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Highly Selective Insertion of Arynes into a C(sp)−O(sp^3) σ Bond

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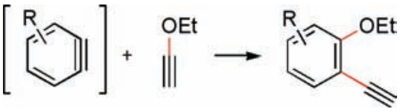
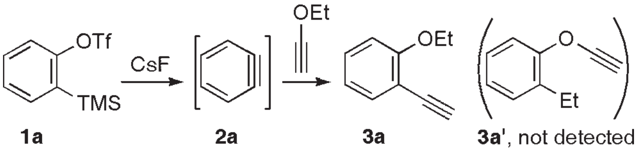
ABSTRACT



Arynes react with ethoxyacetylene to afford 2-ethoxyethynylaryl derivatives through a highly chemo- and regioselective formal insertion of the aryne into the C(sp)−O(sp^3) bond of the alkyne. Computational studies suggest that the reaction does not proceed through a mechanism initiated by the nucleophilic addition of the oxygen atom to the aryne as previously proposed but by the addition of the triple bond of the alkyne to the aryne.

In the past decade, aryne chemistry has undergone an unprecedent revival.[1] This is mainly due to the efficient use of a method to generate benzyne by fluoride-induced β-elimination of *o*-(trimethylsilyl)phenyl triflate (**1a**, Scheme 1), which was first described by Kobayashi and co-workers.[2] The generation of arynes under mild reaction conditions from commercially available or easily prepared precursors,[3] and the compatibility of this method with metal catalysis,[4] led to the development of a highly diverse of new C−C bond-forming processes.[5] In particular, an increasingly developed group of transformations involve aryne insertion into σ bonds.[6] These are interesting reactions from a synthetic point of view, as they allow the one-pot

Scheme 1. Insertion of Benzyne into Ethoxyacetylene



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(1) (a) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. (b) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (c) Peña, D.; Pérez, D.; Guitián, E. *Heterocycles* **2007**, *74*, 89. (d) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215.

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

(3) For example, benzyne precursor **1a** is a commercially available compound which can be easily obtained in high yield from *o*-bromophenol by a one-pot procedure. See: Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Synthesis* **2002**, 1454.

(4) (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) Guitián, E.; Pérez, D.; Peña, D. In *Topics in Organometallic Chemistry*; Tsuji, J., Ed.; Springer-Verlag: Weinheim, 2005; Vol. 14, pp 109−146.

(5) For some recent examples, see: (a) Bhuvaneswary, S.; Jeganmohan, M.; Cheng, C.-H. *Chem. Commun.* **2008**, 5013. (b) Xie, C.; Liu, L.; Zhang, Y.; Xu, P. *Org. Lett.* **2008**, *10*, 2393. (c) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1. (d) Hsieh, J.-C.; Cheng, C.-H. *Chem. Commun.* **2008**, 2992. (e) Xie, C.; Zhang, Y.; Yang, Y. *Chem. Commun.* **2008**, 4810. (f) Worlikar, S. A.; Larock, R. C. *Org. Lett.* **2009**, *11*, 2413. (g) Qiu, Z.; Xie, Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 5729. (h) Yoshida, H.; Morishita, T.; Nakata, H.; Ohshita, J. *Org. Lett.* **2009**, *11*, 373.

(6) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579.

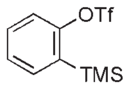
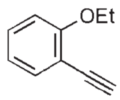
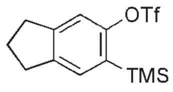
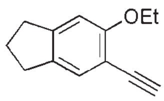
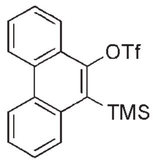
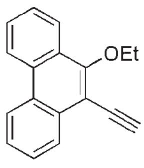
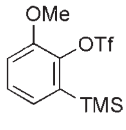
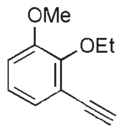
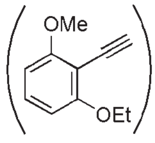
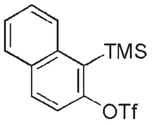
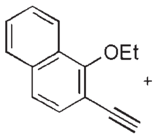
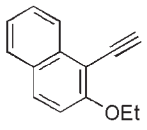
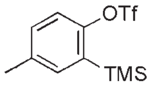
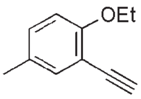
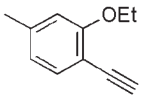
10.1021/ol103001k

ortho-difunctionalization of aromatic rings. Aryne insertion into B−B,[7] Se−Se,[8] C−C,[9] C−N (amides),[10] C=O (amides),[11] CO−Cl (acid chlorides),[12] and C−Br (bromoalkynes)[13] bonds have been recently described. To the best of our knowledge, only two examples of the insertion of arynes into C−O σ bonds have been reported to date: the reaction of benzyne, generated by Kobayashi's method,[2] with styrene oxide,[14] and the unexpected insertion of benzyne, generated by decomposition of benzenediazonium 2-carboxylate, into a C−O bond of ethoxyacetylene, as reported by Stiles et al. in 1962.[15] We thought that the latter approach could be developed into a useful synthesis of *o*-alkoxyarylacetylenes,[16] which are currently obtained by a multistep synthesis involving *o*-halogenation of the corresponding phenols, followed by Williamson alkylation and Sonogashira coupling. We report here the selective ethoxyethynylation of arynes generated by Kobayashi's method and the computational mechanistic study of this intriguing transformation.

The generation of benzyne (**2a**) by treatment of triflate **1a**[3] with CsF at room temperature in the presence of ethoxyacetylene afforded 1-ethoxy-2-ethynylbenzene (**3a**, Scheme 1), resulting from the formal insertion of **2a** into the C(sp)−O(sp^3) bond of the alkyne. Notably, the other possible isomer **3a′**, from the insertion into the C(sp^3)−O(sp^3) bond, was not detected in the reaction mixture. This result confirmed the surprising observation reported by Stiles et al.[15]

This formal insertion reaction was applied to other substituted or polycyclic arynes (Table 1). Moderate to good yields of the corresponding C−O insertion products **3b** (73% yield, entry 2) and **3c** (67%, entry 3) were obtained. Entries 4−6 concern the generation of asymmetric arynes and therefore the possible formation of mixtures of regioisomeric products. For example, the reaction of 3-methoxybenzyne, the aryne generated from triflate **1d** (entry 4), could afford compounds **3d** and **3d′**. However, this insertion took place with complete regioselectivity, affording only isomer **3d** in 54% yield. The structure of the product was established as **3d** by NMR spectroscopy and was confirmed by comparison with a sample obtained by an independent synthesis, as shown in Scheme 2. The *tert*-butylamine-promoted *ortho*-bromination of phenol **4**,[17] followed by alkylation with ethyl bromide, led to compound **5** in a reasonable yield. Palladium-catalyzed cross coupling of this compound with triisopropylsilylacetylene under Sonogashira conditions afforded alkyne **6** in 80% yield. Remarkably, among all the phosphine ligands tested in this reaction, XPhos proved to be superior.[18] Finally, deprotection of the alkyne with fluoride afforded **3d**, which was identical to the product of the reaction of 3-methoxybenzyne with ethoxyacetylene (entry 4, Table 1).

Table 1. Insertion of Arynes into Ethoxyacetylene[a]

entry	precursor	product(s)	yield (%)
1	 **1a**	 **3a**	51
2	 **1b**	 **3b**	73
3	 **1c**	 **3c**	67
4	 **1d**	 **3d**  **3d′**, not detected	54
5	 **1e**	 **3e** +  **3e′** 7:3	43
6	 **1f**	 **3f** +  **3f′** 1:1	54

[a] Reactions were performed using 2 equiv of ethoxyacetylene and 2 equiv of CsF in MeCN at room temperature for 12 h.

Moderate regioselectivity was observed in the reaction of 1,2-naphthyne (entry 5) with ethoxyacetylene, in favor of **3e** (ratio **3e**:**3e′** = 7:3).[19,20] By contrast, the reaction of 4-methylbenzyne, generated from triflate **1f** (entry 6),

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[7] Yoshida, H.; Okada, K.; Kawashima, S.; Tanino, K.; Ohshita, J. *Chem. Commun.* **2010**, *46*, 1763.

[8] Toledo, F. T.; Marques, H.; Comasseto, J. V.; Raminelli, C. *Tetrahedron Lett.* **2007**, *48*, 8125.

[9] (a) Liu, Y. -L.; Liang, Y.; Pi, S. -F.; Li, J. -H. *J. Org. Chem.* **2009**, *74*, 5691. (b) Krishnan, S.; Bagdanoff, J. T.; Ebner, D. C.; Ramtohul, Y. K.; Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 13745. (c) Huang, X.; Xue, J. *J. Org. Chem.* **2007**, *72*, 3965. (d) Yoshida, H.; Kishida, T.; Watanabe, M.; Ohshita, J. *Chem. Commun.* **2008**, 5963. (e) Yoshida, H.; Morishita, T.; Ohshita, J. *Chem. Lett.* **2010**, *39*, 508.

[10] Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168.

[11] Yoshioka, E.; Kohtani, S.; Miyabe, H. *Org. Lett.* **2010**, *12*, 1956.

[12] Yoshida, H.; Mimura, Y.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 2405.

[13] Morishita, T.; Yoshida, H.; Ohshita, J. *Chem. Commun.* **2010**, 640.

[14] Beltrán-Rodil, S.; Peña, D.; Guitián, E. *Synlett* **2007**, 1308.

[15] Stiles, M.; Burkhardt, U.; Haag, A. *J. Org. Chem.* **1962**, *27*, 4715.

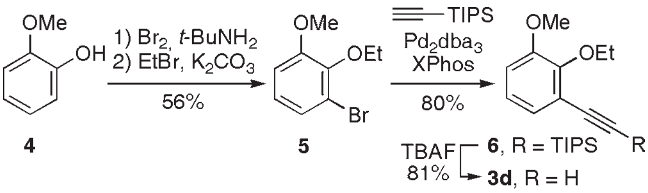
[16] Arylacetylenes are very useful moieties for various synthetic procedures such as azide−alkyne Huisgen cycloaddition, Sonogashira coupling, or poly(aryl acetylene) synthesis.

[17] Ishizaki, M.; Ozaki, K.; Kanematsu, A.; Isoda, T.; Hoshino, O. *J. Org. Chem.* **1993**, *58*, 3877.

[18] XPhos: 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl. See: Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.

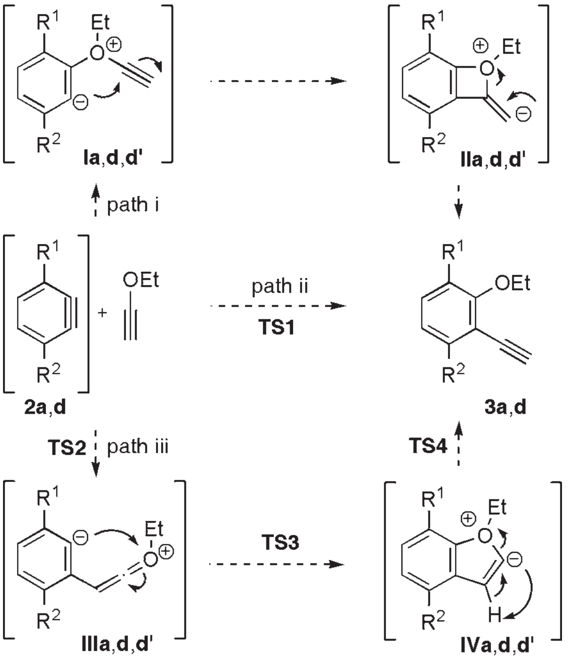
[19] The structures of both regioisomers were confirmed by comparison with a sample of **3e′** obtained by an independent synthesis.

Scheme 2. Alternative Synthesis of Compound **3d**



afforded the two possible isometic products **3f** and **3f′** in a 1:1 ratio. It is known that a methyl group in this position has a limited influence on the reactivity of arynes.[1] Therefore, the lack of regioselectivity in this case supports a mechanism in which the aryne is an intermediate.

Scheme 3. Postulated Mechanistic Pathways[a]



[a] Key: **a**, R^1 = R^2 = H; **d**, R^1 = OMe, R^2 = H; **d'**, R^1 = H, R^2 = OMe.

In a fascinating monograph on aryne chemistry,[1a] Hoffmann proposed a mechanism for the reaction of benzyne with ethoxyacetylene initiated by the nucleophilic attack of the oxygen atom of the alkyne to the triple bond of the aryne to give betaine **Ia** (path i, Scheme 3). Although this could be the more intuitive mechanism based on classical aryne chemistry, the initial formation of betaine **I** would explain neither the highly selective insertion into the C(sp)–O(sp^3) bond of the alkyne nor the regioselective formation of compound **3d**. In particular, it is known that the addition of nucleophiles to 3-methoxybenzyne (**2d**) proceeds with high regioselectivity to give the meta-substituted product, which is attributed to the stabilization of the developing negative charge in the transition state by the polar effect of the methoxy group. Therefore, a mechanism involving path i would probably proceed via intermediate **Id′** (instead of **Id**) to afford compound **3d′**, but this compound was not detected in the reaction mixture. This finding prompted us to initiate a computational study on the mechanistic alternatives of this intriguing transformation.

To study the mechanism of the reaction in detail, DFT calculations were performed at the B3LYP/6-31++G(d,p) level.[20] We analyzed three possible reaction pathways for the reaction of arynes **2a,d** and ethoxyacetylene to afford **3a,d** (Scheme 3). As previously mentioned,[1a] path i involves the initial formation of betaine **Ia**. The aryl carbanion could intramolecularly attack the alkyne to give oxacycle **IIa**, which would evolve to compound **3a** by ring-opening. However, all our attempts to locate intermediates **Ia** and **IIa** were unsuccessful, since all the starting geometries for these species converged upon optimization to the starting materials and to compound **3a**, respectively. Therefore, structures **Ia** and **IIa** are not minima in the potential energy surface.

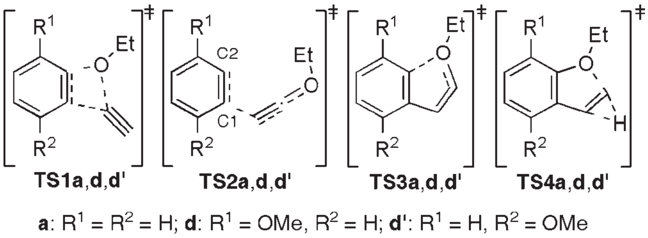


Figure 1. Transition states of pathways shown in Scheme 3.

A concerted pathway involving the one-step insertion of benzyne (**2a**) into the C(sp)–O(sp^3) bond of the alkyne was also considered (path ii). Indeed, it was possible to locate a transition state **TS1a** (Figure 1) that, as predicted, is very asynchronous, with a distance for the forming C–O bond of 1.67 Å, i.e., significantly shorter than that corresponding to the forming C–C bond (2.4 Å). However, this path showed a significant energy barrier of 25.6 kcal/mol (Figure 2).

A more favorable route was found (path iii), and this starts with the nucleophilic addition of the triple bond of ethoxyacetylene to benzyne (**2a**) through the transition state **TS2a**. This step has a very low barrier in terms of electronic energy (2.6 kcal/mol), while the free energy barrier increases to 14.2 kcal/mol due to the entropic contribution associated with a bimolecular reaction (Figure 2). In transition state **TS2a**, the alkyne is perpendicular to the benzyne plane, the forming C1–C bond length is 2.24 Å, while the distance between the O and C2 atoms is 4.47 Å, showing that the formation of this bond has not started. It is worth noting that an Intrinsic Reaction Coordinates (IRC) calculation starting from **TS2a** led to a flat region that corresponds to the zwitterionic structure **IIIa**. However, **IIIa** is not a stationary point and it evolved to structure **IVa** upon optimization (vide infra). The distance between the O and C3 atoms in this structure

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(20) See the Supporting Information for details.

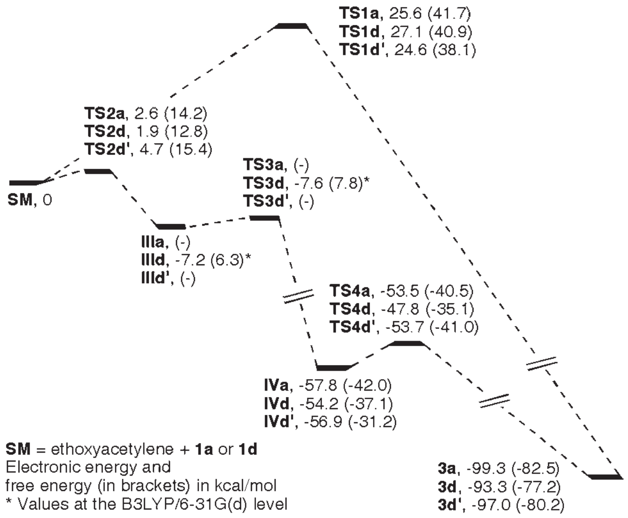

Figure 2. Calculated energetic diagram for paths ii and iii.

is 2.3 Å (Figure 3), suggesting an important contribution of the resonance form corresponding to the free carbene **Va** in the structure of this intermediate. Finally, **IVa** would evolve through simultaneous 1,2-hydrogen migration and ring-opening to afford **3a** in a process with an energy barrier of 4.3 kcal/mol.

The computational study of the reaction of 3-methoxybenzyne (**2d**) with ethoxyacetylene (entry 4, Table 1) afforded similar results. In this case, for the first step of path iii two possible transition states were located: **TS2d**, which would lead to the experimentally isolated product **3d**, and **TS2d′**, which would evolve to regioisomer **3d′** (not isolated experimentally). Notably, the energetic barrier corresponding to **TS2d′** is 2.8 kcal/mol higher than the barrier to **TS2d**, which explains the observed regioselectivity, and both are much lower than the barrier for the concerted reaction via **TS1d,d′** (path ii). It should be mentioned that B3LYP/6-31G(d) calculations showed that in the case of **TS2d**, the transition state progresses to the formation of the zwitterion **IIId**. Remarkably, **TS3d**, which leads to intermediate **IVd**, is located only 0.4 kcal/mol above **IIId**, reflecting how flat this region of the potential energy surface is. This explains the difficulty in finding the minima **IIIa** and **TS3a** for the reaction of ethoxyacetylene with benzyne (**2a**), as mentioned previously. However, with the 6-31++G(d,p) basis set **IIId** and **TS3d** are not stationary points and **TS2d** leads directly to **IVd**. Finally, a facile simultaneous 1,2-hydrogen migration and ring-opening would lead to the final compound **2d** with an electronic barrier of 6.4 kcal/mol.

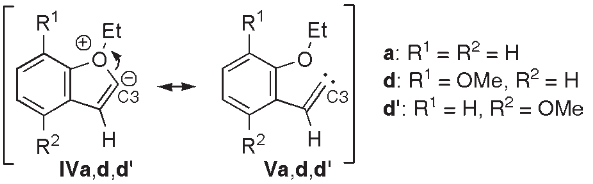

Figure 3. Resonance forms **IVa,d,d′** and **Va,d,d′**.

In conclusion, the synthesis of 2-ethoxyethynylaryl derivatives was performed by a highly chemo- and regioselective insertion of arynes into the C(sp)$-$O(sp^3) bond of ethoxyacetylene. This reaction proceeded under mild conditions and in the absence of metal catalysis. The computational study of this intriguing transformation suggests an unexpected mechanism which explains the observed selectivity.

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Supporting Information Available. Experimental, spectroscopic, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.