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# Brønsted Base-Catalyzed Transformation of α,β-Epoxyketones Utilizing [1,2]-Phospha-Brook Rearrangement for the Synthesis of Allylic Alcohols Having a Tetrasubstituted Alkene Moiety

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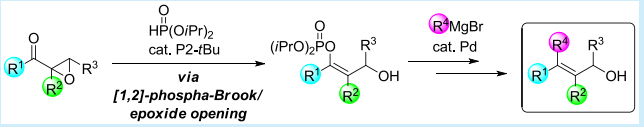
**ABSTRACT:** A stereoselective transformation of α,β-epoxyketones into alkenylphosphates having a hydroxymethyl group on the β-carbon was established by utilizing the [1,2]-phospha-Brook rearrangement under Brønsted base catalysis. The reaction involves the catalytic generation of an α-oxygenated carbanion located at the α-position of an epoxide moiety through the [1,2]-phospha-Brook rearrangement and the following epoxide opening. Further transformation of the alkenylphosphates by the palladium-catalyzed cross-coupling reaction with Grignard reagents provided allylic alcohols having a stereodefined all-carbon tetrasubstituted alkene moiety.






Allylic alcohols are a fundamental structural motif found in useful organic materials and an important class of versatile building blocks for organic synthesis.[1] Therefore, the synthesis of allylic alcohols having various types of substituent patterns has gained considerable attention and been intensively studied. However, the methods for the synthesis of allylic alcohols possessing a stereodefined multisubstituted alkene moiety, particularly a tetrasubstituted one, are still underdeveloped.[2] One of the most direct approaches for the synthesis of allylic alcohols is the 1,2-addition of alkenyl nucleophiles to aldehydes and ketones. However, this approach requires the preparation of alkenyl nucleophiles and is generally troublesome, which limits its application to the synthesis of allylic alcohols possessing a tetrasubstituted alkene moiety.[3] The 1,2-reduction of α,β-unsaturated carbonyl compounds or the 1,2-addition of nucleophiles to those compounds is also a reliable approach for the synthesis of allylic alcohols. However, the preparation of an α,β-unsaturated carbonyl compound having a tetrasubstituted alkene moiety is a formidable task.[2,4] On the other hand, the carbometalation of propargyl alcohols followed by the trapping of the resulting alkenyl metal species with electrophiles or the transformation by the transition-metal-catalyzed cross-coupling reaction was established as an alternative approach for the synthesis of allylic alcohols possessing a tetrasubstituted alkene moiety.[5,6] This approach involves the construction of a tetrasubstituted alkene moiety through the sequential introduction of two substituents onto an alkyne moiety of readily available propargyl alcohols and, thus, is more practical than conventional approaches. However, the accessible allylic alcohols are still limited even with this approach. Therefore, the development of conceptually new approaches characterized by an operationally simple protocol that uses readily available starting compounds is highly anticipated to expand the scope of accessible allylic alcohols.[7]

We have been focusing on the [1,2]-phospha-Brook rearrangement as a useful tool for the development of novel synthetic reactions under Brønsted base catalysis.[8] Specifically, we utilize the rearrangement for the catalytic generation of carbanions of less acidic compounds from the corresponding carbonyl compounds with dialkyl phosphites through the formal umpolung process.[9] During the course of our study on the extension of the utility of the methodology, we envisioned the direct catalytic transformation of α,β-epoxyketones into hydroxymethyl-substituted alkenylphosphates for use in the synthesis of allylic alcohols having a stereodefined tetrasubstituted alkene moiety. The designed reaction is shown in Scheme 1. Treatment of α,β-epoxyketone **1** having a substituent on the α-carbon with dialkyl phosphite **2** in the presence of a catalytic amount of Brønsted base would result in the 1,2-addition of the anion of **2** generated by the deprotonation, providing alkoxide **A**. Subsequently, the migration of the dialkoxyphosphoryl moiety from carbon to oxygen, i.e., the [1,2]-phospha-Brook rearrangement, would proceed to form carbanion **B** located at the α-position of the epoxide moiety. Finally, the epoxide opening, where the release of ring strain serves as the driving force, would occur in a stereoselective manner[10] and the following protonation would proceed to afford trisubstituted alkenylphosphate **3** along with regeneration of the Brønsted base catalyst or the anion of **2** to

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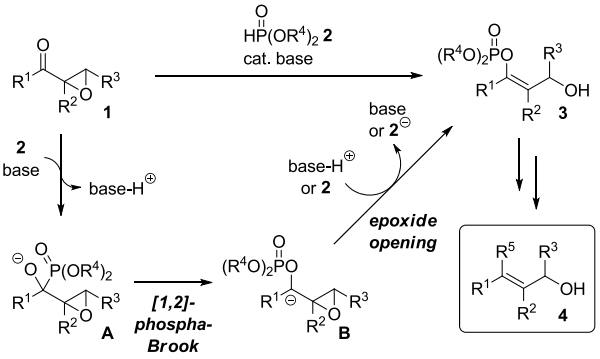
**Scheme 1. Our Reaction Design for the Synthesis of Allylic Alcohols Having a Tetrasubstituted Alkene Moiety**

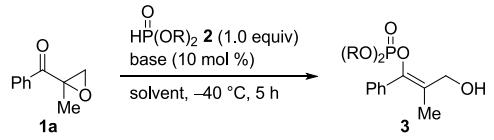



complete the catalytic cycle. Alkenylphosphates are widely used in transition metal-catalyzed cross-coupling reactions.[11] Thus, we expected that the phosphate moiety of **3** would be converted into carbon-based substituents, providing a variety of allylic alcohols **4** having a stereodefined all-carbon tetrasubstituted alkene moiety. Based on this reaction design, we report herein the stereoselective synthesis of trisubstituted alkenylphosphate under Brønsted base catalysis. The transformation of the phosphate moiety into carbon-based substituents via the palladium-catalyzed cross-coupling reaction is also described.

To ascertain the viability of the designed reaction, our investigation commenced with the treatment of **1a**, which has a phenyl group on the keto moiety and a methyl group on the $\alpha$ carbon, with diethyl phosphite (**2a**) in the presence of a catalytic amount of P2-*t*Bu ($pK_{BH+}$ = 21.5 in DMSO)[12] in DMF at −40 °C for 5 h. The intended reaction proceeded smoothly to provide **3aa** as a 91:9 *Z*/*E* mixture in 91% NMR yield along with $\alpha,\beta$-unsaturated ketone **6a** as the byproduct (Table 1. entry 1).[13,14] Thereafter, the screening of Brønsted bases was carried out. Among the organic bases tested, P4-*t*Bu ($pK_{BH+}$ = 30.3) provided **3aa** with a comparable result to P2-*t*Bu (entry 2), whereas the use of less basic P1-*t*Bu ($pK_{BH+}$ = 15.7) and TBD (1,5,7-triazabicyclo[4.4.0.]dec-5-ene) resulted in the reduction of yields of **3aa** and the formation of substantial amounts of epoxy alcohol **5aa** (entries 3 and 4). Furthermore, inorganic bases having strong basicity, such as *t*BuOK and KHMDS, were less effective than P2-*t*Bu (entries 5 and 6). The screening of solvents was then carried out (entries 7−11), and DMF was the solvent of choice from the point of view of both yield and *Z*/*E* selectivity (entry 1 vs entries 7−11). Examination of other dialkyl phosphites revealed that the employment of sterically bulkier diisopropyl phosphite (**2b**) improved *Z*/*E* selectivity (entry 12).[15] Finally, the use of 1.5 equiv of diisopropyl phosphite suppressed the formation of byproduct **6a**, and desired **3ab** was obtained in 97% NMR yield with 96:4 *Z*/*E* ratio (entry 14). Allylic alcohol **3ab** was converted into corresponding *tert*-butyl(dimethyl)silyl ether **7ab** in one-pot for easy isolation in pure form, and **7ab** was obtained in 89% isolated yield (eq 1). The reaction in a larger scale using 2.0 mmol of **1a** and 5.0 mol % P2-*t*Bu proceeded without any problem (94% isolated yield with 96:4 *Z*/*E* ratio).

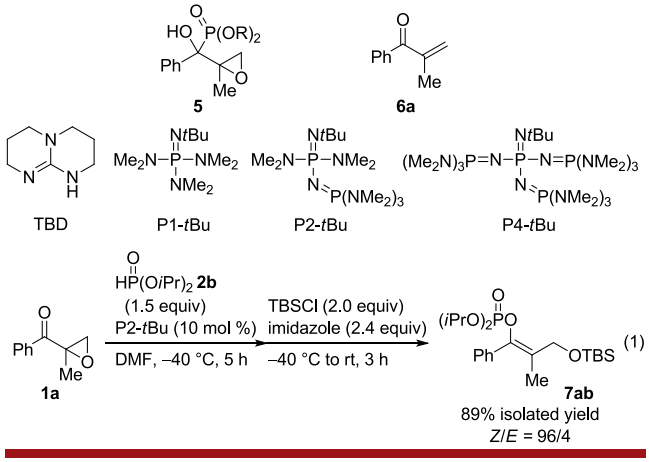
At this stage, some control experiments were carried out (Scheme 2). First, epoxyphosphate **8aa**, which would be potentially formed by the protonation of highly basic carbanion (**B** in Scheme 1), was treated with P2-*t*Bu in DMF. As a result, **3aa** was not formed at all, and most of **8aa**

**Table 1. Screening of Reaction Conditions**[a]

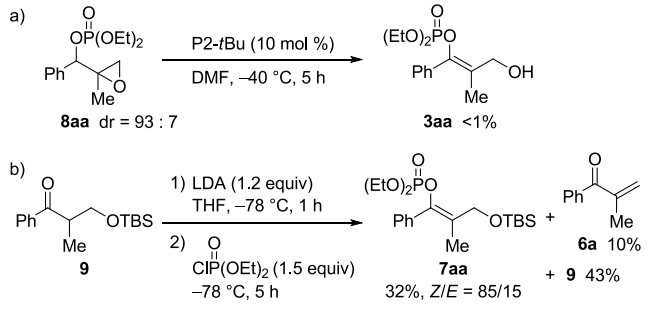



| | | | | | yield[b] (%) | | |
|---|---|---|---|---|---|---|---|
| entry | base | solvent | 2 | R | 3 (*Z*/*E*)[c] | 5 | 6a |
| 1 | P2-*t*Bu | DMF | **2a** | Et | 91 (91/9) | <1 | 5 |
| 2 | P4-*t*Bu | DMF | **2a** | Et | 89 (91/9) | <1 | 7 |
| 3 | P1-*t*Bu | DMF | **2a** | Et | 52 (93/7) | 45 | <1 |
| 4 | TBD | DMF | **2a** | Et | 12 (75/25) | 78 | 4 |
| 5 | *t*BuOK | DMF | **2a** | Et | 77 (86/14) | 7 | 9 |
| 6 | KHMDS | DMF | **2a** | Et | 71 (88/12) | 18 | 4 |
| 7 | P2-*t*Bu | $CH_3CN$ | **2a** | Et | 81 (84/16) | <1 | 7 |
| 8 | P2-*t*Bu | THF | **2a** | Et | 83 (88/12) | 6 | 7 |
| 9 | P2-*t*Bu | $Et_2O$ | **2a** | Et | 66 (89/11) | 16 | 7 |
| 10 | P2-*t*Bu | toluene | **2a** | Et | 66 (87/13) | 5 | 9 |
| 11 | P2-*t*Bu | $CH_2Cl_2$ | **2a** | Et | 86 (86/14) | <1 | 8 |
| 12 | P2-*t*Bu | DMF | **2b** | *i*Pr | 89 (95/5) | <1 | 5 |
| 13 | P2-*t*Bu | DMF | **2c** | Me | 88 (90/10) | <1 | 5 |
| 14[d] | P2-*t*Bu | DMF | **2b** | *i*Pr | 97 (96/4) | <1 | <1 |

[a]Conditions: **1a** (0.25 mmol), **2** (0.25 mmol), base (0.025 mmol), solvent (1.0 mL), −40 °C, 5 h. [b]NMR yields. [c]*Z*/*E* ratio was determined by $^1$H NMR analysis of the crude mixtures. [d]The reaction was conducted with **2b** (1.5 equiv, 0.38 mmol).




**Scheme 2. Control Experiments**




was recovered. This result indicates that **8aa** does not participate in the reaction and the epoxide opening occurs directly from the carbanion generated via the [1,2]-phospha-Brook rearrangement without undergoing the competing undesirable protonation. This result also shows the benefit of our methodology, that is, the catalytic generation of the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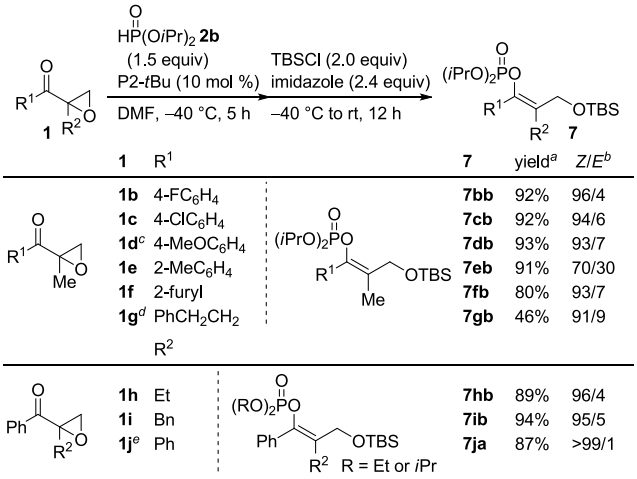
carbanion of a less acidic compound utilizing the [1,2]-phospha-Brook rearrangement. This transformation was accomplished owing to the generation of the carbanion of **8aa**, which was difficult to accomplish by direct deprotonation even with organosuperbases, such as P2-*t*Bu.[16] Next, the synthesis of **7aa** was attempted by using a conventional method for the synthesis of alkenylphosphates. Ketone **9** was treated with a stoichiometric amount of LDA and the resulting lithium enolate was trapped with diethyl chlorophosphate. As a result, **7aa** was obtained in modest yield with moderate *Z*/*E* selectivity along with the formation of byproduct **6a**. This experiment emphasizes the efficiency of the newly developed transformation for the stereoselective synthesis of alkenylphosphates having a hydroxymethyl group on the $\beta$-carbon.

With the optimized reaction conditions in hand, the scope of $\alpha,\beta$-epoxyketones was investigated. First, the scope of substituents on the keto moiety was examined (Scheme 3).

**Scheme 3. Substrate Scope**

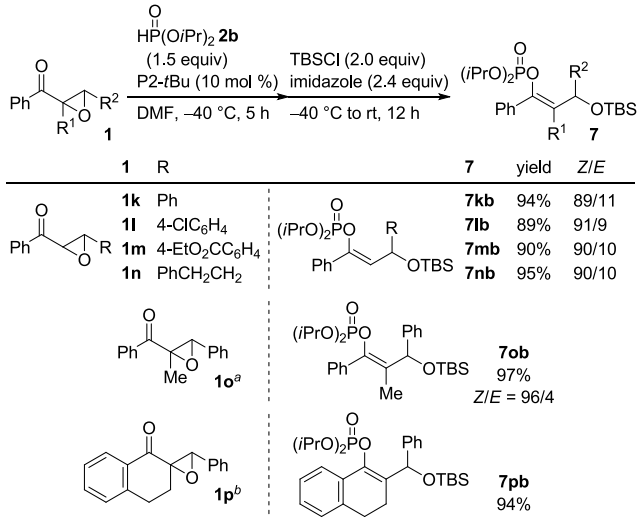



[a]Isolated yields. [b]Determined by $^1$H NMR analysis of the crude mixtures. [c]At −20 °C. [d]At rt. [e]With diethyl phosphite (**2a**) at −60 °C.

A variety of (hetero)aryl groups could be employed as substituents, and the corresponding alkenylphosphates were obtained in good yields. Among them, **1e** having a sterically hindered *o*-tolyl group reduced the *Z*/*E* selectivity. An alkyl group was also applicable as the substituent although the yield was moderate. The substituent on the $\alpha$-carbon was then screened. Substrates having other alkyl groups, such as ethyl and benzyl groups, underwent the reaction without any problem, and the corresponding **7hb** and **7ib** were obtained in high yields with good *Z*/*E* selectivities. In the case of **1j** having a phenyl group, the reaction with diisopropyl phosphite (**2b**) was rather sluggish. On the other hand, the reaction with diethyl phosphite (**2a**) proceeded smoothly to provide **7ja** as a single *Z* isomer in good yield.

Further investigation was carried out with substrates having a substituent on the $\beta$-carbon (Scheme 4). As a result, both aryl and alkyl groups were applicable as a substituent at that position. In the case of substrates without a substituent on the $\alpha$-carbon, **1k**−**1n**, the reaction provided the corresponding trisubstituted alkenylphosphates in good yields with slightly lower *Z*/*E* selectivities. Substrates **1o** and **1p** having substituents on both the $\alpha$- and $\beta$-carbons were also tested, and **7ob** and **7pb** were successfully obtained in high yields, respectively.

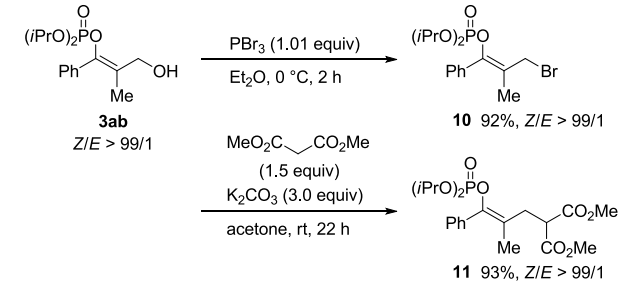
**Scheme 4. Reaction with Substrates Having a Substituent on the $\beta$-Carbon**




[a]TBSCl (5.0 equiv) and imidazole (6.0 equiv) were used. [b]TBSCl (4.0 equiv) and imidazole (4.8 equiv) were used.

Next, derivatization based on the hydroxy group of alkenylphosphates **3** was attempted (Scheme 5). Treatment

**Scheme 5. Derivatization of 3ab**




of *Z* isomer of **3ab** with $PBr_3$ provided corresponding allylic bromide **10**. Subsequently, the alkylation with dimethyl malonate as the pronucleophile was performed to provide **11** in good overall yield. Importantly, in the course of the derivatization, the phosphate moiety was intact and the stereochemistry of the alkene moiety was maintained. Thus, the present reaction would be potentially applicable to the synthesis of a variety of stereodefined multisubstituted alkenylphosphates.

Finally, we examined the palladium-catalyzed cross-coupling reaction of **7** to accomplish the synthesis of allylic alcohols having an all-carbon tetrasubstituted alkene moiety (Scheme 6). Brief screening of the reaction conditions with **7ab** as the substrate revealed that $PdCl_2(PCy_3)_2$ (Cy = cyclohexyl) efficiently catalyzed the cross-coupling reaction with aryl Grignard reagents to provide **12aa** and **12ab** in good yields with retention of the stereochemistry of the alkene moiety.[17] Similar reaction conditions were applied to the reaction with methylmagnesium bromide and corresponding **12ac** was obtained in good yield. The reaction with butylmagnesium bromide resulted in a moderate yield of **12ad** along with a substantial amount of reduced product **14**, whereas the use of cyclopentylmagnesium bromide exclusively provided **14**. The reactions of **7gb** and **7ib** proceeded without any problem. In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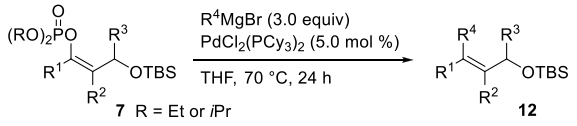
**Scheme 6. Transformation of 7 via Palladium-Catalyzed Cross-Coupling Reaction with Grignard Reagents**[a]




| 7 | 12 | $R^4$ | yield[b] | Z/E[c] |
|---|---|---|---|---|
| **7ab** Z/E = 96/4 (**12aa-12ae**) | **12aa** | 4-MeOC$_6$H$_4$ | (91%) | 96/4 |
| | **12ab** | 4-MeC$_6$H$_4$ | 86% | 95/5 |
| | **12ac** | Me | 91% | 4/96 |
| | **12ad** | *n*Bu | 53%[d] | 6/94 |
| | **12ae** | *c*C$_6$H$_9$ | <1%[e] | - |
| **7gb** Z/E = 90/10 | **12ga** | 4-MeOC$_6$H$_4$ | 73% | 90/10 |
| **7ib** Z/E = 94/6 (**12ia,12jc**) | **12ia** $R^2$ = Bn | 4-MeOC$_6$H$_4$ | 76% | 94/6 |
| **7ja** Z/E >99/1 | **12jc** $R^2$ = Ph | Me | 83% | 2/98 |
| **7kb** Z/E >99/1 (**12ka-c**) | **12ka**[f] | 4-MeOC$_6$H$_4$ | 99% | >99/1 |
| | **12kc** | Me | 77% | 1/>99 |
| **7ob** Z/E >99/1 | **12oa**[g] | 4-MeOC$_6$H$_4$ | 83% | 99/1 |

**13** **14**

[a]Conditions: **7** (0.10 mmol), Grignard reagent (0.30 mmol), $PdCl_2(PCy_3)_2$ (5.0 μmol), THF (1.0 mL), 70 °C, 24 h. [b]NMR yields. Isolated yield is shown in parentheses. [c]Determined by $^1$H NMR analysis of the crude mixtures. [d]**14** was obtained in 20% isolated yield (*Z*/*E* = 6/94). [e]**14** was obtained in 72% NMR yield (*Z*/*E* = 14/86). [f]In $Et_2O$ at 40 °C. [g]With $Pd_2(dba)_3$ (2.5 μmol) and (4-MeC$_6$H$_4$)$_3$P (10 μmol).

the case of **7ja** with methylmagnesium bromide, the reaction provided the corresponding product in good yield albeit with the slight degradation of the *Z*/*E* ratio. **7kb** also participated in the cross-coupling reaction with both aryl- and methylmagnesium bromide and corresponding products **12ka** and **12kc** having a trisubstituted alkene moiety were generated in good to high yields. **7ob** was much less reactive than the other substrates. After additional screening of catalysts, the catalyst generated from $Pd_2(dba)_3$ and tri(*p*-tolyl)phosphine was found to facilitate the reaction to provide **12oa** in 83% NMR yield. Many silylethers **12** were difficult to isolate in pure form by silica gel column chromatography because of the inseparable phosphine residue derived from the palladium complexes, and thus, the products were isolated as the corresponding allylic alcohols **13** after the desilylation by treatment with aqueous HCl in methanol or TBAF in THF.[17]

In conclusion, we have developed a stereoselective transformation of α,β-epoxyketones into alkenylphosphates having a hydroxymethyl group on the β-carbon by utilizing the [1,2]-phospha-Brook rearrangement under Brønsted base catalysis. The reaction involves the catalytic generation of an α-oxygenated carbanion located at the α-position of an epoxide moiety through the [1,2]-phospha-Brook rearrangement and the following epoxide opening. The resulting alkenylphosphates are amenable to further transformation by the palladium-catalyzed cross-coupling reaction with Grignard reagents with retention of the stereochemistry of the alkene moiety. This newly developed operationally simple protocol opens up an avenue for the synthesis of allylic alcohols having a stereodefined tetrasubstituted alkene moiety.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01765.

Additional experimental results, experimental procedures, and characterization data (PDF)

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

(1) (a) Lumbroso, A.; Cooke, M. L.; Breit, B. Catalytic Asymmetric Synthesis of Allylic Alcohols and Derivatives and their Applications in Organic Synthesis. *Angew. Chem., Int. Ed.* **2013**, *52*, 1890−1932. (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. Substrate-Directable Chemical Reactions. *Chem. Rev.* **1993**, *93*, 1307−1370. (c) Cha, J. K.; Kim, N.-S. Acyclic Stereocontrol Induced by Allylic Alkoxy Groups. Synthetic Applications of Stereoselective Dihydroxylation in Natural Product Synthesis. *Chem. Rev.* **1995**, *95*, 1761−1795. (d) Sundararaju, B.; Achard, M.; Bruneau, C. Transition metal catalyzed nucleophilic allylic substitution: activation of allylic alcohols *via* π-allylic species. *Chem. Soc. Rev.* **2012**, *41*, 4467−4483.

(2) (a) Flynn, A. B.; Ogilvie, W. W. Stereocontrolled Synthesis of Tetrasubstituted Olefins. *Chem. Rev.* **2007**, *107*, 4698−4745. (b) Polák, P.; Váňová, H.; Dvořák, D.; Tobrman, T. Recent progress in transition metal-catalyzed stereoselective synthesis of acyclic all-carbon tetrasubstituted alkenes. *Tetrahedron Lett.* **2016**, *57*, 3684−3693.

(3) For selected examples, see: (a) Aikawa, K.; Hioki, Y.; Mikami, K. Highly Enantioselective Alkenylation of Glyoxylate with Vinylsilane Catalyzed by Chiral Dicationic Palladium(II) Complexes. *J. Am. Chem. Soc.* **2009**, *131*, 13922−13923. (b) Xie, M.; Lin, G.; Zhang, J.; Li, M.; Feng, C. Regio- and stereoselective synthesis of tetrasubstituted allylic alcohols by three-component reaction of acetylenic sulfone, dialkylzinc, and aldehyde. *J. Organomet. Chem.* **2010**, *695*,

882−886. (c) Xie, M.; Feng, C.; Zhang, J.; Liu, C.; Fang, K.; Shu, G.; Zuo, W. CuI-catalyzed tandem carbomagnesiation/carbonyl addition of Grignard reagents with acetylenic ketones: Convenient access to tetrasubstituted allylic alcohols. *J. Organomet. Chem.* **2011**, *696*, 3397−3401. (d) Li, Y.; Xu, M.-H. Rhodium-Catalyzed Asymmetric Tandem Cyclization for Efficient and Rapid Access to Underexplored Heterocyclic Tertiary Allylic Alcohols Containing a Tetrasubstituted Olefin. *Org. Lett.* **2014**, *16*, 2712−2715.

(4) For selected recent examples, see: (a) Trost, B. M.; Tracy, J. S. Vanadium-Catalyzed Synthesis of Geometrically Defined Acyclic Tri- and Tetrasubstituted Olefins from Propargyl Alcohols. *ACS Catal.* **2019**, *9*, 1584−1594. (b) Wei, Y.-M.; Ma, X.-D.; Wang, L.; Duan, X.-F. Iron-catalyzed stereospecific arylation of enol tosylates using Grignard reagents. *Chem. Commun.* **2020**, *56*, 1101−1104. (c) Sato, Y.; Ashida, Y.; Yoshitake, D.; Hoshino, M.; Takemoto, T.; Tanabe, Y. Stereoretentive Suzuki-Miyaura and Kumada-Tamao-Corriu Cross-Couplings for Preparing (*E*)- and (*Z*)-Stereodefined, Fully Substituted $\alpha,\beta$-Unsaturated Esters: Application for a Pharmacophore Synthesis. *Synthesis* **2018**, *50*, 4659−4667. (d) Cardinal, S.; Voyer, N. Preparation of 2,3,3-Triarylacylic Acid Esters Using Suzuki-Miyaura Coupling Reactions. *Synthesis* **2016**, *48*, 1202−1216.

(5) For selected reviews, see: (a) Normant, J. F.; Alexakis, A. Carbometallation (*C*-Metallation) of Alkynes: Stereospecific Synthesis of Alkenyl Derivatives. *Synthesis* **1981**, *1981*, 841−870. (b) Murakami, K.; Yorimitsu, H. Recent advances in transition-metal-catalyzed intermolecular carbomagnesiation and carbozincation. *Beilstein J. Org. Chem.* **2013**, *9*, 278−302. (c) Müller, D. S.; Marek, I. Copper mediated carbometalation reactions. *Chem. Soc. Rev.* **2016**, *45*, 4552−4566.

(6) For selected examples, see: (a) Jin, H.; Fürstner, A. Regioselective *trans*-Carboboration of Propargyl Alcohols. *Org. Lett.* **2019**, *21*, 3446−3450. (b) Zhang, X.; Lu, Z.; Fu, C.; Ma, S. Synthesis of highly substituted allylic alcohols by a regio- and stereo-defined CuCl-mediated carbometallation reaction of 3-aryl-substituted secondary propargylic alcohols with Grignard reagents. *Org. Biomol. Chem.* **2009**, *7*, 3258−3263. (c) Tessier, P. E.; Penwell, A. J.; Souza, F. E. S.; Fallis, A. G. (*Z*)-Tamoxifen and Tetrasubstituted Alkenes and Dienes via a Regio- and Stereospecific Three-Component Magnesium Carbometalation Palladium(0) Cross-Coupling Strategy. *Org. Lett.* **2003**, *5*, 2989−2992.

(7) For selected other examples, see: (a) Majhi, J.; Turnbull, B. W. H.; Ryu, H.; Park, J.; Baik, M.-H.; Evans, P. A. Dynamic Kinetic Resolution of Alkenyl Cyanohydrins Derived from $\alpha,\beta$-Unsaturated Aldehydes: Stereoselective Synthesis of *E*-Tetrasubstituted Olefins. *J. Am. Chem. Soc.* **2019**, *141*, 11770−11774. (b) Shi, L.; He, Y.; Gong, J.; Yang, Z. Pd-Catalyzed Decarboxylative Allylation for Stereoselective Syntheses of Allylic Alcohols bearing a Quaternary Carbon Center. *Asian J. Org. Chem.* **2019**, *8*, 823−827. (c) Zhang, J.; Liang, Z.; Wang, J.; Guo, Z.; Liu, C.; Xie, M. Metal-Free Synthesis of Functionalized Tetrasubstituted Alkenes by Three-Component Reaction of Alkynes, Iodine, and Sodium Sulfinates. *ACS Omega* **2018**, *3*, 18002−18015. (d) Gómez, J. E.; Guo, W.; Kleij, A. J. Palladium-Catalyzed Stereoselective Formation of Substituted Allylic Thioethers and Sulfones. *Org. Lett.* **2016**, *18*, 6042−6045. (e) Guo, W.; Martínez-Rodríguez, L.; Kuniyil, R.; Martin, E.; Escudero-Adán, E. C.; Maseras, F.; Kleij, A. W. Stereoselective and Versatile Preparation of Tri- and Tetrasubstituted Allylic Amine Scaffolds under Mild Conditions. *J. Am. Chem. Soc.* **2016**, *138*, 11970−11978. (f) He, Z.; Kirchberg, S.; Fröhlich, R.; Studer, A. Oxidative Heck Arylation for the Stereoselective Synthesis of Tetrasubstituted Olefins Using Nitroxides as Oxidants. *Angew. Chem., Int. Ed.* **2012**, *51*, 3699−3702. (g) Fernández-Mateos, A.; Madrazo, S. E.; Teijón, P. H.; González, R. R. Titanocene-Promoted Eliminations on Epoxy Alcohols and Epoxy Esters. *Eur. J. Org. Chem.* **2010**, *2010*, 856−861. (h) Yang, Y.; Zhu, S.-F.; Zhou, C.-Y.; Zhou, Q.-L. Nickel-Catalyzed Enantioselective Alkylative Coupling of Alkynes and Aldehydes: Synthesis of Chiral Allylic Alcohols with Tetrasubstituted Olefins. *J. Am. Chem. Soc.* **2008**, *130*, 14052−14053. (i) Yamago, S.; Fujita, K.; Miyoshi, M.; Kotani, M.; Yoshida, J. Stereoselective Synthesis of Multisubstituted Alkenes via Conformationally Labile Alkenyllithium Species. *Org. Lett.* **2005**, *7*, 909−911.

(8) For selected recent examples, see: (a) Horwitz, M. A.; Zavesky, B. P.; Martinez-Alvarado, J. I.; Johnson, J. S. Asymmetric Organocatalytic Reductive Coupling Reactions between Benzylidene Pyruvates and Aldehydes. *Org. Lett.* **2016**, *18*, 36−39. (b) Horwitz, M. A.; Tanaka, N.; Yokosaka, T.; Uraguchi, D.; Johnson, J. S.; Ooi, T. Enantioselective reducitive multicomponent coupling reactions between isatins and aldehydes. *Chem. Sci.* **2015**, *6*, 6086−6090. (c) Corbett, M. T.; Uraguchi, D.; Ooi, T.; Johnson, J. S. Base-Catalyzed Direct Aldolization of $\alpha$-Alkyl-$\alpha$-Hydroxy Trialkyl Phosphonoacetates. *Angew. Chem., Int. Ed.* **2012**, *51*, 4685−4689. (d) Demir, A. S.; Esiringü, I.; Göllü, M.; Reis, Ö. Catalytic Intermolecular Aldehyde-Ketone Coupling via Acyl Phosphonates. *J. Org. Chem.* **2009**, *74*, 2197−2199. (e) Demir, A. S.; Eymur, S. Addition of Trifluoromethyltrimethylsilane to Acyl Phophonates: Synthesis of TMS-Protected 1-Alkyl-1-trifluoromethyl-1-hydroxyphophonates and 1-Aryldifluoroethenyl Phosphates. *J. Org. Chem.* **2007**, *72*, 8527−8530. (f) Bausch, C. C.; Johnson, J. S. Cyanide-Catalyzed Additions of Acyl Phophonates to Aldehydes: A New Acyl Donor for Benzoin-Type Reactions. *Adv. Synth. Catal.* **2005**, *347*, 1207−1211. (g) Demir, A. S.; Reis, Ö.; İğdir, A. Ç.; Esiringü, İ.; Eymur, S. Generation of Acyl Anion Equivalents from Acylphosphonates via Phosphonate-Phosphate Rearrangement: A Highly Practical Method for Cross-Benzoin Reaction. *J. Org. Chem.* **2005**, *70*, 10584−10587. (h) Kondoh, A.; Terada, M. Brønsted Base Catalyzed [2,3]-Wittig/Phospha-Brook Tandem Rearragement Sequence. *Org. Lett.* **2013**, *15*, 4568−4571. (i) Hayashi, M.; Nakamura, S. Catalytic Enantioselective Protonation of $\alpha$-Oxygenated Ester Enolates Prepared through Phospha-Brook Rearrangement. *Angew. Chem., Int. Ed.* **2011**, *50*, 2249−2252. (j) El Kaïm, L.; Gaultier, L.; Grimaud, L.; Dos Santos, A. Formation of New Phosphates from Aldehydes by a DBU-Catalysed Phospha-Brook Rearrangement in a Polar Solvent. *Synlett* **2005**, 2335−2236.

(9) (a) Kondoh, A.; Iino, A.; Ishikawa, S.; Aoki, T.; Terada, M. Efficient Synthesis of Polysubstituted Pyrroles Based on [3 + 2] Cycloaddition Strategy Utilizing [1,2]-Phospha-Brook Rearrangement under Brønsted Base Catalysis. *Chem. - Eur. J.* **2018**, *24*, 15246−15253. (b) Kondoh, A.; Terada, M. Brønsted Base-Catalyzed Umpolung Intramolecular Cyclization of Alkynyl Imines. *Chem. - Eur. J.* **2018**, *24*, 3998−4001. (c) Kondoh, A.; Ozawa, R.; Aoki, T.; Terada, M. Intramolecular addition of benzyl anion to alkyne utilizing [1,2]-phospha-Brook rearrangement under Brønsted base catalysis. *Org. Biomol. Chem.* **2017**, *15*, 7277−7281. (d) Kondoh, A.; Aoki, T.; Terada, M. Generation and Application of Homoenolate Equivalents Utilizing [1,2]-phospha-Brook Rearrangemnt under Brønsted Base Catalysis. *Chem. - Eur. J.* **2017**, *23*, 2769−2773. (e) Kondoh, A.; Terada, M. Brønsted base-catalyzed three-component coupling reaction of $\alpha$-ketoesters, imines, and diethyl phosphite utilizing [1,2]-phospha-Brook rearrangement. *Org. Biomol. Chem.* **2016**, *14*, 4704−4711. (f) Kondoh, A.; Aoki, T.; Terada, M. Synthesis of Phenanthrene Derivatives by Intramolecular Cyclization Utilizing the [1,2]-Phospha-Brook Rearrangemnet Catalyzed by a Brønsted Base. *Chem. - Eur. J.* **2015**, *21*, 12577−12580. (g) Kondoh, A.; Aoki, T.; Terada, M. Intramolecular Cyclization of Alkynyl $\alpha$-Ketoanilide Utilizing [1,2]-Phospha-Brook Rearrangement Catalyzed by Phosphazene Base. *Org. Lett.* **2014**, *16*, 3528−3531.

(10) Kondoh, A.; Akahira, S.; Oishi, M.; Terada, M. Enantioselective Formal [3 + 2] Cycloaddition of Epoxides with Imines under Brønsted Base Catalysis: Synthesis of 1,3-Oxazolidines with Quaternary Stereogenic Center. *Angew. Chem., Int. Ed.* **2018**, *57*, 6299−6303.

(11) For selected reviews, see: (a) Protti, S.; Fagnoni, M. Phosphate esters as "tunable" reagents in organic synthesis. *Chem. Commun.* **2008**, 3611−3621. (b) Sellars, J. D.; Steel, P. G. Transition metal-catalyzed cross-coupling reactions of P-activated enols. *Chem. Soc. Rev.* **2011**, *40*, 5170−5180.

(12) Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletschinger, M.; Boele, J.;



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Fritz, H.; Putzas, D.; Rotter, H. W.; Boldwell, F. G.; Satish, A. V.; Ji, G.-Z.; Peters, E. M.; Peters, K.; von Schnering, H. G.; Walz, L. Extremely Strong, Uncharged Auxiliary Bases: Monomeric and Polymer-Supported Polyaminophosphazenes ($P_2$-$P_5$). *Liebigs Ann.* **1996**, *1996*, 1055−1081.
(13) The *Z*/*E* configuration of **3aa** was determined by NOE analysis. See the Supporting Information for details
(14) **6a** would form through the 1,5-migration of the diethoxyphosphoryl group followed by *β*-elimination.
(15) The use of diphenyl phosphite resulted in no reaction.
(16) Treatment of **8aa** with P4-*t*Bu provided results similar to those of P2-*t*Bu.
(17) See the Supporting Information for details.



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