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Phosphinative cyclopropanation of allyl phosphates with lithium phosphides

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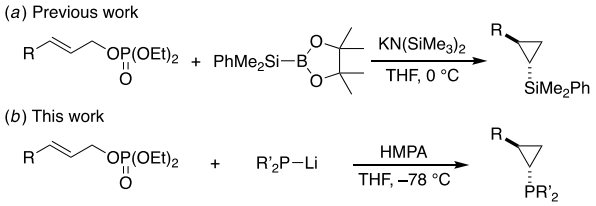
Ryo Shintani,* Ayase Ohzono and Kentaro Shirota

A new cyclopropanation reaction of allyl phosphates with lithium phosphides has been developed to give cyclopropylphosphines through the formation of both a C–P bond and a cyclopropane ring at the same time, and high selectivity toward cyclopropanation over allylic substitution has been realized by conducting the reaction in the presence of HMPA.

Cyclopropanation of allylic electrophiles by nucleophilic attack at their β-position represents one of the attractive approaches for the synthesis of substituted cyclopropanes from relatively simple precursors, although it requires suppression of competing allylic substitution.[1] Applicable nucleophiles to this mode of cyclopropanation are typically enolate-type carbon nucleophiles under palladium catalysis.[2] On the other hand, the use of heteroatom nucleophiles under palladium catalysis is limited to intramolecular processes using nitrogen[3] or oxygen[4] nucleophiles. Only boron[5] and silicon (Scheme 1*a*)[6] nucleophiles have been utilized as effective heteroatom nucleophiles for intermolecular reactions so far under copper catalysis and uncatalyzed stoichiometric conditions, respectively. In addition, a photocatalytic process was recently reported for the intramolecular synthesis of chlorinated cyclopropanes by isomerization of cinnamyl chlorides through a radical



Scheme 1 (*a*) Silylative (previous work) and (*b*) phosphinative (this work) cyclopropanation of allyl phosphates**.**

mechanism.[7]

Phosphorus-substituted cyclopropanes such as cyclopropylphosphines constitute a useful class of compounds that can be applied as ligands for transition metals in various catalytic organic transformations.[8] They are also found in biologically active molecules such as antimalarial agents.[9] Synthesis of these compounds always relies either on C–P bond formation using pre-existing three-membered carbocycles such as cyclopropanes[8a,c–f,10] and cyclopropenes[11] or on C–C bond-forming cyclopropanation using substrates possessing preinstalled C–P bonds.[8b,12] In contrast, despite its potential versatility and efficiency of the overall process, no reports have been made that achieves both C–P bond formation and cyclopropane-ring formation at the same time, as far as we are aware. In this context, herein we describe the first such process by the reaction of allyl phosphates with lithium phosphides in the presence of hexamethylphosphoric triamide (HMPA) (Scheme 1*b*).

Initially, we chose (*E*)-cinnamyl diethyl phosphate (**1a**) as a model substrate and treated it with lithium dicyclohexylphosphide (**2a**), which was prepared from dicyclohexylphosphine and *n*-butyllithium, in various solvents at 20 °C, and the products were analyzed after oxidation of phosphorus with hydrogen peroxide (Table 1). The reaction in toluene resulted in no formation of cyclopropanation product **3aa** with 5% yield of allylic substitution product **4aa** (entry 1).[13] Selective formation of **4aa** over **3aa** was also observed with improved chemical yields when the reaction was conducted in acyclic ethereal solvents such as diethyl ether, *tert*-butyl methyl ether, and cyclopentyl methyl ether, although the formation of **3aa** was also confirmed as a minor component (**3aa**/**4aa** = 6/94–3/97; entries 2–4). The best result toward the formation of **4aa** was achieved by conducting the reaction in cyclopentyl methyl ether (71% yield, **3aa**/**4aa** = 3/97; entry 4). On the other hand, a significant amount of desired cyclopropane **3aa** was obtained when the solvent was switched to THF (**3aa**/(**4aa**+**4aa'**) = 43/57; entry 5), and a slightly higher ratio was observed by conducting the reaction at –78 °C instead of 20 °C (**3aa**/(**4aa**+**4aa'**) = 47/53;

Table 1 Reaction of Allyl Phosphate **1a** with Lithium Phosphide **2a**

Division of Chemistry, Department of Materials Engineering Science, Graduate School of Engineering Science, Osaka University, Toyonaka, Osaka 560-8531, Japan. E-mail: shintani@chem.es.osaka-u.ac.jp

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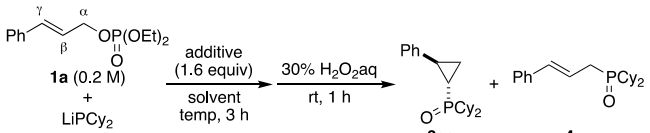
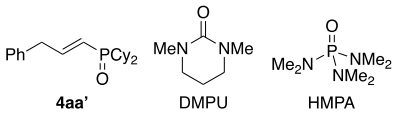


Entry	Additive	Solvent	Temp (°C)	Yield of **3aa**+**4aa** (%)[a]	**3aa**/**4aa**[b]
1	None	Toluene	20	5[b]	0/100
2	None	Et_2O	20	55[b]	6/94
3	None	*t*BuOMe	20	73	5/95
4	None	*c*PentOMe	20	71	3/97
5	None	THF	20	86[b]	43/57[c]
6	None	THF	–78	91	47/53[d]
7	DMPU	THF	–78	86	60/40[e]
8	HMPA	THF	–78	77[f]	92/8[g]

[a] Combined isolated yield. *trans*/*cis* > 99/1 for both **3aa** and **4aa** unless otherwise noted. [b] Determined by ^{1}H NMR. [c] **4aa/4aa'** = 67/33. [d] **4aa/4aa'** = 93/7. [e] **4aa/4aa'** = 85/15. [f] Containing inseparable dicyclohexyl(3-phenylpropyl)phosphine oxide (≤4%). [g] **4aa/4aa'** = 88/12.



entry 6). The different reaction outcomes between acyclic ethers and THF may indicate that better coordination ability of oxygen atom of THF to lithium phosphide **2a** increased its nucleophilicity, which facilitated the attack to less electrophilic β-carbon of **1a** compared to its α-carbon. Based on this hypothesis, we decided to examine several Lewis bases as an additive. Although nitrogen donors such as 4-dimethylaminopyridine (DMAP) and *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) showed no effect (data not shown), the use of *N*,*N'*-dimethylpropyleneurea (DMPU) improved the selectivity toward **3aa** to some extent (**3aa**/(**4aa**+**4aa'**) = 60/40; entry 7), and high selectivity of **3aa** was observed by using hexamethylphosphoric triamide (HMPA) as an additive (**3aa**/(**4aa**+**4aa'**) = 92/8; entry 8).[14]

Under the conditions using HMPA as an additive, cyclopropanation with lithium phosphide **2a** effectively proceeds for various allyl phosphates **1** (Table 2). For example, in addition to parent cinnamyl phosphate **1a** (entry 1), cinnamyl phosphates **1b–e** having substituents at *para*, *meta*, or *ortho* positions could all be employed to give the corresponding cyclopropanation products **3ba–ea** in reasonably high yields with 90–99% selectivity (entries 2–5).[15] Naphthyl, thienyl, and alkenyl-substituted allyl phosphates **1f–i** also gave cyclopropanes **3fa–ia** with high selectivity (90/10–97/3; entries 6–9), but only allylic substitution took place for alkyl-substituted allyl phosphate **1j** under the current reaction conditions (entry 10). On the other hand, more electron-deficient allyl phosphate **1k** readily underwent selective cyclopropanation in the absence of HMPA, as expected from its ability as a Michael acceptor (entry 11).[16] The use of γ,γ-diphenyl allyl phosphate **1l** also provided cyclopropanation product **3la** with relatively high selectivity (85/15; eqn (1)), and the reaction of α-methyl-γ-phenyl allyl phosphate **1m** with **2a** mostly gave cyclopropanation product **3ma** (97/3) as a mixture of stereoisomers (dr = 87/13; eqn(2)). With regard to the substituents on the phosphorus atom of lithium phosphides, other secondary alkyl groups such as cyclopentyl (**2b**) and isopropyl (**2c**) groups could be used for the reaction with allyl phosphate **1b** to give cyclopropanation products **3bb–bc** in good yields with excellent selectivity (≥97/3; entries 12 and 13). In addition, both primary and tertiary alkyl groups were effectively employed as well to give **3bd** with perfect selectivity and **3be** with 89% selectivity (entries 14 and 15). Unfortunately,

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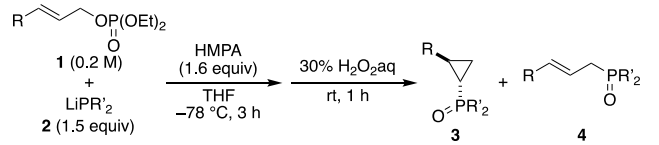
Table 2 Cyclopropanation of Allyl Phosphates **1** with Lithium Phosphides **2**



Entry	R	R'	**3**[a]	Yield of **3**+**4** (%)[b]	**3**/**4**[c]
1	(**1a**)	(**2a**)	**3aa**	77[d]	92/8[e]
2	Ph (**1b**)	**2a**	**3ba**	80	97/3
3	Cl (**1c**)	**2a**	**3ca**	76	99/1
4	OMe (**1d**)	**2a**	**3da**	86[d]	90/10[f]
5	Me (**1e**)	**2a**	**3ea**	67[d]	90/10[g]
6	(**1f**)	**2a**	**3fa**	97	97/3[h]
7	(**1g**)	**2a**	**3ga**	86	97/3[i]
8	S (**1h**)	**2a**	**3ha**	82	90/10[j]
9[k]	Ph, Ph (**1i**)	**2a**	**3ia**[l]	95	96/4
10[m]	Me (**1j**)	**2a**	**3ja**	90	0/100[n]
11[k]	O, OtBu (**1k**)	**2a**	**3ka**	70	100/0
12	**1b**	(**2b**)	**3bb**	70	100/0
13	**1b**	Me, Me (**2c**)	**3bc**	82	97/3
14	**1b**	Me, Me (**2d**)	**3bd**	86	100/0
15	**1b**	Me, Me, Me (**2e**)	**3be**	88	89/11[o]
16	**1b**	(**2f**)	**3bf**	80	0/100
17	CO_2Me (**1n**)	**2f**	**3nf**	76	100/0

[a] *trans*/*cis* > 99/1. [b] Combined isolated yield. [c] Determined by ^{1}H NMR. [d] Containing inseparable dicyclohexyl(3-arylpropyl)phosphine oxide (2–4%). [e] **4aa/4aa'** = 88/12. [f] **4da/4da'** = 89/11. [g] **4ea/4ea'** = 65/35. [h] **4fa/4fa'** = 50/50. [i] **4ga/4ga'** = 96/4. [j] **4ha/4ha'** = 80/20. [k] The reaction was conducted in the absence of HMPA. [l] *trans*/*cis* = 96/4. [m]

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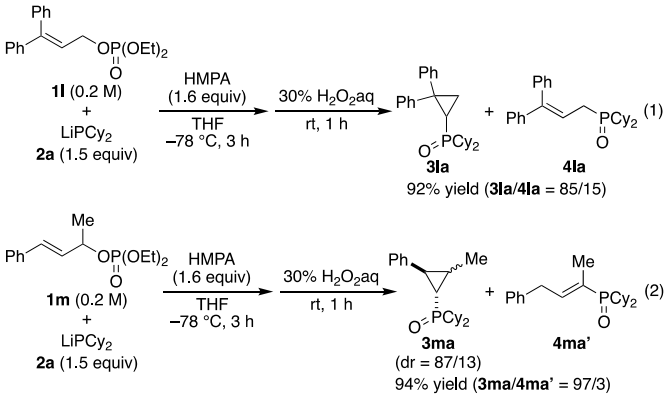
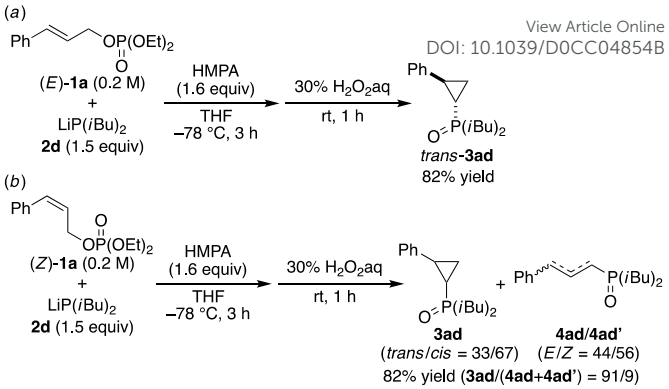
The reaction time for the first step was 30 min. [n] **4ja/4ja'** = 94/6. [o] **4be/4be'** = 62/38.

the use of lithium diphenylphosphide (**2f**) gave only allylic substitution product **4bf** from substrate **1b** under the present reaction conditions (entry 16), but somewhat electron-deficient 4-methoxycarbonyl-substituted cinnamyl phosphate **1n** completely reversed the selectivity to give cyclopropane **3nf** as the sole product in 76% yield (entry 17). It is worth noting that the present phosphinative cyclopropanation of (*E*)-allyl phosphates gives *trans*-cyclopropanes **3** with no formation of the corresponding *cis*-isomers in most cases as exemplified in the reaction of (*E*)-**1a** with **2d** (Scheme 2*a*). On the other hand, the reaction of (*Z*)-**1a** gave a mixture of *trans*-**3ad** and *cis*-**3ad** in favor of the *cis*-isomer along with some allylic substitution product **4ad** (Scheme 2*b*). These results indicate that addition of phosphide nucleophile and following three-membered ring formation take place more or less in a concerted manner on the opposite sides of the alkene with each other, rather than discrete formation of a carbanion intermediate in a stepwise fashion.

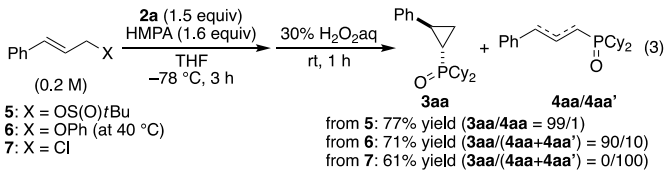


We subsequently examined the effect of the nature of leaving groups to gain further insight into the origin of selectivity in the present reaction. Cinnamyl *tert*-butylsulfinate **5**, presumably having a slightly weaker leaving group ability than **1a** based on the pK_a values of their conjugate acids (*t*BuS(O)(OH): 2.75[17] versus $(EtO)_2P(O)(OH)$: 1.39[18]), was found to react with **2a** to give cyclopropanation product **3aa** in 77% yield with a somewhat higher selectivity of 99/1 under the same reaction conditions (eqn (3)). Selective cyclopropanation (90/10) was also observed for the reaction of cinnamyl phenyl ether **6** with an even weaker leaving group (pK_a value of phenol: 10.0[19]),



Scheme 2 Comparison of reactions using (*a*) *E*- and (*b*) *Z*-cinnamyl phosphates.

although the reaction had to be conducted at a higher temperature. In contrast, cinnamyl chloride **7** having a much stronger leaving group resulted in the formation of allylic substitution product. These results, along with the trend observed in Table 2, indicate that the selectivity between cyclopropanation and allylic substitution seems to be partly controlled by the balance between electrophilicity at the β-position, which is mainly governed by the substituent at the γ-position, and the leaving group ability at the α-position.



In summary, we have developed a new cyclopropanation reaction of allyl phosphates with lithium phosphides to give cyclopropylphosphines through the formation of both a C–P bond and a cyclopropane ring at the same time. High selectivity toward cyclopropanation over allylic substitution has been realized by conducting the reaction in the presence of HMPA. We have also demonstrated the importance of choice of leaving groups and future studies will be directed toward further understanding of the origin of selectivity as well as development of cyclopropanation reactions with other nucleophiles.

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Conflicts of interest

There are no conflicts to declare.

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14 For the comparison between phosphorus and silicon nucleophiles, the reaction of **1a** with $LiSiMe_2Ph$ in THF at 0 °C gave the silylative cyclopropanation product selectively over allylic substitution (97/3) in the absence of HMPA (see ESI for details), indicating that a silyllithium is more nucleophilic than a lithium phosphide, and HMPA presumably coordinates to lithium to increase the nucleophilicity of the phosphide.

15 The structure of compound **3ca** was determined by X-ray crystallographic analysis. CCDC 2016109 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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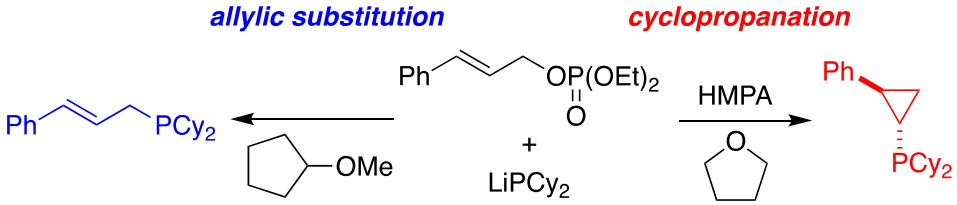

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