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Sequential Deprotonation−Alkylation of Binaphthyloxy-Substituted Phosphonochalcogenoates: Chiral Tri- and Tetrasubstituted Carbon Centers Adjacent to a Phosphorus Atom

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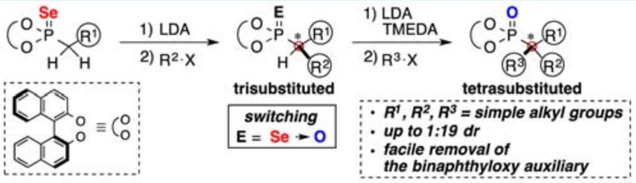
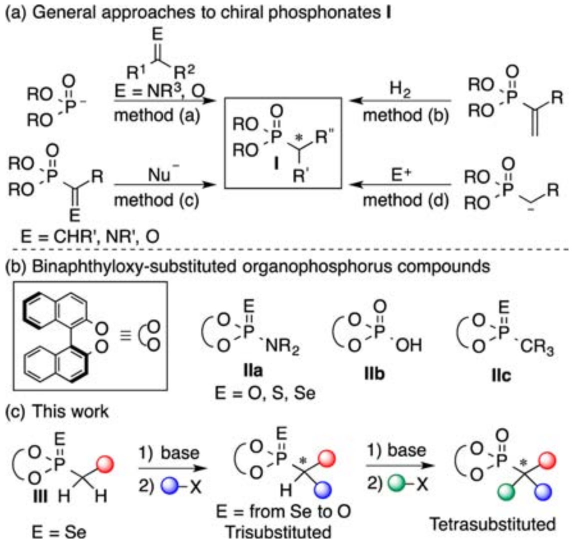
Supporting Information

ABSTRACT: Sequential deprotonation and alkylation of 1,1′-binaphthyloxy-substituted phosphonoselenoates and phosphonates resulted in the diastereoselective formation of chiral tri- and tetrasubstituted carbon centers adjacent to a phosphorus atom.



Optically active phosphonic acids and their derivatives (**I**) with chiral carbon centers adjacent to the phosphorus atom are not only biologically relevant[1] but also versatile synthetic intermediates toward optically active organophosphorus compounds.[2] Accordingly, several synthetic methods for the formation of **I** with trisubstituted carbon atoms have been developed in past decades[3−5] involving the asymmetric addition of phosphorus anions to unsaturated compounds such as carbonyl compounds and imines (Scheme 1a, method a),[3] the asymmetric reduction of vinyl phosphonates (Scheme 1a, method b),[4] the asymmetric addition of carbon nucleophiles to unsaturated carbon atoms adjacent to the phosphorus atom (Scheme 1a, method c),[5] and the addition of carbanions adjacent to the phosphorus atom to electrophiles with chiral ligands (Scheme 1a, method d).[6] Alternatively, the use of chiral auxiliaries is a reliable method to control the stereochemistry of the reaction of carbanions, whereby the judicious choice of chiral auxiliary is crucial. In fact, optically active 1,2-amino-alcohol-,[7] 1,2-diamine-,[8] and menthyl-tethered[9] phosphonates have been used as precursors for chiral organophosphorus compounds such as **I**. However, even with these established methods, the construction of chiral centers substituted with only simple alkyl groups next to the phosphorus atom remains a challenging task. Meanwhile, a large variety of synthetic reactions involving organophosphorus compounds with binaphthyloxy groups, such as phosphoric amides **IIa**[10] and phosphoric acids **IIb**,[11] have been developed over the past decades (Scheme 1b). In contrast, substantially less attention has been paid to phosphonates such as **IIc**,[12] despite the fact that the binaphthyloxy group in **IIc** exerts a strong influence on the stereochemical fate of the carbon atom connected to the phosphorus atom (Scheme 1a, method d). Indeed, our recent studies showed that the chirality of the α carbon atoms relative to the phosphorus atom in phosphonochalcogenoates **III** can be discriminated by ^{31}P NMR spectroscopy.[13] Moreover, carbanions at these positions may exhibit chirally distinct environments. Herein, we report the sequential deprotonation−alkylation of phosphonochalcogenoates **III** (Scheme 1c). Changing the elements attached to the phosphorus atom from selenium to oxygen in **III** afforded control over highly efficient diastereoselective reactions leading to tri- and tetrasubstituted chiral carbon centers.

Scheme 1. Synthetic Routes to Chiral Phosphonate Derivatives



Initially, we treated *P*-phenethyl phosphonate **1a** consecutively with a base and methyl iodide (MeI) as an electrophile (Table 1, entry 1). Several bases including lithium diisopropylamide (LDA) were tested at −70 °C, followed by the addition of MeI, which resulted in the formation of **4a** and **7a** in 49 and 27% yield, respectively. To suppress the formation of **7a**, which is probably formed via the dimethylation of **1a**, the varying

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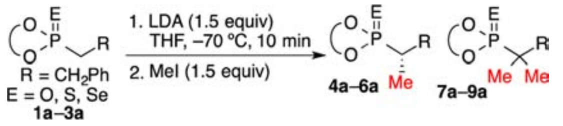
Table 1. Successive Deprotonation−Methylation of Phosphonates and Phosphonochalcogenoates[a]



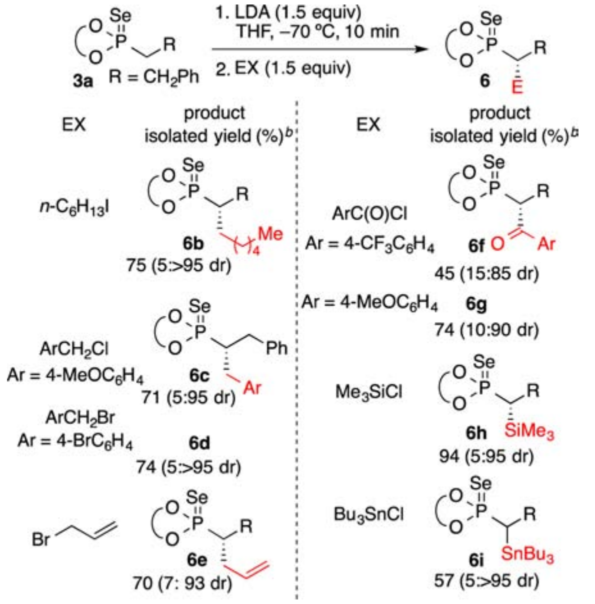
entry	E	**4a**−**6a** yield (%)	dr	**7a**−**9a** yield (%)
1	O (**1a**)	49[b] (**4a**)	10:90	27[b] (**7a**)
2	S (**2a**)	85 (**5a**)	8:92	0 (**8a**)
3	Se (**3a**)	89 (**6a**)	5:95	0 (**9a**)

[a] Isolated yield; dr determined by ^{31}P NMR analysis of the crude reaction mixtures. [b] Yield determined by the NMR analysis.

conditions for the reaction between **1a** and LDA were examined. Unfortunately, these attempts remained unsuccessful. Under the aforementioned conditions, *P*-phenethyl phosphonothioate **2a** and -selenoate **3a**[14] furnished an increased yield of **5a** and **6a**, respectively, and the corresponding dimethylated products were not observed (entries 2 and 3). It is particularly noteworthy that the reaction of phosphonoselenoate **3a** afforded the highest diastereoselectivity and yield among **1a**−**3a**.[15]

With these results in hand, we examined the sequential reaction of **3a** with LDA and a range of electrophiles (Table 2).

Table 2. Reaction Scope with Respect to Electrophiles[a]

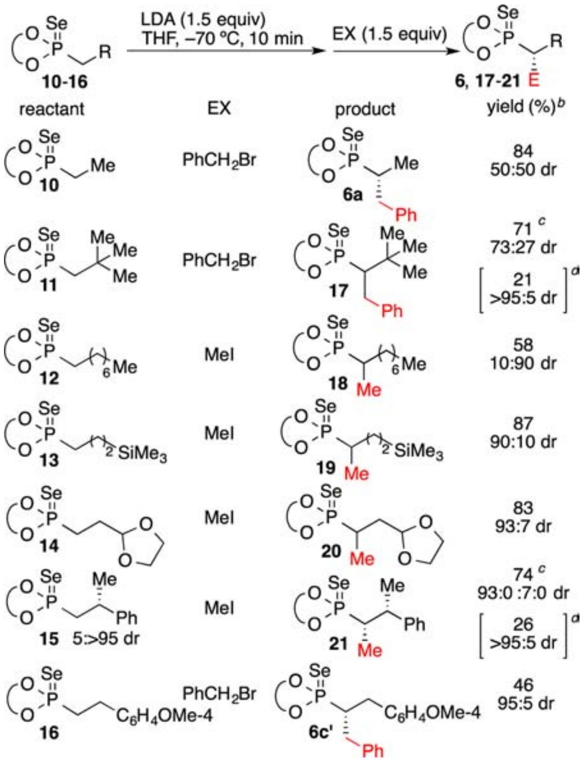


[a] Two procedures were employed for these reactions, see Supporting Information. [b] Isolated yield; dr determined by ^{31}P NMR analysis of the crude reaction mixtures.

Under the previously established optimal conditions, the reaction proceeded with various halides, affording the corresponding products (**6b**−**6i**) in high diastereoselectivity and good to high yield. The use of benzyl halides bearing electron-withdrawing and -donating groups on an aromatic ring furnished **6c** and **6d** in high diastereoselectivity. Notably, the chirality of the α carbon atom in **6c** and **6d** originates from a remote position, that is, from the different substituents at the *para*-positions of the aromatic ring. Nevertheless, during the reaction, those differences were clearly discriminated. α-Acylated products **6f** and **6g** were prepared in good diastereoselectivity from the reaction with acid halides, containing electron-withdrawing and -donating groups on an aromatic ring. Furthermore, the α-functionalization of **3a** with Me$_3$SiCl and Bu$_3$SnCl also proceeded smoothly to generate **6h** and **6i** in high diastereoselectivity.

Subsequently, we explored the scope of this reaction with respect to phosphonoselenoates (Table 3). Even though the successive reaction of *P*-ethyl phosphonoselenoate **10** with LDA and benzyl bromide proceeded smoothly at −70 °C and afforded **6a** in high yield, no diastereoselectivity was observed. Sterically hindered ester **11**, containing a *tert*-butyl group, also generated the corresponding carbanion at −40 °C, and the alkylation of the resulting carbanion furnished **17** in good diastereoselectivity. Surprisingly, when ester **12**, bearing a long-chain alkyl group, was used as a substrate, methylated **18** was also obtained in high diastereoselectivity. Under the applied reaction conditions, silyl and acetal groups were tolerated well, and esters **19** and **20** were obtained in high diastereoselectivity.

Table 3. Reaction Scope with Respect to Phosphonoselenoates[a]



[a] Two procedures were employed for these reactions; see Supporting Information. [b] Isolated yield; dr determined by ^{31}P NMR analysis of the crude reaction mixtures. [c] Reaction conducted at −40 °C. [d] Yield and dr after recrystallization are shown in parentheses.

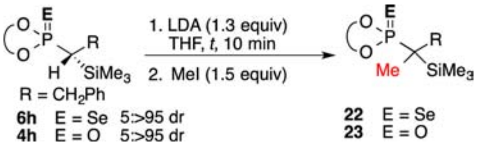
Methylation of ester **15**, bearing one chiral carbon center, afforded ester **21**, which contains two adjacent chiral carbon centers at the α and β position relative to the phosphorus atom, in high diastereomeric excess. The reaction of ester **16** with benzyl bromide also proceeded with high efficiency and diastereoselectivity to furnish diastereoisomer **6c′** exclusively. The stereochemistry of **6c′** is antipodal to that of **6c**, which is derived from ester **3a**. This result suggests that the stereochemistry of the reaction of the anions generated from the phosphonoselenoates and electrophiles is controlled kinetically.

In some cases, the obtained diastereomers could be separated by ordinary recrystallization or column chromatography on silica gel.

The absolute configurations of **6a**, **6c**, and **21** were unequivocally determined by single-crystal X-ray diffraction analysis.[16]

To construct rare examples of chiral tetrasubstituted carbon centers,[17] in particular, with three carbon-containing substituents,[18] adjacent to a phosphorus atom, we then attempted the lithiation of ester **6h** (Table 4). However, under a variety of reaction conditions employing other bases and increasing the reaction temperature, the lithiation was unsuccessful and **6h** remained mostly intact. Based on the results in Table 1, we subsequently focused on phosphonate **4h**, as the deprotonation may occur at the carbon atom adjacent to the phosphorus atom in **4h**. As expected, the lithiation of phosphonate **4h** at −40 °C, followed by the addition of MeI, afforded **23** in high diastereoselectivity (Table 4, entry 3). The use of TMEDA (1.6 equiv) as an additive enhanced the yield of **23** (Table 4, entry 4).

Table 4. Construction of Tetrasubstituted Carbon Atoms Adjacent to a Phosphorus Atom[a]

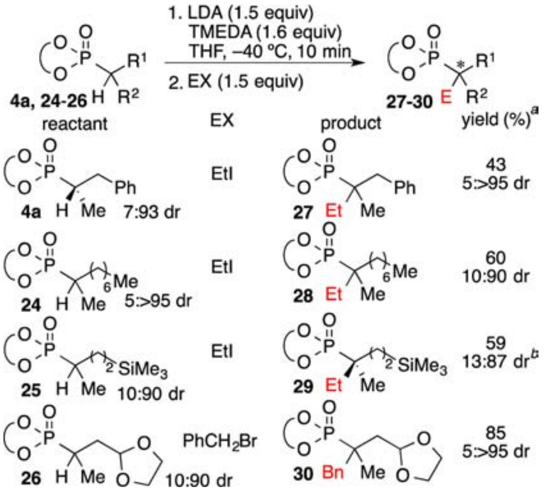


entry	E	t (°C)	yield (%)	dr
1	Se (**6h**)	−70	nr (**22**)	
2	O (**4h**)	−70	nr (**23**)	
3	O (**4h**)	−40	59 (**23**)	5:>95
4[b]	O (**4h**)	−40	80 (**23**)	7:93

[a] Isolated yield; dr determined by ^{31}P NMR analysis of the crude reaction mixtures. [b] TMEDA (3.3 equiv) was used as an additive.

Under optimized reaction conditions, phosphonates with a trisubstituted carbon atom at the *α* position relative to the phosphorus atom also engaged in this reaction sequence (Table 5). The lithiation−alkylation of phosphonates containing aryl, long alkyl, silyl, or acetal protective groups (**4a**, **24**−**26**) also provided the corresponding esters (**27**−**30**) in high diastereoselectivity.

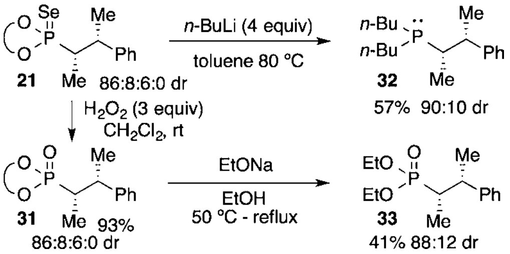
Table 5. Reaction Scope with Respect to Phosphonates



[a] Isolated yield; dr determined by ^{31}P NMR analysis of the crude reaction mixtures. [b] Detail of the elucidation of the absolute configuration is shown in the Supporting Information.

The obtained phosphonochalcogenoates can be further derivatized (Scheme 2). For example, chiral phosphine **32**, which can be used in nucleophilic asymmetric catalysis,[19] was obtained from dialkylation−deselenation of phosphonoselenoate **21** with *n*-BuLi. Moreover, the alcoholysis of phosphonate **31** with sodium ethoxide afforded diethyl phosphonate **33**. Under the applied conditions, binaphthol was recovered in both cases.

Scheme 2. Derivatization of Phosphonoselenoate 21 and Phosphonate 31



In conclusion, we have demonstrated the diastereoselective formation of chiral carbon centers in binaphthyloxy-substituted phosphonochalcogenoates through a deprotonation−alkylation sequence. The judicious choice of the elements on the phosphorus(V) atom provides control over the reactivity of the phosphorus reactants and thus affords products with tri- and tetrasubstituted chiral carbon centers, which represent key precursors for a range of optically active organophosphorus compounds. Current studies in our laboratories are focused on developing asymmetric reactions with the obtained products as well as gaining more detailed insights into the stereochemistry and the reaction mechanism.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02578.

Experimental details and data (PDF)
X-ray data for **6a** (CIF)
X-ray data for **6c** (CIF)
X-ray data for **21** (CIF)

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Notes

The authors declare no competing financial interest.

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