Unprecedented Intramolecular Nucleophilic Aromatic Additions of Allyloxy Anions to Diphenylphosphinoyl-Substituted Benzene Rings: A Facile Method for Preparing Multisubstituted Benzopyrans

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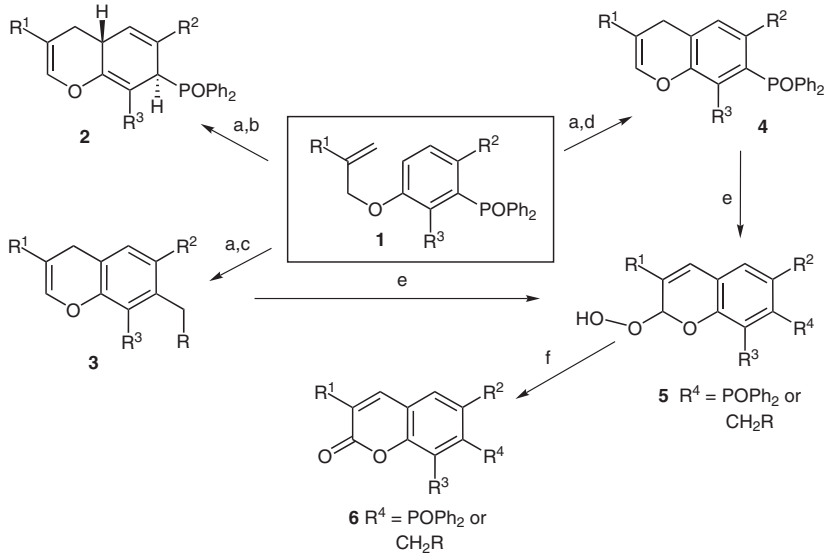
Abstract: A new synthetic method for the preparation of multisubstituted benzopyrans that involves an intramolecular conjugate addition of allyloxy anions to diphenylphosphinoyl-substituted benzene rings is described. The intermediate anion is trapped with electrophiles providing benzopyrans that are readily oxidized with O_2 to intermediates containing a peroxide that is easily converted into benzopyran-2-ones (i.e. coumarins).

Key words: nucleophilic aromatic additions, cyclizations, benzopyrans, coumarins

During studies aimed at developing new 3,3′-disubstituted biphenyl-2,2-diylbis(diphenylphosphine) (BIPHEP) and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) ligands,[1] we discovered a new reaction involving an intramolecular nucleophilic aromatic addition of an allyloxy anion to diphenylphosphinoyl-substituted benzene rings (Scheme 1). The resultant intermediate, diphenylphosphinoyl-stabilized anion, can react in situ with a variety of electrophiles resulting in the formation of multisubstituted benzopyran derivatives **2**–**4** depending on the substituents present in **1**. Further air oxidation of **4** led to peroxide **5** that was easily converted into coumarin **6** thereby providing a new preparation[2] of this ubiquitous class of natural products which often display a wide range of biological activity.[2a,3] The scope and limitations of this new reaction is described herein.

Although treatment of allyl-protected phenol **1a** with LDA (THF, –78 °C) followed by the addition of I_2 gave the expected iodinated product **7** (Scheme 2), allyl-protected phenol **1b** under identical conditions provided **8**. The structure of compound **8** was initially assigned using ^1H and ^{13}C NMR spectra and MS data; however, attempts to grow crystals of **8** under an atmosphere of air resulted in the formation of a new compound (by ^1H NMR spectroscopy). X-ray crystallography (Figure 1) indicated the newly formed compound contained a peroxide and had the structure **9**. Since something unique was happening when **1b** was treated with LDA followed by I_2, we decided to investigate the mechanism of this reaction.

Since methallyl-protected phenol **1c** exhibited similar behavior to **1b** when treated with LDA and I_2 (giving **10**), we decided to study the mechanism of this reaction using **1c** since **10** was less prone to oxidation to its corresponding peroxide (not shown). Treatment of **1c** with LDA/THF at



Scheme 1 *Reagents and conditions*: (a) LDA, THF, –78 °C; (b) H^+ source; (c) RCHO; (d) I_2; (e) O_2, r.t.; (f) Ac_2O, DMAP.

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–78 °C for four hours followed by the addition of H_2O (or D_2O) gave a mixture of three compounds (3.2:2:1 ratio) of which the major isomer **11** crystallized and was analyzed by X-ray crystallography (Figure 2). Two other components of the mixture were identified as *cis*-**11** and a double bond isomer of **11**.[4]

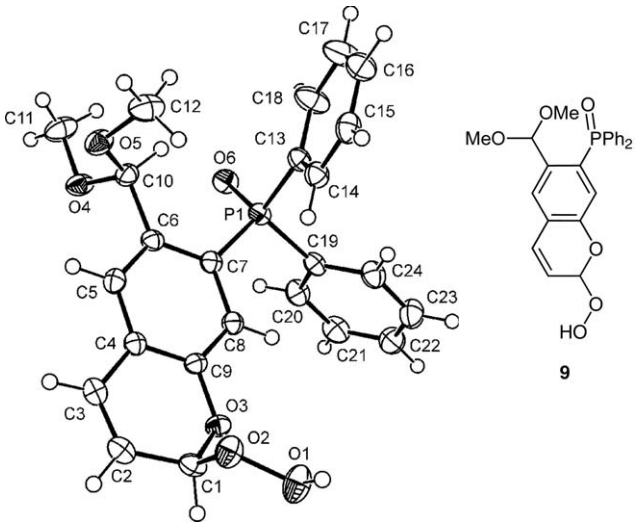


Figure 1 X-ray crystal structure of **9**

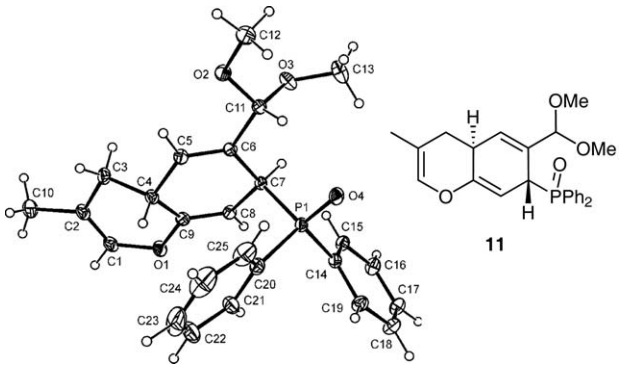
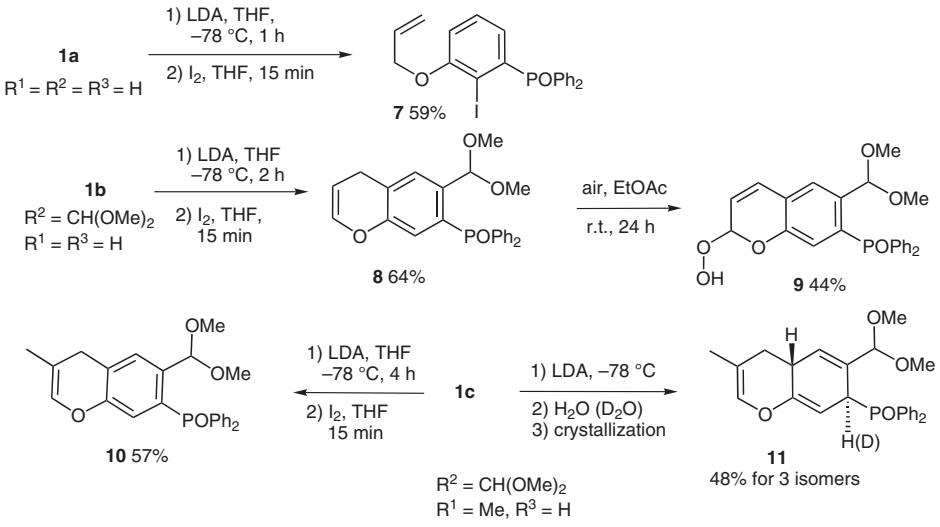


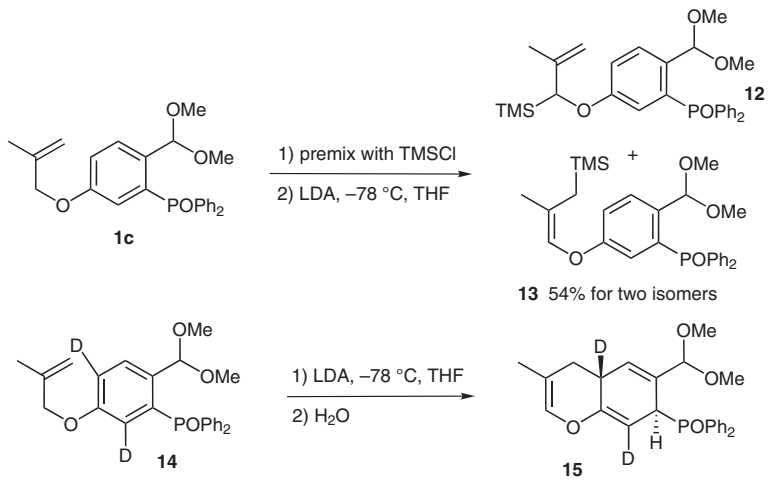
Figure 2 X-ray crystal structure of **11**

To determine if the initial site of deprotonation with LDA was on the methallyloxy group or the aromatic ring followed by an anionic migration to the methallyl group, **1c** was premixed with TMSCl[5] and then treated with LDA in THF at –78 °C (Scheme 3). A mixture of four compounds was obtained with the two major isomers being assigned **12** and **13** (1:1). The other two isomers were **12** and **13** with an additional TMS group on one of the aromatic rings of the diphenylphosphinoyl moiety. This result indicated that LDA initially abstracted a proton from the methallyl group in **1c**. Further evidence to support a direct hydrogen abstraction from the methallyl group was realized when **14** (containing two deuterium atoms) was treated with LDA at –78 °C. Again a mixture of three isomers was obtained with **15** being isolated as the major product. Compound **15** contained the two deuterium atoms that were present in **14** confirming that LDA was not initially abstracting a proton from the aromatic ring in **14** (or **1c**).

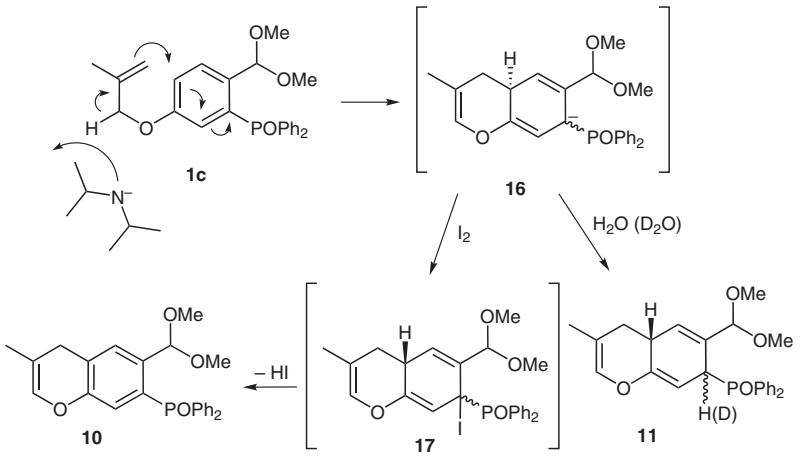
Based on the evidence above, we propose the following mechanism for this new cyclization (Scheme 4). Abstraction of a methallyl proton in **1c** (or allyl proton in **1b**) by LDA leads to an anion that undergoes a nucleophilic attack on the aromatic ring *para* to the $POPh_2$ group, resulting in stabilized anion **16**. This anion can either pick up a proton (or deuteron) upon workup with water to form **11** (as a mixture of configurational and double bond isomers) or react with I_2 to form intermediate **17** that eliminates HI upon workup to regenerate the aromatic ring giving **10**. While there have been sporadic reports involving aryl anions and *t*-BuLi adding to aromatic rings containing a diphenylphosphinoyl moiety, these have been reported as unwanted side reactions during various lithiation attempts of BINAP(O),[6a] triphenylphosphine oxide,[6b] and 2-(diphenylphosphinoyl)naphthalene.[7] The steric influence of the dimethyl acetal group must result in the diphenylphosphinoyl rotating in such a way as to block abstraction of the aromatic proton at C2 in **1b** and **1c** resulting in abstraction of the allylic or methallylic proton. With the absence of the acetal group in **1a**, the diphenylphosphi-



Scheme 2



Scheme 3

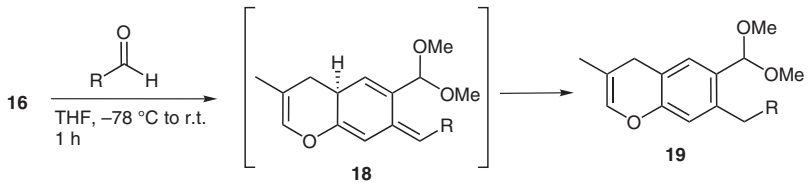


Scheme 4

noyl group acts as an *ortho*-lithiation director[7] resulting in the expected abstraction of the C2 proton leading to **7** when the anion is treated with iodine.

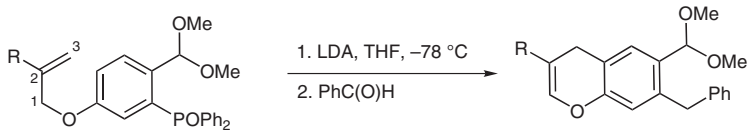
We then investigated whether anion **16** could be used in situ to perform Horner–Wittig reaction[8] with a variety of aldehydes. Treatment of anion **16** (formed by treating **1c** with LDA at –78 °C in THF) with benzaldehyde at –78 °C followed by warming the mixture to room temperature resulted in the formation of **19a**[9] (R = Ph) in 62% yield after workup with water (Scheme 5). Interestingly, compound **18** (R = Ph) could not be isolated as it immediately isomerized to **19a** (R = Ph) during workup. The in situ Horner–Wittig reaction was found to be a general reaction. Three other aldehydes reacted with **16** to provide benzopyrans **19b–d** in reasonable yields (58–64%) after purification (Scheme 5).[10]

With the above results in hand, we turned to expanding the scope of this reaction by investigating what type of groups could be tolerated on the allyl moiety. Initially, we investigated the effect of groups at the C2 position of the



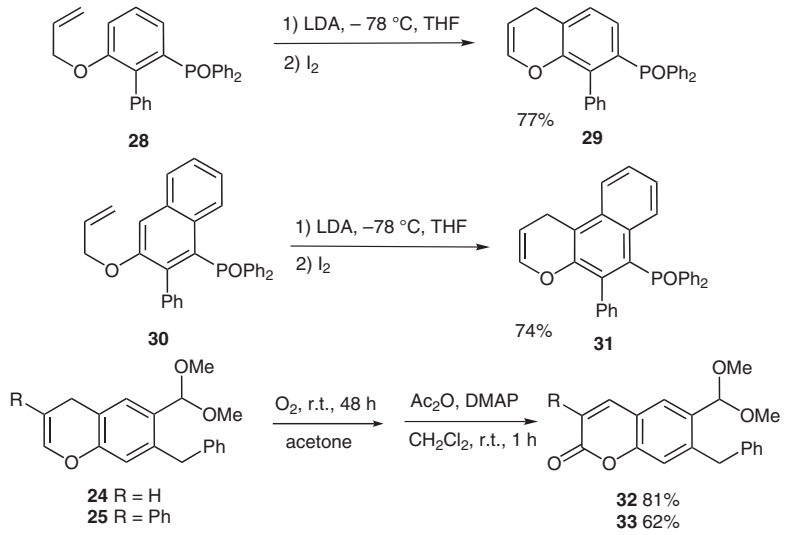
R	Yield (%)
a Ph	62
b cyclohexyl	64
c 2-furyl	58
d $CH_2CH_2N(Bn)Boc$	62

Scheme 5



R	Yield (%)
20 H	**24** 67
21 Ph	**25** 63
22 CH_2OTBS	**26** 63
23 $CH{=}CH_2$	**27** 59

Scheme 6



Scheme 7

allyl group (Scheme 6). Compounds **20**–**23** provided **24**–**27**,[11] respectively, with yields ranging from 59–67%. Unfortunately, substitution of the allyl group at C1 and C3 or just at C3 shut down the cyclization reaction in favor of the LDA abstracting a proton from one of the phenyl rings attached to the diphenylphosphinoyl group.

The presence of the dimethylacetal group in compounds **1b**, **1c** and **20**–**23** is necessary since in its absence, LDA just abstracts the aromatic proton *ortho* to both the allyloxy and the $Ph_2P{=}O$ groups (see **1a** → **7**, Scheme 2). We reasoned that the presence of a functional group between the allyloxy and $Ph_2P{=}O$ groups might lead to a cyclization in the absence of the dimethylacetal group. This was realized when compound **28** was treated with LDA at –78 °C and the resulting anion was subsequently treated with I_2 (Scheme 7) providing the expected product **29** in 77% yield. Finally, the reaction was not restricted to substituted benzene rings as naphthalene **30** cyclized as expected to give **31** (Scheme 7) thus expanding the scope of the cyclization reaction.

As noted above, benzopyran **8** was unstable in air and oxidized readily to peroxide **9** (Scheme 2). We took advantage of this reaction to prepare some benzopyran-2-ones (Scheme 7). Stirring an acetone solution of **24** and **25** under an atmosphere of O_2 for 48 hours gave intermediate peroxides (not shown) that without purification[12] were treated with acetic anhydride–DMAP in CH_2Cl_2 to give benzopyran-2-ones **32** and **33** in good yield.

In summary, we have reported a new route towards the synthesis of multisubstituted benzopyrans that involves an intramolecular conjugate addition of allyloxy anions to diphenylphosphinoyl-substituted benzene rings. The intermediate anion can be trapped with electrophiles providing benzopyrans that are easily oxidized by oxygen to peroxide intermediates that can be subsequently converted into benzopyran-2-ones (i.e. coumarins). Extensions of this work to determine if the dimethylacetal group is necessary for the cyclization, if other functional groups can be tolerated and applications to the synthesis of natural products are currently underway.

Acknowledgment

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References and Notes

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(4) Interestingly, selection of a different proton source significantly improved both selectivity of the reaction and yield. For example, adding *N*-Boc-2-methylalanine methyl ester to anion **16** instead of H_2O improved the isomeric ratio to 14:1:1.4 in favor of *trans*-**11** and the yield from 48% to 85%.

(5) It is well known that TMSCl does not react with LDA at –78 °C. See: Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155.

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(9) **7-Benzyl-6-dimethoxymethyl-3-methyl-4*H*-chromene (19a)**: To a solution of allylbenzene **1c** (0.61 g, 1.45 mmol) in THF (15 mL) was added a solution LDA over 5 min (1.74 mmol) in THF (6 mL) at –78 °C. After 4 h at this temperature a solution of benzaldehyde (0.21 g, 2.0 mmol) in THF (3 mL) was added at –78 °C over 5 min upon which the dark cherry color disappeared. After 15 min of stirring at this temperature the reaction mixture was allowed to warm to r.t. for 1 h and quenched with aq sat. NH_4Cl solution (5 mL) and H_2O (5 mL) under stirring. After 10 min the organic phase was separated and the aqueous one was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic extract was washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was forwarded to silica gel column chromatography (35 g, hexanes–EtOAc–Et_3N, 135:15:1) to give oily **19a** (0.28 g, 62% yield). Please note **19a** was easily oxidized to the corresponding peroxide (like **9**) if left exposed to air. ^{1}H NMR (200 MHz, C_6D_6): δ = 7.58 (s, 1 H, CH), 7.05–7.25 (m, 5 H, CH), 6.91 (s, 1 H, CH), 6.24 (q, *J* = 1.5 Hz, 1 H, CH), 5.50 [s, 1 H, $CH(OMe)_2$], 4.10 (s, 2 H, Bn), 3.17 (s, 6 H, MeO), 3.05 (s, 2 H, CH_2Ar), 1.32 (s, 3 H, Me). ^{13}C NMR (50 MHz, C_6D_6): δ = 151.2 (C), 140.6 (C), 138.5 (C), 135.1 (CH), 130.7 (C), 128.9 (CH), 128.4 (CH), 128.3 (CH), 125.9 (CH), 118.3 (CH), 116.8 (C), 108.3 (C), 100.9 [$CH(OMe)_2$], 52.0 (MeO), 37.7 (CH_2), 28.3 (CH_2), 17.5 (Me). IR (film): 3326, 2939, 2908, 2830, 1691, 1626, 1573, 1496, 1452, 1356, 1186, 1108, 1047, 987, 956, 735, 696 cm^{-1}. MS (EI): *m*/*z* (rel. intensity) = 165 (11), 178 (14), 231 (11), 247 (100), 277 (11), 278 (100), 310 (38) [M^+]. HRMS: *m*/*z* [M^+] calcd for $C_{20}H_{22}O_3$: 310.1569; found: 310.1546.

(10) The moderate yields of this reaction were due to the products being easily oxidized to their corresponding peroxides upon workup.

(11) Compounds with similar structures to **24** have displayed interesting fragrances: Demyttenaere, J.; Van Syngel, K.; Markusse, A. P.; Vervisch, S.; Debenedetti, S.; De Kimpe, N. *Tetrahedron* **2002**, *58*, 2163.

(12) The peroxides did not survive silica gel purification so they were used immediately in the next reaction. The peroxide was formed in 80–85% yield (by ^{1}H NMR spectroscopy).