ORGANIC
LETTERS

2010
Vol. 12, No. 9
1956−1959

Sequential Reaction of Arynes via Insertion into the π-Bond of Amides and Trapping Reaction with Dialkylzincs

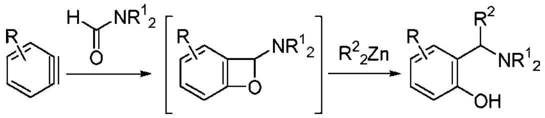
Eito Yoshioka, Shigeru Kohtani, and Hideto Miyabe*

*School of Pharmacy, Hyogo University of Health Sciences, Minatojima, Chuo-ku,
Kobe 650-8530, Japan*

miyabe@huhs.ac.jp

Received February 15, 2010

ABSTRACT



The sequential transformation of arynes into *ortho*-disubstituted arenes is achieved by a one-pot procedure using formamides and dialkylzincs. This reaction proceeded via a route involving the trapping reaction of the formal [2 + 2] cycloaddition adducts or quinone methides generated by the insertion of arynes into the C=O bond of amides.

Arynes are highly strained and kinetically unstable intermediates that have received much attention as powerful electrophiles in organic chemistry.[1,2] In particular, the introduction of *o*-(trimethylsilyl)aryl triflates as mild aryne precursors led to growing activity in this field,[3] resulting in the development of new aryne-based reactions for preparing complex *ortho*-disubstituted arenes.[4−10] In most cases, arynes have been utilized in transition-metal-catalyzed reactions involving cross-coupling processes.[4,5] Recently, much effort has been directed toward the transition-metal-free reactions, which comprise the initial addition of nucleophiles to arynes and the subsequent trapping step with electrophiles.[6−8]

---

(1) For reviews, see: (a) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 483−515. (b) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (c) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (d) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502. (e) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579.

(2) For some recent studies, see: (a) Dockendorff, C.; Sahli, S.; Olsen, M.; Mihau, L.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 15028. (b) Asao, N.; Sato, K. *Org. Lett.* **2006**, *8*, 5361. (c) Soorukram, D.; Qu, T.; Barrett, A. G. M. *Org. Lett.* **2008**, *10*, 3833. (d) Ganta, A.; Snowden, T. S. *Org. Lett.* **2008**, *10*, 5103. (e) Akai, S.; Ikawa, T.; Takayanagi, S.; Morikawa, Y.; Mohri, S.; Tsubakiyama, M.; Egi, M.; Wada, Y.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 7673. (f) Cant, A. A.; Bertrand, G. H. V.; Henderson, J. L.; Roberts, L.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5199.

(3) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

(4) For selected examples of [2 + 2 + 2] cycloaddition, see: (a) Peña, D.; Escudero, S.; Pérez, D.; Guitián, E.; Castedo, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2659. (b) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Am. Chem. Soc.* **1999**, *121*, 5827. (c) Sato, Y.; Tamura, T.; Mori, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2436. (d) Qiu, Z.; Xie, Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 5729. (e) Saito, N.; Shiotani, K.; Kinbara, A.; Sato, Y. *Chem. Commun.* **2009**, 4284.

(5) For selected examples of coupling reactions, see: (a) Yoshikawa, E.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 173. (b) Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2004**, *6*, 2821. (c) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *J. Am. Chem. Soc.* **2006**, *128*, 7426. (d) Liu, Z.; Larock, R. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 2535. (e) Jayanth, T. T.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5921. (f) Xie, C.; Zhang, Y.; Yang, Y. *Chem. Commun.* **2008**, 4810. (g) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2009**, *48*, 391. (h) Gerfaud, T.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 572. For transition-metal-catalyzed insertion into the σ-bond, see: (i) Yoshida, H.; Ikadai, J.; Shudo, M.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2003**, *125*, 6638. (j) Yoshida, H.; Tanino, K.; Ohshita, J.; Kunai, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5052.

(6) For some reactions of arynes with nucleophile followed by electrophile, see :(a) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3935. (b) Zhao, J.; Larock, R. C. *Org. Lett.* **2005**, *7*, 4273. (c) Raminelli, C.; Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 4689. (d) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2006**, *128*, 11040. (e) Yoshida, H.; Morishita, T.; Fukushima, H.; Ohshita, J.; Kunai, A. *Org. Lett.* **2007**, *9*, 3367. (f) Okuma, K.; Nojima, A.; Matsunaga, N.; Shioji, K. *Org. Lett.* **2009**, *11*, 169. (g) Cant, A. A.; Bertrand, G. H. V.; Henderson, J. L.; Roberts, L.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5199. For some reactions involving the nucleophilic addition and subsequent protonation, see: (h) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 99. (i) Jeganmohan, M.; Cheng, C.-H. *Chem. Commun.* **2006**, 2454. (j) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 4689. (k) Ramtohul, Y. K.; Chartrand, A. *Org. Lett.* **2007**, *9*, 1029. (l) Sha, F.; Huang, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 3458.

10.1021/ol100387h © 2010 American Chemical Society
Published on Web 04/02/2010

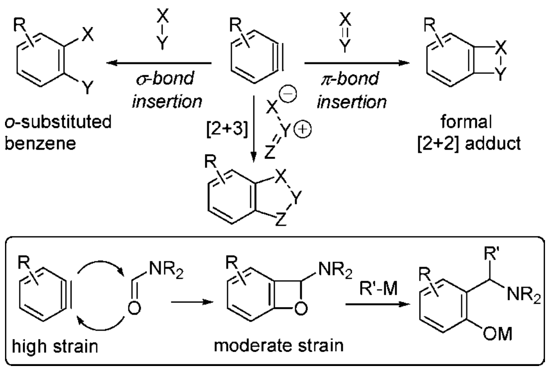
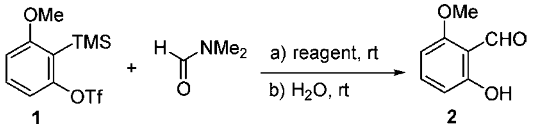


Figure 1. Insertion of arynes into the C═O bond of amides.

When nucleophile and electrophile belong to the same molecule, however, most useful reactions are restricted to insertion into the σ-bond (X−Y)[7] and [2 + 3] cycloaddition[8] (Figure 1). Little success was achieved in the insertion into the π-bond (X═Y) classified as [2 + 2] cycloaddition,[9,10] except for Suzuki's study on the insertion into the C═C bond giving stable benzocyclobutenes.[11] Thus, the insertion of arynes into the carbon−heteroatom double bond is a challenging task. As the only example of the synthetically useful insertion into the π-bond of carbonyl compounds, the 2:1 coupling reaction of arynes and aldehydes was recently developed by Yoshida, Kunai, and others.[12] Therefore, there have been no reports on the trapping reaction of the formal [2 + 2] cycloaddition adducts, generated by the insertion of arynes into the C═O bond, with organometallic reagents. In this paper, we describe the sequential reaction involving the insertion into the carbonyl group of amides and the subsequent trapping process of the intermediates with dialkylzincs. In general, the [2 + 2] adducts containing heteroatoms are considerably unstable due to strain energy. Thus, the success of this sequential transformation reflects the overall difference in the strain energy of arynes and the four-membered intermediates.[11e,f]

Table 1. Reaction of Aryne Precursor **1** with DMF[a]



entry	reagent (3.0 equiv)	DMF (equiv)	solvent	yield[b] (%)
1	TBAF·3H_2O	3.0	CH_3CN	31[c]
2	TBAF	3.0	CH_3CN	56
3	TBAF	3.0	THF	46
4	TBAF	3.0	CH_2Cl_2	43
5	TBAF	3.0	CH_3OH	no reaction
6	TBAF	10	CH_3CN	70
7	TBAF		DMF	84
8	CsF		DMF	72
9	$TBAHF_2$		DMF	67
10	TBAT		DMF	31

[a] Reactions were carried out at rt for 3 h. [b] Isolated yield. [c] The starting material **1** was recovered in 31% yield.

As a preliminary experiment, we selected amides as a carbonyl compound[10] and first probed the utility of *N*,*N*-dimethylformamide (DMF) without organometallic reagents (Table 1). 3-Methoxy-2-(trimethylsilyl)phenyl triflate **1** was employed as an aryne precursor, since the electronic effect of polarized aryne having an electron-donating group was expected to show excellent reactivity and regioselectivity toward the C═O bond. All reactions of triflate **1** with DMF were evaluated at room temperature for 3 h in the presence of several fluoride ion sources. Initially, we allowed triflate **1** to react with 3 equiv of DMF and 3 equiv of TBAF·3H_2O in CH_3CN. The desired salicylaldehyde derivative **2** was obtained in 31% yield, accompanied by 31% yield of the recovered starting material **1** (entry 1). The presence of water influenced the chemical efficiency; thus, improvement in the chemical yield was observed by changing TBAF·3H_2O into anhydrous TBAF (entry 2). In regard to the solvent effect, the replacement of CH_3CN with THF or CH_2Cl_2 led to a decrease in the chemical yields and the reaction in MeOH did not proceed effectively (entries 3−5). Increasing the amount of DMF improved the chemical yields (entry 6). The chemical yield was increased into 84% when DMF was used as a solvent (entry 7). Next, the effect of fluoride ion sources was studied (entries 8−10). The good chemical yields were also observed when CsF or tetrabutylammonium bifluoride ($TBAHF_2$) was employed, although the use of tetrabutylammonium difluorotriphenylsilicate (TBAT) was

---

(7) For selected examples of insertion into the σ-bond, see: (a) Yoshida, H.; Terayama, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2004**, 1980. (b) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340. (c) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2005**, *46*, 6729. (d) Tambar, U. K.; Ebner, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11752. (e) Huang, X.; Xue, J. *J. Org. Chem.* **2007**, *72*, 3965. (f) Yoshida, H.; Mimura, Y.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 2405. (g) Zhang, T.; Huang, X.; Xue, J.; Sun, S. *Tetrahedron Lett.* **2009**, *50*, 1290. (h) Stoltz, B. M.; Ebner, D.; Tambar, U. K.; Storgaard, M.; Ide, N. D. J. A. *Org. Synth.* **2009**, *86*, 161.

(8) For selected examples of [3 + 2] cycloaddition reactions of arynes, see: (a) Jin, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3323. (b) Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219. (c) Huang, X.-C.; Liu, Y.-L.; Liang, Y.; Pi, S.-F.; Wang, F.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1525. (d) Dai, M.; Wang, Z.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, *49*, 6613. (e) Huang, X.; Zhang, T. *Tetrahedron Lett.* **2009**, *50*, 208.

(9) For reports on insertion into the π-bond, see: (a) Gompper, R.; Kutter, E.; Seybold, G. *Chem. Ber.* **1968**, *101*, 2340. (b) Heaney, H.; Jablonski, J. M.; McCarty, C. T. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2903. (c) Nakayama, J.; Yoshida, M.; Simamura, O. *Chem. Lett.* **1973**, 451. (d) Nakayama, J.; Midorikawa, H.; Yoshida, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1063. (e) Aly, A. A.; Mohamed, N. K. A. A.; Hassan, A. A.; Mourad, A.-F. E. *Tetrahedron* **1999**, *55*, 1111. (f) Okuma, K.; Shiki, K.; Sonoda, S.; Koga, Y.; Shioji, K.; Kitamura, T.; Fujiwara, Y.; Yokomori, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 155. (g) Okuma, K.; Okada, A.; Koga, Y.; Yokomori, Y. *J. Am. Chem. Soc.* **2001**, *123*, 7166.

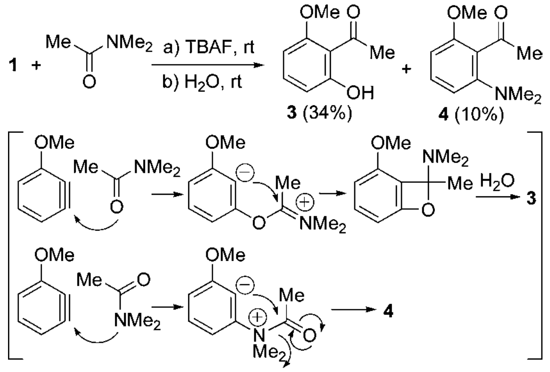
(10) Yaroslavsky, S. *Tetrahedron Lett.* **1965**, *6*, 1503.

(11) (a) Hamura, T.; Ibusuki, Y.; Uekusa, H.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **2006**, *128*, 3534. (b) Hamura, T.; Ibusuki, Y.; Uekusa, H.; Matsumoto, T.; Siegel, J. S.; Baldridge, K. K.; Suzuki, K. *J. Am. Chem. Soc.* **2006**, *128*, 10032. (c) Hamura, T.; Arisawa, T.; Matsumoto, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 6842. (d) Kraus, G. A.; Wu, T. *Tetrahedron* **2010**, *66*, 569. For some examples of the reaction of benzocyclobutenes, see: (e) Suzuki, T.; Hamura, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 2248. (f) Feltenberger, J. B.; Hayashi, R.; Tang, Y.; Babiash, E. S. C.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 3666.

(12) Yoshida, H.; Watanabe, M.; Fukushima, H.; Ohshita, J.; Kunai, A. *Org. Lett.* **2004**, *6*, 4049.

less effective. It is also noteworthy that the high regioselectivity was achieved due to the methoxy group and the formation of regioisomer was not observed.

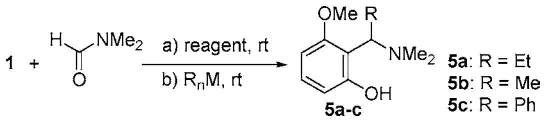
Scheme 1. Reaction of Aryne Precursor **1** with DMA

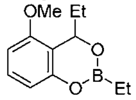
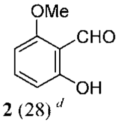


As a related study, in 1965, Yaroslavsky reported the reaction of benzenediazonium chloride or benzenediazonium-2-carboxylate with DMF giving low yields of salicylaldehyde.[10] However, in general, the regiochemical course of insertion into amides was limited to the insertion into the N−C σ-bond, although the various reactions of arynes with amides including sulfinamide, enamide, and urea have recently been investigated.[13] Therefore, the reaction of **1** was next studied with the use of bulky *N*,*N*-dimethylacetamide (DMA) as a solvent instead of DMF (Scheme 1). In marked contrast to DMF, the competitive insertion into the N−C bond of DMA was observed. In the presence of anhydrous TBAF, treatment of **1** with DMA predominantly gave the desired product **3** in 34% yield, accompanied by another adduct **4** in 10% yield as a result of insertion into the N−C σ-bond. Thus, the sterically less hindered formamides are highly promising nucleophiles for the present reaction.[14]

With these results in mind, we next investigated the sequential reaction involving the trapping process of an intermediate with organometallic reagents (Table 2). The key issues of this reaction are the sufficient nucleophilicity of carbonyl oxygen atom toward arynes and the compatibility of carbonyl compounds and organometallic reagents. Among several evaluated reagents, dialkylzincs trapped an intermediate with high activity to form the aminophenols **5a**−**c** by a one-pot procedure. After a solution of triflate **1** and anhydrous TBAF in DMF was stirred at room temperature for 15 min, a solution of Et_2Zn in hexane (1.0 M) was added to the reaction mixture (entry 1). As expected, the desired aminophenol **5a** was obtained in 50% yield after being stirred at room temperature for 12 h. Good yield was obtained when CsF was employed as a fluoride ion source (entry 2). Under the optimized conditions, Me_2Zn and Ph_2Zn worked well, allowing facile incorporation of structural variety (entries 3 and 4). In particular, the reaction using Ph_2Zn proceeded with excellent chemical efficiency to give the adduct **5c** in 97% yield. In contrast, EtMgBr did not work (entry 5). Dialkylzincs are known to be a radical initiator,[15] and we also studied the Et_2Zn-induced radical reactions.[16] To gain further insight into the reaction mechanism, Et_3B was tested as an ethyl radical source under the similar reaction conditions (entry 6). However, the addition of ethyl radical to the intermediate was not observed as a major process; thus, the radical mechanism would be excluded.

Table 2. Trapping Reaction Using Organometallic Reagents[a]



entry	reagents	product (% yield)[b]
1	Et_2Zn, TBAF	**5a** (50)
2	Et_2Zn, CsF	**5a** (71)
3	Me_2Zn, CsF	**5b** (69)
4	Ph_2Zn, CsF	**5c** (97)
5	EtMgBr, CsF	Complex mixture[c]
6	Et_3B, CsF	 **6** (13)  **2** (28)[d]

[a] Reactions were carried out in DMF at rt. [b] Isolated yield. [c] The starting material **1** was recovered in 16% yield. [d] A trace amount of **5a** was obtained.

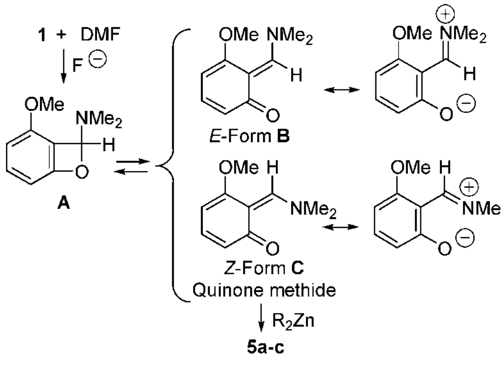


Figure 2. Reaction pathway.

Encouraged by the successful trapping reaction, we calculated the stability of possible intermediates **A-C** (Figure 2).[17] The calculation supports that the quinone methide *E*- and *Z*-forms **B** and **C** would be thermodynamically the stable intermediates. As a major reaction pathway, we assumed that dialkylzincs added to not the four-membered intermediate **A** but the intermediates **B** and **C**.

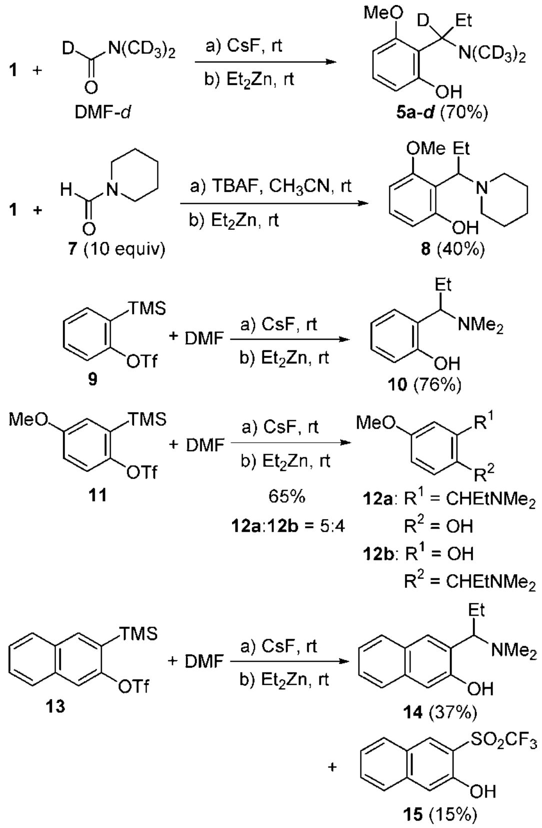
Further investigations using other formamides and aryne precursors were performed (Scheme 2). At first, we allowed

---

(13) (a) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3247. (b) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112. (c) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558. (d) Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 17270. (e) Pintori, D.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168.

(14) Reactions were tested by employing dimethyl carbonate and ethyl formate instead of DMF as a carbonyl compound. However, the desired *ortho*-disubstituted arenes were not obtained.

Scheme 2. Trapping Reaction Using Et_2Zn



DMF-d_7 to react with triflate **1** under similar reaction conditions using CsF and Et_2Zn. As expected, the deuterated product **5a-*d*** was isolated in 70% yield. The one-pot procedure was improved for the reaction with 1-formylpiperidine **7** because this amide could not be used as a solvent. The reaction of triflate **1** with **7** (10 equiv) was carried out in CH_3CN by using anhydrous TBAF to afford the desired adduct **8** in 40%. To test the electronic effect around the triple bond of arynes, the simple triflate **9** was next employed. The nucleophilicity of carbonyl oxygen atom of DMF toward uncharged triple bond was sufficient to bring about insertion of benzyne into the C=O bond to give the adduct **10** in 76% yield. In contrast to triflate **1** having a methoxy group at 3-position, the use of triflate **11** having a methoxy group at the 4-position led to a decrease in regioselectivity to give the adducts **12a** and **12b** in a 5:4 ratio. In the case of triflate **13**, the chemical yield of adduct **14** was decreased to 37% because of the competitive formation of thia-Fries rearrangement product **15**.[18]

In summary, we have demonstrated that the sequential transformation of arynes into *ortho*-disubstituted arenes is achieved by one-pot procedure using formamides and dialkylzincs. This transformation proceeded smoothly via a route involving the trapping reaction of quinone methide intermediates, derived from the formal [2 + 2] cycloaddition adducts, with dialkylzincs.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research (C) (H.M.) and for Young Scientists (B) (E.Y.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan and Astellas Foundation for Research on Metabolic Disorders (H.M.).

Supporting Information Available: Experimental procedure, characterization data, ^1H and ^{13}C NMR spectra, and calculation of intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100387H

---

(15) (a) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *J. Org. Chem.* **1999**, *64*, 9189. (b) Cougnon, F.; Feray, L.; Bazin, S.; Bertrand, M. P. *Tetrahedron.* **2007**, *63*, 11959.

(16) (a) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176. (b) Miyabe, H.; Asada, R.; Takemoto, Y. *Tetrahedron.* **2005**, *61*, 385.

(17) Details are provided in the Supporting Information. For this calculation, the effect of Lewis acidic R_2Zn was neglected.

(18) Dyke, A. M.; Gill, D. M.; Harvey, J. N.; Hester, A. J.; Lloyd-Jones, G. C.; Muñoz, M. P.; Shepperson, I. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 5067.