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Remarkable Electron-Withdrawing Effect of Ph2P(O)-Ethynyl Group: Ph2P(O)-Ethynyl-Substituted Aryl Halides and Copper Acetylides for Tailor-Made Sonogashira Couplings

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Remarkable Electron-Withdrawing Effect of Ph$_2$P(O)-Ethynyl Group: Ph$_2$P(O)-Ethynyl-Substituted Aryl Halides and Copper Acetylides for Tailor-Made Sonogashira Couplings†

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Electronic effect of Ph$_2$P(O)-ethynyl group in Sonogashira coupling was investigated. Ph$_2$P(O)-ethynylphenyl iodide showed higher reactivity than diiodobenzene because of the electron-withdrawing effect of Ph$_2$P(O) group. Copper acetylide which was in situ prepared from Ph$_2$P(O)-ethyne indicated a poor nucleophilicity and reacted with aryl iodides in Sonogashira coupling, but did not with aryl bromides. This high selectivity enabled practical syntheses of a cyclic phenyleneethynylene and unsymmetrically substituted 9,10-bis(ethynyl)anthracenes.

Phenyleneethynylenes can be used as organic materials for electroluminescence (EL),[1] for organic transistor[2] and for dye-sensitized solar cell.[3] For tuning physical properties of phenyleneethynylenes having rigid structures and highly expanded π-systems, it is required to change lengths of their π-conjugated system. To this end, Sonogashira coupling is one of the powerful technologies to synthesize arylalkynes by using the corresponding aryl halide and terminal alkyne as starting compounds.[4] Although trimethylsilyl (TMS) group is a routinely used protection of terminal ethynes, we developed phosphoryl group (Ph$_2$P(O)) as a new protecting group.[5] The high polarity of the phosphoryl group enabled easy separation of the desired products from the less polar hydrocarbon byproducts.[5c] More recently we succeeded in an one-pot synthesis of arylethynes by invoking dephosphorylation followed by transition metal-catalyzed coupling reactions such as Sonogashira and Migita-Kosugi-Stille couplings.[5a,b] Although the usability of the polar phosphoryl protecting group was exhibited, the electronic effect of the phosphorylethynyl group and the resulting reactivity and selectivity in the coupling reactions have not been explored.

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We are intrigued in these issues and investigated in the reactivities of Ph$_2$P(O)-substituted alkynes and aryl halides in Sonogashira coupling. We report herein that strong electron-withdrawing effect of the Ph$_2$P(O) group enables to tune the reactivities of Ph$_2$P(O)-substituted substrates and reagents.

Firstly, we carried out competitive Sonogashira coupling of phenyl iodides **1** vs **2** with terminal ethyne **3** (Scheme 1). When a 1:1 mixture of **1** and **2** was heated with **3** at 80 °C in the presence of Pd and Cu catalysts, the desired couplings occurred to give **4** (73% yield) and **5** (22% yield). The ratio of **4** and **5** (77:23) reflects the comparable reactivity of **1** and **2** in the coupling reaction, and this result indicates that phosphorylethynyl-substituted iodide **1** reacts more rapidly with **3**.
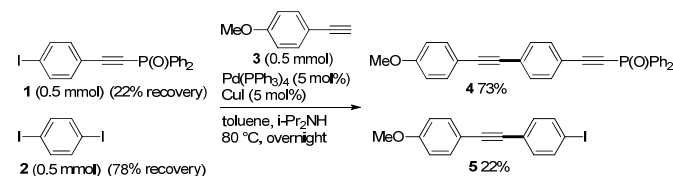
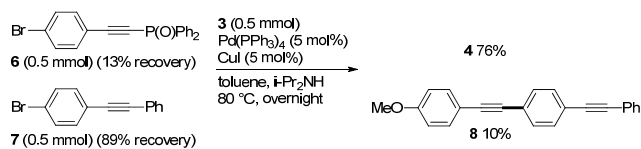Scheme 1 Competitive Sonogashira coupling of 1 VS 2 with 3

Another competitive reaction in bromides **6** vs **7** provided a similar result, and the corresponding coupling products **4** and **8** were obtained in 76% and 10% yields, respectively (Scheme 2). The high reactivities of phosphorylethynyl-substituted halides **1** and **6** observed in these competitive reactions could be explained in terms of an acceleration of the couplings by electron-withdrawing effect of the phosphorylethynyl group.[6]

Scheme 2 Competitive Sonogashira coupling of **6** VS **7** with **3**

In order to gain further insights into the enhanced reactivities of Ph$_2$P(O)-substituted ethynylphenyl halides **1** and **6**, DFT calculations were performed on **1**, **2**, **6** and **7** at the B3LYP/6-31G(d) level (I: LANL2DZ). In Figure 1 are shown the LUMO energy levels of **1** and **2**. The LUMO of **1** is located at lower potential level than that of **2** by 0.38 eV, and this result supports that **1** could undergo oxidative addition of nucleophilic Pd(0) species more rapidly than **2**.[7] DFT calculation demonstrated that the LUMO of **1** is expanded over iodobenzene moiety as well as the Ph$_2$P(O)-ethynyl groups, and thus the electron-withdrawing effect of the phosphoryl group serves efficiently leading to the lower potential energy of LUMO in **1** (Figure 1 inset).[8]
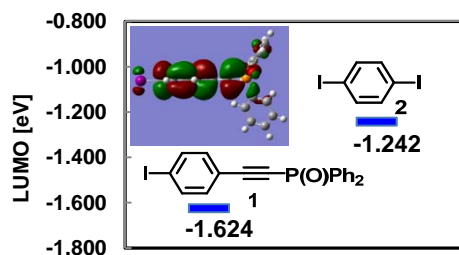
Fig. 1 LUMO energy diagrams of **1** and **2**, and a diagram for LUMO of **1** (inset).

In a competitive coupling of *para*- and *meta*-bromo, phosphorylethynylbenzenes **6** and **9** with **3**, *para*-adduct **4** was furnished in 56% yield as a major product while **10** was obtained in 20% yield (Scheme 3). Consistently, DFT calculations on **6** and **9** presented that electron-withdrawing effect of the phosphorylethynyl group served more efficiently in **6** than in **9** to provide the lower LUMO energy level of **6** (Figure 2).[9]
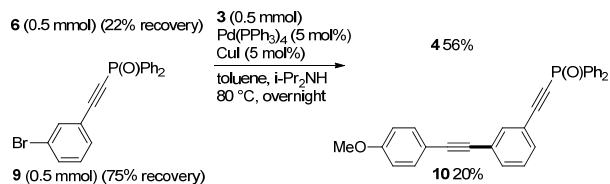
Scheme 3 Competitive Sonogashira coupling of **6** VS **9** with **3**
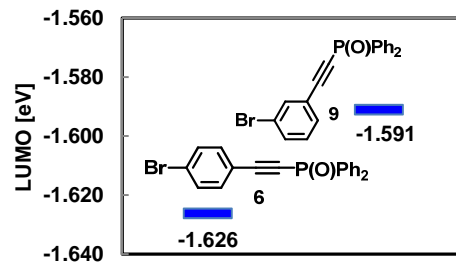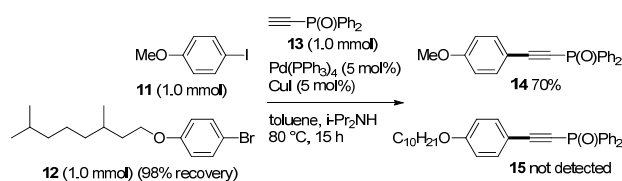
Fig. 2 LUMO energy diagrams of **6** and **9**.

Secondly, unique selectivity of iodide vs bromide in Sonogashira coupling was investigated. When a mixture of phenyl iodide **11** and bromide **12** was subjected to Sonogashira coupling with **13**, the iodide **11** selectively underwent the desired coupling (**14**: 70%, **15**: not detected), and **12** was recovered quantitatively (Scheme 4).

Scheme 4 Competitive Sonogashira coupling of **11** VS **12** with **13**

In intramolecular Br vs I-competitive couplings in **16a-c**, only phenyl iodide moieties reacted with **13** to afford the corresponding phosphorylethynyl-substituted bromobenzenes **17a-c** in moderate to good yields (Scheme 5). The bromides thus obtained **17a-c** reacted with **3** in the consecutive coupling to provide **18a-c**, respectively.
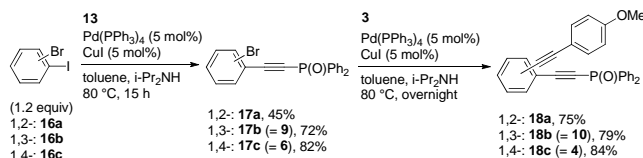
Scheme 5 Preferential Sonogashira coupling of iodide moiety in **16** with **13**

When two equivalents of **13** were used in Sonogashira coupling of **16c**, **17c** was obtained in 96% yield while bis(Ph$_2$P(O)-ethynyl) adduct **19** was formed in only 2% yield (Scheme 6). These results demonstrate that phenyl iodide undergoes Sonogashira coupling with phosphorylethyne **13**, but that the bromide does not.

Scheme 6 Sonogashira coupling of **16c** with an excess amount of **13**

When phosphorylethyne **13** and 4-phosphorylethynylphenylethyne **20** were subjected to a competitive coupling with iodide **11**, the diyne **20** reacted more rapidly, and **4** and **14** were provided in 69% and 18% yields, respectively (Scheme 7).
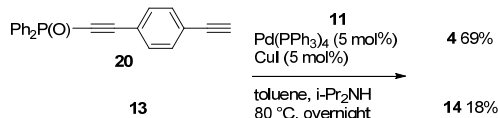
Scheme 7 Competitive Sonogashira coupling of 20 VS 13 with 11

In order to rationalize a low reactivity of **13** in Sonogashira coupling, HOMO energy levels of copper acetylides (**3-Cu**, **20-Cu** and **13-Cu**) which might be in situ produced in the coupling were calculated at the B3LYP/6-31G(d) (Cu: LANL2DZ)) level (Figure 3). The low HOMO energy level of **13-Cu** indicated the low nucleophilicity which enabled transmetallation with only reactive iodopalladium species which was in situ produced from the oxidative addition of Pd(0) to aryl iodide.
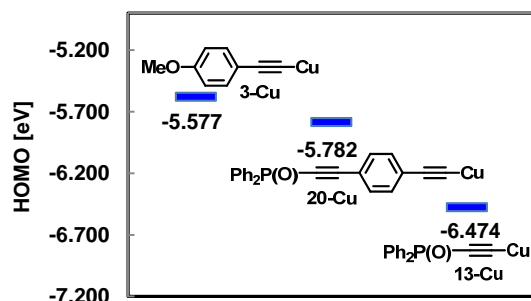

Fig. 3 HOMO energy diagrams of 3-Cu, 20-Cu and 13-Cu.

Although the high energy level of copper acetylide promoted Sonogashira coupling as shown in Figure 3, the similar electronic effect was observed in click reaction. For instance, **21** reacted with benzyl azide **22** rapidly to give triazole **23** (79%, 2 h). In contrast to this, **13** provided sluggishly **24** (73% (6 h), 42% (2 h)) (Scheme 8). The difference of reaction rates in these click reactions was also rationalized in terms of the HOMO energy levels of the corresponding Cu acetylides which could be obtained from **21** and **13**, respectively; HOMO energy level: -5.909 eV for **21-Cu**, -6.474 eV for **13-Cu**.[10]
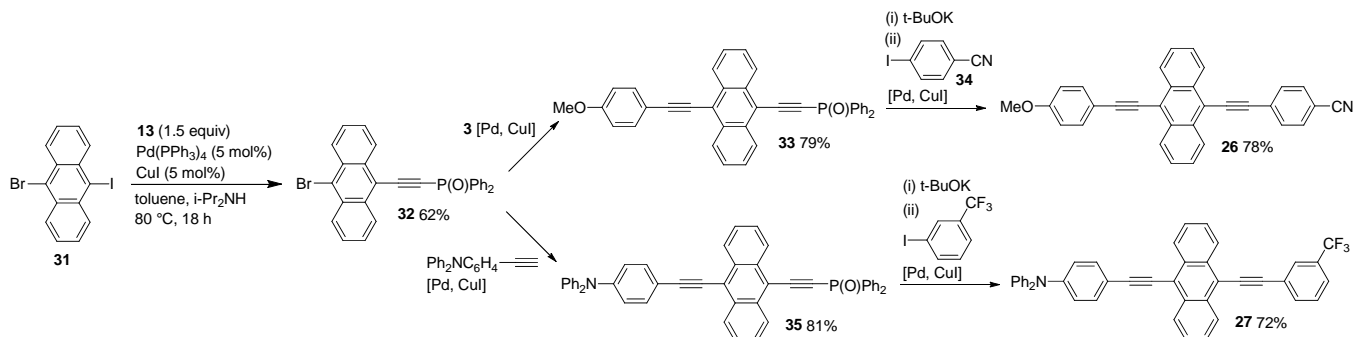

Scheme 10 Synthesis of unsymmetrically substituted anthracenes
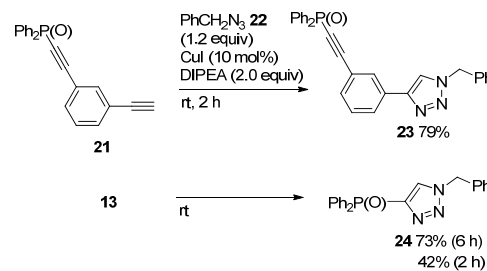
Scheme
Competitive click reaction of 21 VS 13 with 22 **8**

Finally, we performed syntheses of cyclic phenyleneethynylene **25** and unsymmetrically substituted 9,10-bis(ethynyl)anthracenes **26** and **27** by making use of the high iodo-preference of phosphorylethyne **13** in Sonogashira coupling (Schemes 9 and 10). In synthesis of **25**, a key starting compound **17a**, phosphorylethynyl bromide, was obtained easily from Sonogashira coupling of **16a** with **13** as shown in Scheme 5. The bromide **17a** was transformed to **28** by one-pot dephosphorylation/Sonogashira coupling with **29** in 62% yield. Subjection of **28** to the same one-pot deprotection-coupling provided **30**. When **30** was treated with t-BuOK and then Pd/Cu catalysts, the desired intramolecular cyclization took place to afford **25** in 68% yields
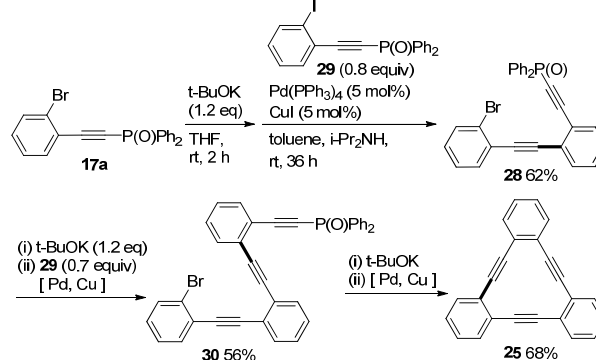
Scheme 9 Synthesis of cyclic phenyleneethynylene 25

Sonogashira coupling of **31** with phosphorylethyne **13** gave **32** exclusively in 62% yield, and **32** was transformed to **33** in 79% yield by coupling with 4-methoxyphenylethyne (**3**) (Scheme 10). In these couplings, high polarity of the $Ph_2P(O)$ group enabled easy isolation of the desired coupling products.[5]

Successive subjection of **33** to t-BuOK-promoted dephosphorylation and the coupling with **34** provided **26** in 78% yield. Similarly, Ph$_2$P(O)-ethynylanthranyl bromide **32** was converted to **27** through phosphorylethynylanthracene intermediate **35**.

Conclusions

Phosphorylethynyl-substituted aryl iodides and bromides revealed high reactivity in Sonogashira coupling, and the high reactivity was explained by the electron-withdrawing nature of the phosphorylethynyl group leading to the lower LUMO potential energy of the corresponding aryl halides. When phosphorylethyne was used in Sonogashira coupling with aryl halides, the unique iodide preference was observed, and only aryl iodides reacted with phosphorylethyne, with aryl bromides remained intact even though an excess amount of phosphorylethyne was used. This iodide preference was explained in terms of sluggish transmetallation of copper acetylide which was in-situ prepared from phosphorylethyne in Sonogashira coupling because of the low HOMO energy level. By invoking this iodo preference of phosphorylethyne, syntheses of cyclic phenyleneethynylene and unsymmetrically substituted 9,10-bis(ethynyl)anthracenes were achieved. Further application of the electron-withdrawing effect of phosphorylethyny group is under investigation.

Acknowledgements

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6   It was reported that an electron-withdrawing group on aryl halides accelerated an oxidative addition of transition-metal catalyst to aryl halides to promote the coupling reaction. See also In Chapter 3, "Principles and Applications of Organotransition Metal Chemistry" J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke, University Science Book, Mill Valley, California, 1987.

7   In sharp contrast to **1**, 1-iodo-4-(trimethylsilylethynyl)benzene exhibited the higher potential level of LUMO (-1.208 eV) in comparison with **2**.

8   The DFT calculations indicated similarly that the LUMO energy level of **6** was lower than that of **7**: -1.626 eV for **6**, -1.482 eV for **7**.

9   The LUMO energy level calculated for bromobenzene is -0.343 eV, and this value is much higher than those of **6** and **9**.

10 Although the mechanism of the click reaction is ambiguous, the strong electron-withdrawing effect of Ph$_2$P(O) group in **13** might lead to the sluggish formation of a triazole ring through addition of the less nucleophilic acetylenic carbon to the azide terminal nitrogen. (a) M. Meldal and C. W. Tornøe, *Chem. Rev.* 2008, **108**, 2952. (b) B. T. Worrell, J. A. Malik and V. V. Fokin, *Science* 2013, **340**, 457. (c) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem. Int. Ed.* 2002, **41**, 2596.