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Validation of Diethoxyphosphonate as an Effective Agent for Charge Transfer in Anion Relay Chemistry (ARC)

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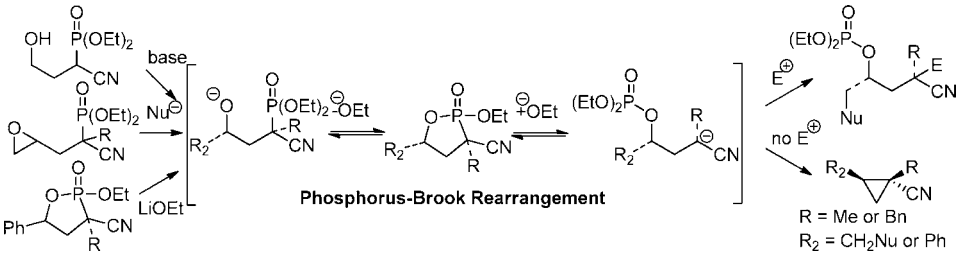
ABSTRACT



The diethoxyphosphonate group comprises an effective agent to achieve negative charge migration in Type II Anion Relay Chemistry (ARC). The process involves a [1,4]-phosphorus-Brook rearrangement that proceeds via a phosphacyclic intermediate leading to an anion that can be captured by reactive electrophiles. In the absence of an exogenous electrophile, the anion derived via phosphorus migration undergoes internal displacement of the phosphonate group to produce a diastereomeric mixture of cyclopropanes.

Anion Relay Chemistry (ARC) (Figure 1) has emerged as a powerful tactic for the rapid assembly of molecular complexity.[1,2] The Type II ARC protocol (Figure 1B), in particular, holds considerable significance given the potential to mimic what in polymer chemistry is known as "living polymerization".[3] That is, the controlled addition of individual bifunctional linchpins in an iterative fashion, followed by termination with an electrophile, can effectively provide access to complex molecular scaffolds. To augment the potential of the Type II ARC tactic, the design, synthesis, and validation of effective new linchpins with diverse migrating groups is required, which possess both orthogonal reactivity and the kinetic potential to undergo the requisite "Brook-like" migration under mild conditions. In this communication, we validate the diethoxyphosphonate group as an effective transfer agent to achieve negative charge migration in Type II ARC.

We were attracted to the phosphonate group for two major reasons. First, phosphorus shares with silicon the propensity to form a strong σ-bond with oxygen in preference to carbon, with the oxygen−phosphorus bond favored by ca. 20 kcal/mol.[4] Second, unlike silicon, nucleophilic attack at the phosphonate group held the promise of generating a neutral five-coordinate phosphorus ring intermediate with expulsion of an ethoxy anion.[5] Assuming the presence of an anion stabilizing group (ASG) α to the phosphonate, readdition of the displaced alkoxide under equilibrium conditions could in turn lead to a carbanion capable of reacting with an electrophile (Figure 2A).

A number of [1,2]-,[6] [1,3]-,[7,8] and [1,4]-[9,10]phosphorus-Brook rearrangements are known. The most common

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(2) Smith, A. B.; Xian, M. *J. Am. Chem. Soc.* **2005**, *128*, 66.
(3) Webster, O. *Science* **1991**, *251*, 887.

(4) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley-Interscience: New York, 2000. For comparison, the silicon−oxygen bond is stronger by ca. 40 kcal/mol (Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77).
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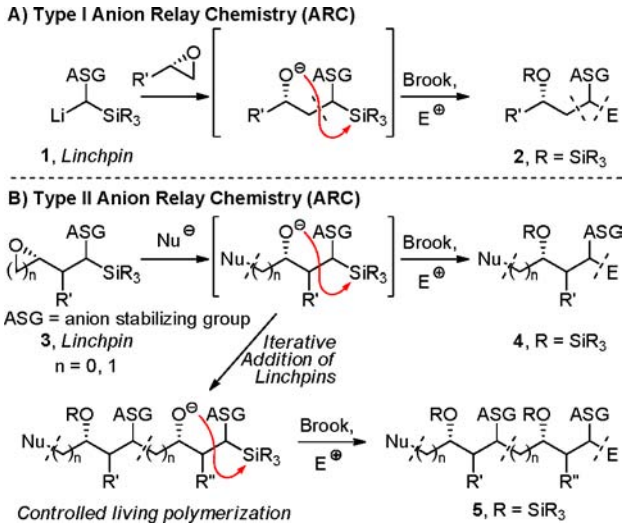

Figure 1. (A) Type I ARC; (B) Type II ARC.

prototype, orginally reported by Wadsworth and Emmons,[9] entails the reaction of stabilized phosphonate anions with epoxides to form cyclopropanes (Figure 2A), a reaction process that typically requires both a high temperature and prolonged reaction time. Independent studies by Singh,[11] Merschaert,[12] and Ghirardelli[5] suggested that the reaction proceeds through a mechanism similar to what we now term Type I ARC, involving a stepwise "Brook-like" rearrangement involving initial explusion of an ethoxide anion. Readdition of the ethoxide and completion of the C→O phosphorus migration furnishes a stabilized anion that undergoes intramolecular displacement of the diethoxyphosphate to generate the *trans* cyclopropane.

More recently, Krawczyk et al.[13] reported that the rearranged adduct **9**, obtained by addition of a nucleophile to the aldehyde of bifunctional phosphonate linchpin **8** (Figure 2B), after isolation and deprotonation, can undergo intramolecular cyclization to form a cyclopropane ring. To the best of our knowledge, this is the only example of what is a formal Type II phorphorus "ARC-like" process, albeit achieved in a stepwise fashion.

Given that ring closure has been implicated as the rate-determing step in the Wadsworth–Emmons cyclopropanation reaction,[9] the possibility of performing the phosphorus-Brook rearrangement at lower temperature might permit the derived anion to react with an exogenous electrophile, thus expanding the scope of the ARC tactic (Figure 2C).

(9) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

(10) Bray, C. D.; de Faveri, G. *J. Org. Chem.* **2010**, *75*, 4652 and references cited therein.

(11) Singh, A. K.; Rao, M. N.; Simpson, J. H.; Li, W.-S.; Thornton, J. E.; Kuehner, D. E.; Kacsur, D. J. *Org. Process Res. Dev.* **2002**, *6*, 618.

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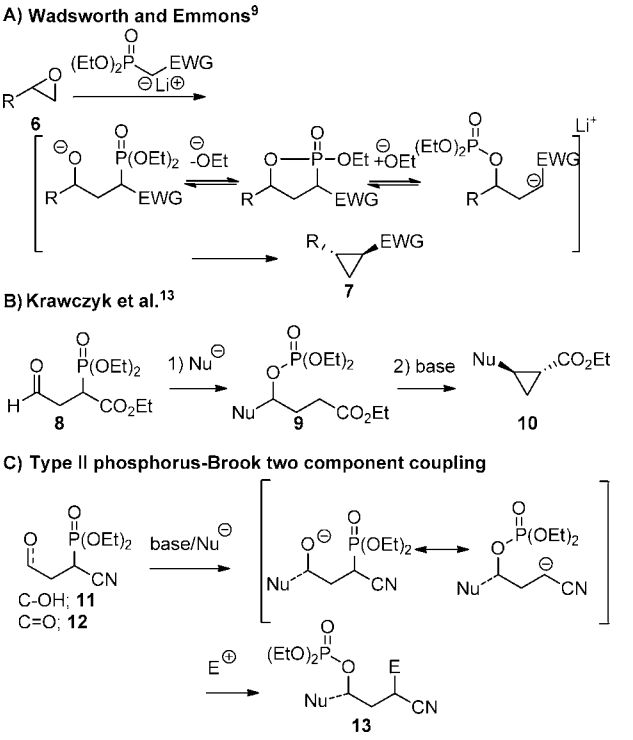


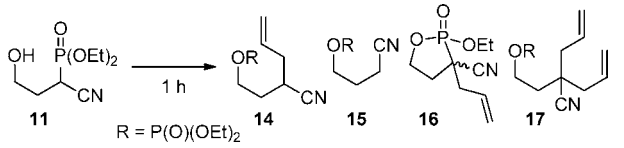
Figure 2. Phosphorus-Brook rearrangement.

To explore this scenario, we examined the reaction of alcohol **11** possessing a β-diethoxyphosphonate group, envisioned to furnish two-component adduct **13** (Figure 2C). If successful, we would turn to a three-component Type II ARC process involving generation of the corresponding oxyanion by nucleophilic addition to aldehyde **12.**

To this end, alcohol **11** was treated with potassium hexamethyldisilazide (KHMDS), followed by addition of allyl bromide, initially employing tetrahydrofuran (THF), dichloroethane (DCE), and/or dimethylformamide (DMF) as solvent systems at −78 °C. Under these conditions, only the phosphorus-Brook rearranged product **15** was observed (Table 1, entries 1–3). However, upon addition of an increasing amount of hexamethylphosphoramide (HMPA), employing first THF and then DMF as the solvent system with allyl bromide as the electrophile, the two component adduct **14** was observed, in conjunction with diallylated adduct **17**, allylated phosphacycle **16**, and the phosphorus-Brook product **15** (Table 1, entries 4–6).

Further reaction optimization was guided by the mechanistic hypothesis outlined in Figure 3, which accounts for the formation of **14** as well as byproducts **15**, **16**, and **17**. Specifically, initial deprotonation of **11** was envisioned to lead to phosphacycle **18**, which in the presence of excess base, could undergo deprotonation at the carbon bearing the phosphonate. Alkylation with allyl bromide would lead to **16**. Alternatively, in the presence of only 1.0 equiv of KHMDS, the liberated alkoxide and phosphacycle **18**, presumably in equilibrium with carbanion **A**, would lead to alkylation with allyl bromide to furnish the Type II

Table 1. Two Component Study



entry	solvent	KHMDS (equiv)	HMPA (mL)	temp (°C)	14:15:16:17[a]	yield of 14 (%)
1	THF	1.2	0	−78	0:1:0:0	0
2	DCE	1.2	0	−78	0:1:0:0	0
3	DMF	1.2	0	−78	0:1:0:0	0
4	THF	1.1	1	−78 to rt	2.5:0:0:1	46
5	THF	1.2	2	−78 to rt	3:0:0:1	49
6	THF	1.1	2	−20	1:1.1:.2:0	43
7	**DMF**	**1.0**	**1**	**−60**	**1:0:0:0**	**90**
8	**DMF**	**1.0**	**0.2**	**−60**	**1:0:0:0**	**90**

[a] Determined by ^{1}H NMR of the crude product mixture following workup.

ARC product **14**. At higher temperatures, **14** can be deprotonated by carbanion **A** to reversibly yield carbanion **B**, which, in turn, could react with excess allyl bromide to furnish the diallylated product **17**. Accordingly, the use of 1.0 equiv of both KHMDS and allyl bromide eliminated formation of both **16** and **17** and allowed adduct **14** to be isolated in 90% yield (Table 1, entries 7−8).

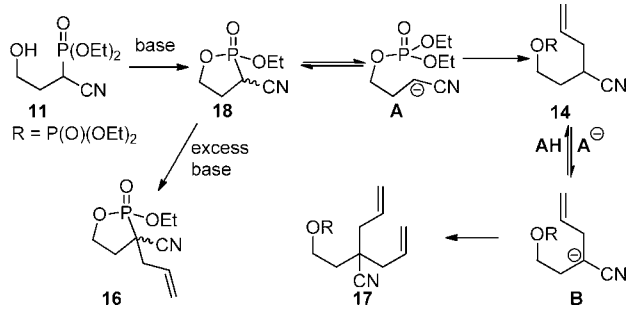


Figure 3. Proposed phorphorus-Brook reaction sequence.

Turning to the proposed three-component union, linchpins **19** and **20** (Figure 4), possessing aldehydic and epoxide electrophilic sites, respectively, were prepared (see Supporting Information). Unfortunately, both linchpins proved untenable due to rapid and exclusive deprotonation of the acidic proton α to the phosphonate. To circumvent this issue, we introduced an α-alkyl substituent to provide linchpins **21**−**23**.

Initial experiments were conducted with linchpin **21** employing *n*-butyllithium as the initiating nucleophile and methyl iodide as the terminating electrophile. Pleasingly, when *n*-butyllithium was added to an ethereal solution of **21** at −78 °C, followed by rapid addition of methyl iodide in a solution of THF and HMPA (4:1) (Figure 5), adduct **24** was isolated in 42% yield, along with 20−30%

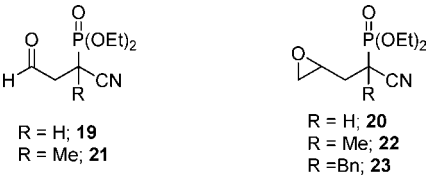


Figure 4. Bifunctional linchpins.

of enol ethers **25**.[14] A variety of temperature regimes and additives did not improve the ratio of **24** relative to **25**.

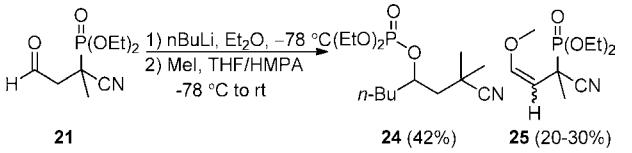
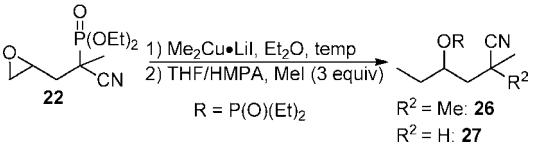


Figure 5. Three-component coupling with linchpin **21**.

We therefore turned to epoxide linchpin **22**, employing methyl cuprate as the initiating nucleophile and methyl iodide as the terminating electrophile[15] (Table 2). After

Table 2. Optimization of Three-Component Type II ARC with Linchpin **22**



entry	temp (°C)	%THF	HMPA (equiv)	yield of 26[a](%)	26:27[b]
1	−20	50	0	27	>10:1
2	−20	50	10	45	>10:1
3	−40	25	10	66	>10:1
4[c]	−40	0	20	60	7:1
5	**40**	**25**	5	**82**	**10:1**
6	−40	25	2	55	>10:1
7[d]	−40	25	5	55	10:1

[a] Isolated yields. [b] Ratio determined by ^{1}H NMR. [c] Reaction was run at 0.1 M. [d] Reaction was run with 1.5 equiv of MeI.

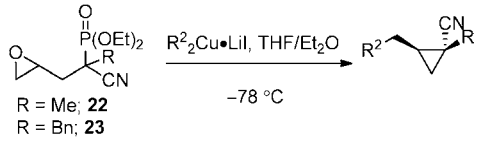
significant optimization, we discovered that addition of the linchpin in diethyl ether to an ethereal solution of cuprate at −40 °C, followed immediately by addition of a solution of methyl iodide in THF and HMPA (5 equiv) with rapid warming to room temperature produced an 82% yield of the desired three-component adduct **26** after 1 h.

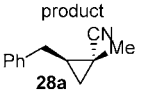
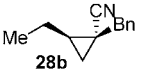
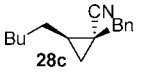
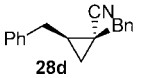
(14) This side product arises from enolization followed by trapping with methyl iodide.

(15) Methyl iodide was chosen to avoid diastereomeric product mixtures.

However, when the addition of the nucleophile and electrophile was not carried out in rapid succession, a significant amount of cyclopropane ring formation was observed. Equally important, as illustrated in Table 3, when a terminating electrophile was not employed, cyclopropane derivatives were rapidly formed in good yield at low temperature (−78 °C).[16] Both methyl linchpin **22** and benzyl linchpin **23** were competent substrates for alkyl and phenyl cuprates. Importantly, these conditions are quite mild compared to typical Type I ARC cyclopropanations.

Table 3. Cyclopropane Synthesis



entry	linchpin	nucleophile	product	yield	dr
1	**22**	phenyl	 **28a**	61%	7.7:1
2	**23**	methyl	 **28b**	89%	4:1
3	**23**	butyl	 **28c**	87%	1.7:1
4	**23**	phenyl	 **28d**	81%	7.5:1

Finally, we were intrigued by the similarity of the phosphacycle **29** (Figure 6), presumably formed by nucleophilic addition to **22** followed by cyclization with elimination of ethoxide, and siloxane **30**, which we recently reported to be an alternative entry point to the silicon-ARC manifold.[17,18] In particular, reaction of **30** with an organolithium species generates a hypervalent silicate, which is implicated to be an intermediate or transition state in the silicon migration. We wondered if similar activation of phosphacycle **29**, here by the addition of lithium ethoxide, would lead to a similar hypervalent phosphorus species in the phosphorus-Brook manifold.

Accordingly, we prepared the related phosphacycle **31** (see Supporting Information). Upon addition of lithium ethoxide to **31** in the presence of MeI employing the previously developed three-component reaction conditions, **33** was obtained in 69% yield, along with **32** and cyclopropane **34**, both in 15% yield. Alternatively, without an exogenous electrophile, cylopropane **34** resulted in 65% yield as a single diastereomer.[16] Thus, the phosphorus-Brook reaction manifold can be accessed via stable phosphacycles, in a similar fashion as siloxanes in the silicone ARC tactic.[17,18]

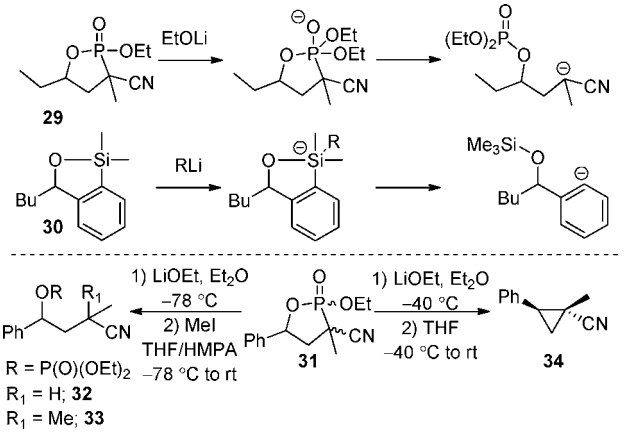


Figure 6. Phosphorus-Brook from a cyclic intermediate.

In summary, the diethoxyphosphonate group has been validated as an effective transfer agent in the phorphorus-Brook rearrangement leading to Type II Anion Relay Chemistry (ARC). In addition, we have demonstrated that a neutral five-coordinate phorphorus ring intermediate can provide access to the phosphorus-Brook/ARC reaction coordinate. Taken together, these results significantly augment the Type II ARC tactic. Studies to increase the scope and synthetic utility of the phorphorus-Brook rearrangement continue in our laboratory.

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Supporting Information Available. Experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(16) Cyclopropane stereochemistry assigned by NOESY and chemical shift correlation (see Supporting Information).

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