.; Durante-Rodríguez, G.; Juárez, J. F.; Valderrama, J. A.; Barragán, M. J. L.; García, J. L.; Díaz, E. *Microbiol. Mol. Biol. Rev.* **2009**, *73*, 71. (b) Schleyer, P. v. R. *Chem. Rev.* **2001**, *101*, 1115.

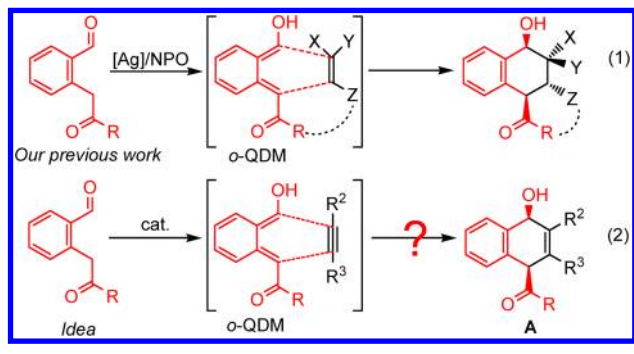
(2) (a) Fang, X.-L.; Tang, R. Y.; Zhang, X.-G.; Zhong, P.; Deng, C.-L.; Li, J.-H. *J. Organomet. Chem.* **2011**, *696*, 352. (b) Meyers, A. I.; Willemsen, J. J. *Tetrahedron Lett.* **1996**, *37*, 791. (c) Medarde, M.; Ramos, A. C.; Caballero, E.; Lopez, J. L. *Tetrahedron Lett.* **1996**, *37*, 2663. (d) Katritzky, A. R.; Zhang, G.; Xie, L. *J. Org. Chem.* **1997**, *62*, 721. (e) Svoboda, J.; Novotná, V.; Kozmik, V.; Glogarova, M.; Weissflog, W.; Diele, S.; Pelzl, G. *J. Mater. Chem.* **2003**, *13*, 2104. (f) Reddy, R. A.; Baumeister, U.; Keith, C.; Tschierske, C. *J. Mater. Chem.* **2007**, *17*, 62. (g) Barrett, A. G. M.; Blaney, F.; Campbell, A. D.; Hamprecht, D.; Meyer, T.; White, A. J. P.; Witty, D.; Williams, D. J. *J. Org. Chem.* **2002**, *67*, 2735. (h) Anthony, J. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 452. (i) Katritzky, A. R.; Li, J.; Xie, L. *Tetrahedron* **1999**, *55*, 8263. (j) Ward, R. S. *Nat. Prod. Rep.* **1995**, *12*, 183. (k) Shore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (l) Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, *28*, 187. (m) *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002. (n) *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, 2005. (o) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3802. (p) Mal, D.; Pahari, P. *Chem. Rev.* **2007**, *107*, 1892. (q) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (r) Yamamoto, Y. *Curr. Org. Chem.* **2005**, *9*, 503. (s) Galan, B. R.; Rovis, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2830.

(3) For a recent review of BINOL-based catalysts, see: Shibasaki, M.; Matsunaga, S. *BINOL. In Privileged Chiral Ligands and Catalysts*; Zhou, Q.-L., Ed.; Wiley: New York, 2011; pp 295–332.

(4) (a) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921. (b) Asao, N.; Aikawa, H. *J. Org. Chem.* **2006**, *71*, 5249. (c) Asao, N.; Sato, K.; Menggenbater; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 3682. (d) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458. (e) Fan, X.-L.; Tang, R.-Y.; Zhang, X.-G.; Zhong, P.; Deng, C.-L.; Li, J.-H. *J. Organomet. Chem.* **2011**, *696*, 352. (f) Zhao, X.; Zhang, X.-G.; Tang, R.-Y.; Deng, C.-L.; Li, J.-H. *Eur. J. Org. Chem.* **2010**, *22*, 4211. (g) Liang, Y.; Jiang, X.; Yu, Z.-X. *Org. Lett.* **2009**, *11*, 5302. (h) Liu, L.; Wei, L.; Zhang, J. *Adv. Synth. Catal.* **2010**, *352*, 1920. (i) Chen, Y.; Chen, M.; Liu, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 6181.

(5) Zhu, S. F.; Liang, R. X.; Jiang, H. F.; Wu, W. Q. *Angew. Chem., Int. Ed.* **2012**, *51*, 10861.

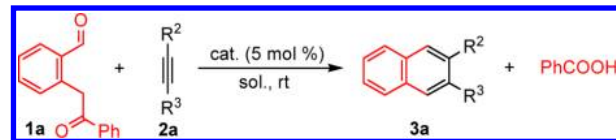
Scheme 1



develop the methods for the synthesis of benzannulated structures, we envisaged that this method might be applied to synthesize 1,4-dihydronaphthol **A** when alkynes were used as the substrates instead (Scheme 1, eq 2).

We initiated our study with the benzannulation of 2-(2-oxoethyl)-benzaldehyde **1a** and phenylacetylene **2a** upon treatment with various Lewis acids. First, four different silver salts were chosen as the catalysts because they were the catalysts of choice for the corresponding alkenes partners.⁵ As summarized in Table 1, when the reactions were conducted in DCE at room temperature by using 5.0 equivalents of phenylacetylene **2a**, excellent yields can be achieved with all four silver salts being tested (entries 1–4). The decarboxylated naphthalene **3a**, not 1,4-dihydronaphthols **A**, was obtained instead. Among four different silver salts, AgSbF₆ gave the product **3a** in almost quantitative yield (entry 4). Further experiments indicated that the reaction can occur smoothly even with 1.1 equivalents of phenylacetylene **2a** at room temperature to afford **3a** in 90% yield after 5 h (entry 5). More surprisingly, it was found that the reaction actually completed in only 20 min (entry 6). Except silver salts, Zn⁶ and Fe⁷ based catalysts were also tested for this transformation owing to their abundance, affordability, and environmental friendliness.⁸ When the reaction was treated with a catalytic amount of ZnCl₂ and FeCl₃ in DCE, the desired naphthalene **3a** could be obtained in excellent yields as well (entries 7–8). It is important to note that almost quantitative yield was obtained in the case of FeCl₃ system (entry 8). Interestingly, only trace product was detected when CuCl₂ was used as the catalyst (entry 9). The reaction worked equally well in DCM (entry 10). The coordinating solvents, such as THF, EtOAc, or toluene, were not suitable for this

Table 1. Optimized Reaction Conditions^a



entry	cat.	1a:2a	sol.	time	yield ^b
1	AgOTf	1.0:5.0	DCE	5 h	87%
2	AgNTf ₂	1.0:5.0	DCE	5 h	90%
3	AgBF ₄	1.0:5.0	DCE	5 h	92%
4	AgSbF ₆	1.0:5.0	DCE	5 h	99%
5	AgSbF ₆	1.0:1.1	DCE	5 h	98%
6	AgSbF ₆	1.0:1.1	DCE	20 min	96% ^c
7	ZnCl ₂	1.0:1.1	DCE	20 min	96%
8	FeCl ₃	1.0:1.1	DCE	20 min	98% ^c
9	CuCl ₂	1.0:1.1	DCE	5 h	trace
10	FeCl ₃	1.0:1.1	DCM	5 h	72%
11	FeCl ₃	1.0:1.1	THF	5 h	trace
12	FeCl ₃	1.0:1.1	EtOAc	5 h	trace
13	FeCl ₃	1.0:1.1	Toluene	5 h	trace
14		1.0:1.1	DCE	5 h	NR
15	TfOH	1.0:1.1	DCE	5 h	trace

^a[1a] = 0.25 M. ^bNMR yield. ^cIsolated yield.

transformation (entries 11–13). The control reactions indicated that the metal salts were essential for the reactions (entry 14). Furthermore, only trace product was detected when TsOH was used instead (entry 15), which implied that the reaction was not a proton-catalyzed reaction.

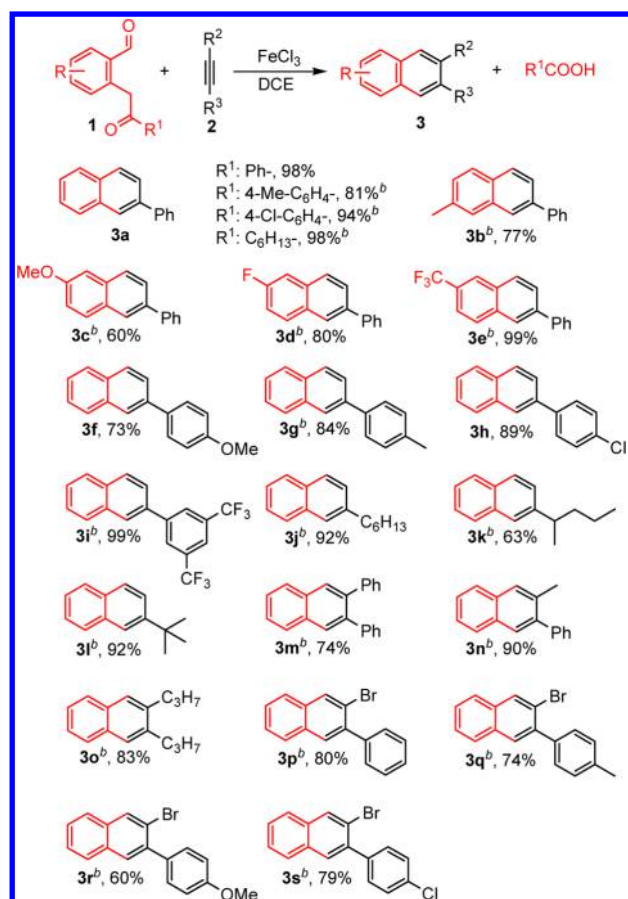
As shown in Table 1, the reaction could be efficiently catalyzed by silver salts, ZnCl₂, or FeCl₃. In consideration of the obvious advantages of iron,^{7,8} the substrate scope was then examined by using FeCl₃ as catalyst (Scheme 2). As summarized in Scheme 2, the catalytic process could be successfully applied to a variety of 2-ethanone benzaldehydes **1** and different kinds of alkynes substrates **2**. For example, when the analogues of 2-ethanone benzaldehyde **1a** were used instead, the reactions proceeded efficiently as well (**3a**–**3e**, Scheme 2). Both electron-donating and electron-withdrawing groups on the phenyl rings had little effects upon the product yields. The yields of the products derived from 2-ethanone benzaldehydes substituted with electron-donating groups are generally lower than those with electron-withdrawing groups. The reactions typically completed in 1–2 h at 60 °C. In addition to phenylacetylene **2a**, various terminal aromatic alkynes derivatives could be effectively reacted with **1a** as well (**3f**–**3i**). The same trends of the reaction yields were observed for different substituted groups on the phenyl rings of phenylacetylene derivatives. For example, the yield for 4-MeO-substituted phenylacetylene was 73% (**3f**); however, the yield for 3,5-difluoromethyl-phenyl-acetylene was almost quantitative (**3i**). Terminal aliphatic alkynes, including linear (**3j**) and branched ones (**3k**, **3l**), were also successfully converted into the desired products (63–92%). In addition to terminal alkynes, internal alkynes (both symmetric and dissymmetric) could

(6) (a) Malosh, C. F.; Ready, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 10240. (b) Patil, N. T.; Singh, V. *Chem. Commun.* **2011**, *47*, 11116. (c) Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11446.

(7) For recent reviews of iron catalysis, see: (a) Bolm, C.; Legros, J.; Pailh, J. L.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (b) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317. (c) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (d) Czaplik, W. M.; Mayer, M.; Cvengros, J.; Wangelin, A. J. V. *ChemSusChem* **2009**, *2*, 396. (e) *Iron Catalysis in Organic Chemistry*; Plietker, B., Ed.; Wiley-VCH: Weinheim, 2008.

(8) Senadi, G. C.; Hu, W.-P.; Hsiao, J.-S.; Vandavasi, J. K.; Chen, C.-Y.; Wang, J.-J. *Org. Lett.* **2012**, *14*, 4478.

Scheme 2. FeCl₃-catalyzed Benzannulation of 2-(2-Oxoethyl)-Benzaldehydes with Alkynes^a

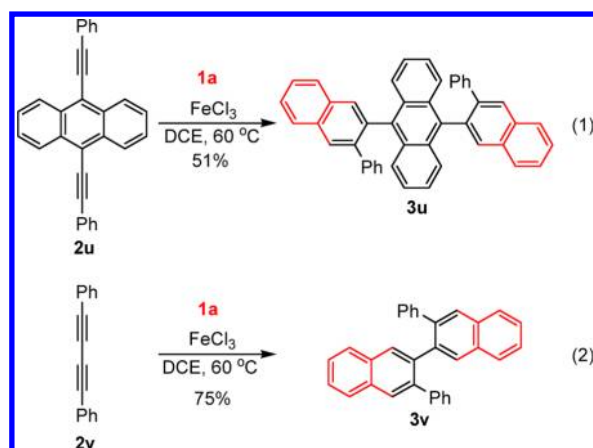


^a Without other noted, the reaction was performed at rt using 5 mol % FeCl₃ under N₂. R₁ = Ph, [I] = 0.25 M. Yields refer to isolated yield. 60 °C.

be used as efficient substrates as well (**3m–3o**). Haloaromatic compounds are extremely valuable not only as precursors of aryl-metals but also as substrates for transition metal-catalyzed cross coupling reactions. When bromoalkynes were used as the substrates, bromonaphthalenes (**3p–3s**) were obtained in 60–80% yields. The bromine atoms would allow for further useful transformations.

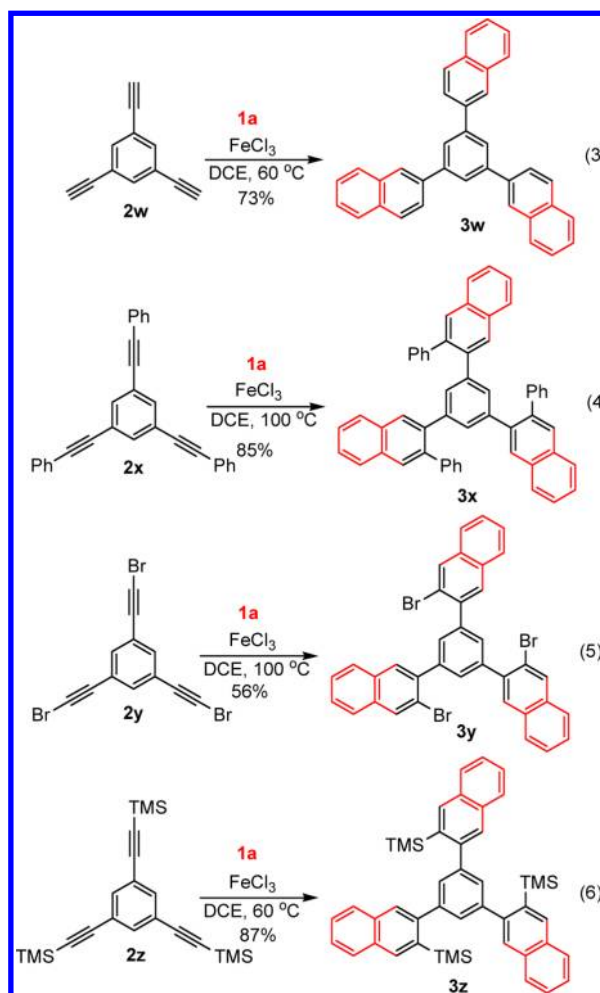
Having established the reaction of 2-ethanone benzaldehydes **1** and alkynes **2** as a reliable and efficient synthetic process, we are curious about the possibility to apply this system to diynes or triynes. Two diynes **2u**, **2v** were then prepared for this purpose (Scheme 3). As expected, under the similar reaction conditions, both diynes could furnish the benzannulation products **3u** and **3v** in good yields (Scheme 3). In addition to diynes, triynes were also investigated. As shown in Scheme 4, terminal alkyne (**2w**), internal alkyne (**2x**), and tribromoalkyne (**2y**) could afford the desired products **3w**, **3x**, **3y** in good to excellent yields. Notably, three bromine atoms could be introduced when tribromoalkyne **2y** was used as substrate, a paddle wheel-type molecule **3y** was formed in 56% yield. More interestingly, the TMS-protected trialkyne **2z**, which is a fragile

Scheme 3. FeCl₃-Catalyzed Benzannulation of 2-(2-Oxoethyl)-Benzaldehydes with Dialkynes

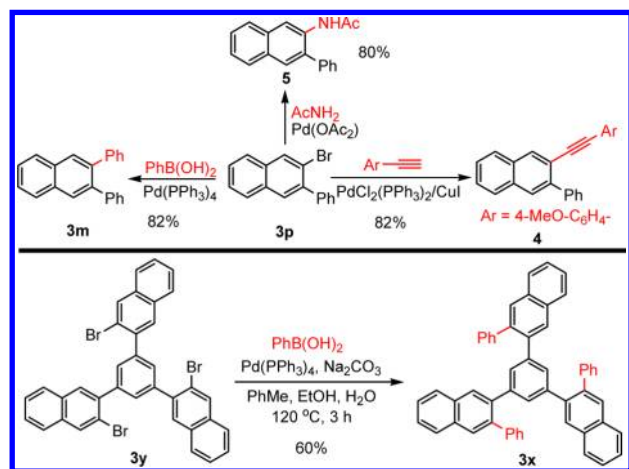


and unstable substrate, could be used as substrate as well. In this case, the desired TMS-substituted product **3z** was obtained in 87% yield.

Scheme 4. FeCl₃-catalyzed Benzannulation of 2-(2-Oxoethyl)-Benzaldehydes with Trialkynes



Scheme 5. Applications of Bromonaphthalene Derivatives

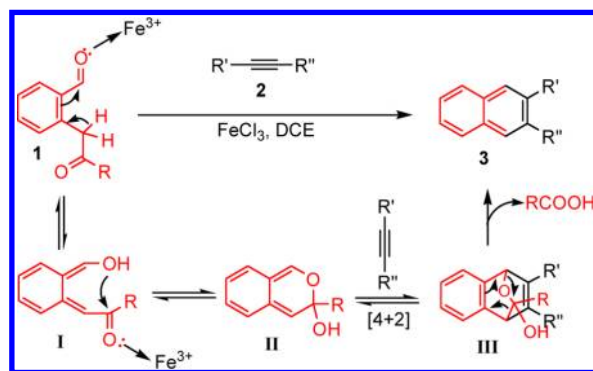


As mentioned above, bromine atoms could be introduced into the naphthalene skeleton when bromoalkynes were used as substrates. With the bromo-naphthalenes in hands, we then explored the further chemical transformations. Taking **3p** and **3y** as examples, different applications were then performed (Scheme 5). For instance, the 2-bromonaphthalene **3p** could be efficiently converted into the corresponding naphthalene derivatives **3m**, **4**, and **5** through the well-established palladium-catalyzed Suzuki coupling reaction, Sonogashira coupling reaction, and Buchwald amination reaction in excellent yields (Scheme 5). Furthermore, the trinaphthalenylbenzene **3x** could also be accessed through the Suzuki coupling reaction from **3y** in 60% yield.

A plausible mechanism as outlined in Scheme 6 was proposed on the basis of our previous work.⁵ The reaction commenced with the enolization of **1** to form the dienol **I**, which then underwent an intramolecular nucleophilic attack to form the hemiketal **II**. The hemiketal **II** was trapped by alkyne **2** leading to the corresponding bridge intermediate **III**. Driven by aromatization, the desired naphthalene product **3** was then formed, accompanying with a carboxylic acid (RCOOH) being released.

In summary, we have developed a very efficient method for the synthesis of naphthalene derivatives *via* iron-catalyzed

Scheme 6. Proposed Mechanism



benzannulation of 2-(2-oxoethyl)-benzaldehydes **1** and alkynes **2**. In addition to the simple alkynes, this system could be successfully applied to different bromoalkynes, diynes, and triynes. This system holds the advantages of wide substrate scope and mild reaction conditions. Furthermore, the obvious merits of FeCl_3 employed in this system make this system even more appealing for construction of different types of naphthalene derivatives. Further synthetic applications are underway in our laboratory.

Acknowledgment. We are grateful to the National NSFC (20902028 and 21172077), the Program for New Century Excellent Talents in University (NCET-10-0403), Guangdong NSF (10351064101000000), and The National Basic Research Program of China (973) (2011CB808600) for financial support. This project was also sponsored by the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry and The Fundamental Research Funds for the Central Universities, SCUT (2012ZZ0038).

Supporting Information Available. Typical experimental procedure and characterization for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.