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# Modular and Highly Stereoselective Approach to All-Carbon Tetrasubstituted Alkenes

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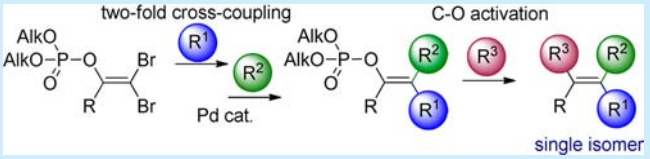
Supporting Information

**ABSTRACT:** A modular and completely stereoselective approach for the construction of all-carbon tetrasubstituted alkenes is described. It is based on the three-fold, sequential metal-catalyzed, cross-coupling functionalization of simple enolphosphate dibromide templates with carbon nucleophiles, affording tetrasubstituted alkenes as single isomers.



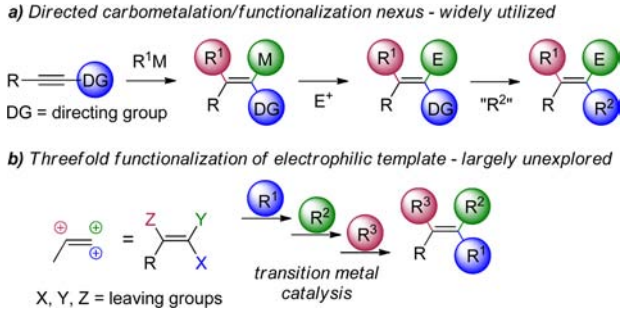

Tetrasubstituted alkene is a simple, yet important motif occurring in many substances, including pharmaceuticals and bioactive natural products.[1−3] In addition, all-carbon tetrasubstituted alkenes possess extraordinary structural, electronic, and chemical properties and are also key substrates in various asymmetric processes (hydrogenations, epoxidations, etc.), generating highly congested vicinal stereogenic centers.[4−6]

Efficient synthesis of noncyclic, single-isomer tetrasubstituted alkenes represents a daunting challenge for organic chemists. Among many routes to tetrasubstituted alkenes, direct carbometalation of internal alkynes is by far the most frequently utilized strategy, and remarkable achievements have been made.[7] However, to achieve both regio- and stereocontrolled synthesis, the structure of the starting alkyne must fulfill certain steric conditions or require the presence of a suitable directing group. The most successful and selective approaches utilize regioselective carbometalation to generate multimetalated templates, which serve as formal doubly or triply nucleophilic synthons amenable to further elaboration. This ultimately creates an elementometalation/functionalization nexus.[8] Transition-metal-catalyzed cascade reactions,[9] oxidative Heck reaction,[10] metathesis reaction,[11] or protocols based on chemistry of ynolates[12a,b] or ketenes[12c] can be mentioned as other frequently used methods for the synthesis of tetrasubstituted alkenes.

Surprisingly, significantly less attention has been paid to the use of solely electrophilic templates (Scheme 1). Thus, the two-fold cross-coupling reactions of tetrasubstituted double bonds bearing vicinal[13] or geminal[14] substituents have been reported, but the most versatile (and challenging at the same time) approaches would take advantage of three consecutive cross-coupling reactions of the olefin template. Only one example of such an approach utilizing $CF_3$-substituted alkenes has been reported so far, but separation of isomers was required in this case.[15]

As a part of our ongoing project for the development of new bioactive compounds, we envisioned the cross-coupling functionalization of simple halogenated enol-type templates as an amenable route to tetrasubstituted olefins. The structure of the proposed template plays a crucial role in terms of controlling

**Scheme 1. Electrophilic Templates in the Stereoselective Synthesis of Tetrasubstituted Alkenes**




the regio- and stereochemical outcome of the overall process. The presence of the activated C−O bond allows the discrimination of geminal halogen atoms with subsequent formation of two carbon−carbon bonds. At the same time, it serves as a latent leaving group for the formation of a third C−C bond.

Therefore, several types of halogenated enolesters **1a−f** were prepared, sulfonates, carboxylate, or phosphate esters,[16] and conditions for their selective monoarylation were screened (Table 1). After the exhaustive optimization, Negishi reaction of chlorinated phosphate **1a** with *p*-tolylzinc chloride in the presence of $PdCl_2$(dppp) afforded alkene (*Z*)-**3a** in 84% yield (Table 1, entry 1). On the contrary, reaction of phenylzinc chloride or phenylmagnesium chloride with the brominated analogue afforded only the product of the elimination (Table 1, entry 2). Switching to phenylboronic acid restored the stereospecific coupling and gave the product (*Z*)-**3b** in 89% yield (Table 1, entry 3), indicating that the fine-tuning of the reaction conditions is necessary for obtaining the desired product. It was important to use optimized conditions for the cross-coupling reaction; otherwise, the reaction failed to give the

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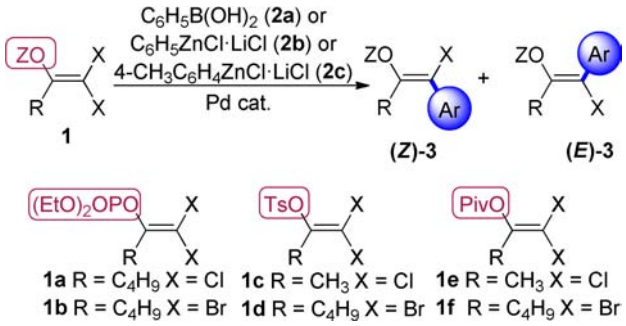
**Table 1. Optimization of Stereo- and Regioselective Cross-Coupling Reaction of Enolesters 1a−f with Phenylboronic Acid and Phenylzinc Chloride**




| entry | 1 | 2 | catalyst | product (%)[a] |
|---|---|---|---|---|
| 1 | **1a** | **2c** | $PdCl_2$(dppp) | (*Z*)-**3a**, 84[b] |
| 2 | **1b** | **2c** | $PdCl_2$(dppp) | *c* |
| 3 | **1b** | **2a** | $Pd(OAc)_2$, $PPh_3$ | (*Z*)-**3b**, 89[b] |
| 4 | **1c** | **2a** | $Pd(OAc)_2$, $PPh_3$ | 40,[d] 5:1[e] |
| 5 | **1d** | **2a** | $Pd(OAc)_2$, $PPh_3$ | 100,[d] 3:1[e] |
| 6 | **1e** | **2b** | $PdCl_2$(dppp) | *f* |
| 7 | **1f** | **2a** | $Pd(OAc)_2$, $PPh_3$ | <10[d] |

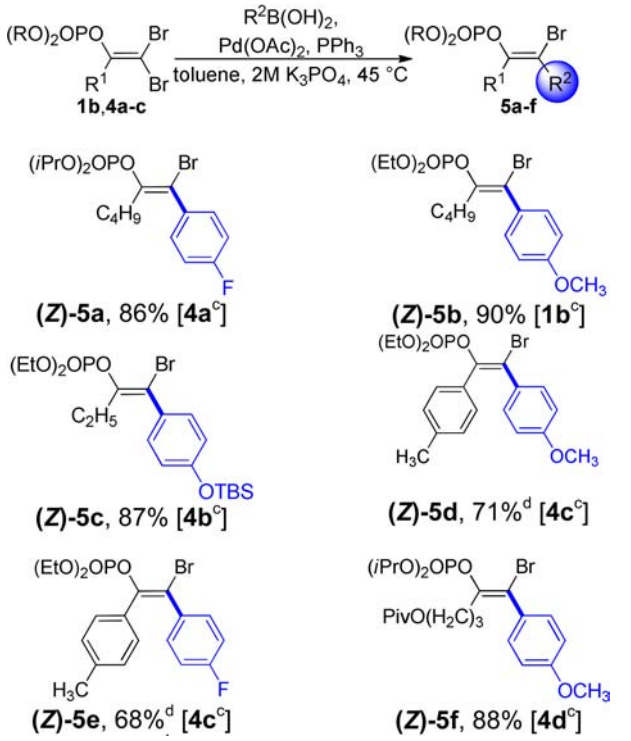
[a]Isolated yield. [b]Isolated product was >98% *Z*. [c]Formation of 1-phenyl-1-hexyne was observed. [d]Conversion of starting compound. [e]*Z*/*E* ratio. [f]No cross-coupling reaction was observed.

expected alkenes (*Z*)-**3a,b**, and side reactions including elimination occurred. In case of tosylates **1c,d**, the Suzuki reaction with phenylboronic acid proceeded smoothly; however, a mixture of (*Z*)- and (*E*)-alkenes was formed (Table 1, entries 4 and 5). Pivalates **1e,f** failed to give the expected alkenes, and unreacted starting compounds were detected in the crude reaction mixture. These observations indicate that the rate of oxidation addition of enolphosphates **1a,b** is responsible for the chemo- and stereoselectivity outcome of the reaction.[17]

After establishing the optimized reaction condition for selective arylation, we applied the Suzuki reaction of enol phosphates **1a−c** with boronic acid to the reaction of phosphates **4a−d** with various boronic acids. Thus, boronic acids bearing fluorine atoms or electron-donating groups were successfully coupled with phosphate substituted with a simple alkyl group (Scheme 2). The presence of a functionality in the structure of starting phosphates **4c,d** was well-tolerated, as shown in the preparation of functionalized phosphate (*Z*)-**5f**.

In the next step, we again took advantage of the different reactivity of C−Br and C−O bonds to install the second carbon group. To this end, Suzuki reaction was chosen again; however, an undesired erosion of the double bond geometry was observed with the majority of tested catalytic systems. Only the use of a RuPhos supported Pd catalyst allowed the functionalization of the starting material without any isomerization of the double bond. As shown in Scheme 3, boronic acids coupled with enolphosphates (*Z*)-**3b** and (*Z*)-**5b,d,e** afforded the expected stereoisomers (*Z*)-**6a,b** and (*E*)-**6a,b** in high yields. The structure and isomeric purity of the stereoisomers (*Z*)-**6a,b** and (*E*)-**6a,b** were determined by comparison of $^{13}C$ NMR spectra and NOE experiment. The Negishi reaction of (*Z*)-**5f** with 3-$CF_3C_6H_4ZnCl$·LiCl also proceeded successfully (Scheme 3). The functionalized neopentylglycol boronate and styrenylboronic acid were used as starting compounds for the production of the expected products (*E*)-**6d** and (*Z*)-**6e** in uniformly high yields. All attempts to introduce alkyl groups using alkylboron

**Scheme 2. Stereoselective Cross-Coupling of Enolphosphates 1b and 4a−c with Arylboronic Acid[a,b]**




[a]Isolated yield. [b]Alkenes were isolated as a single stereoisomer (>98% *Z*). [c]Starting compound. [d]Reaction was carried out at 60 °C.

reagents, alkylzinc halides, or trialkylaluminums were not successful. Only products of elimination and/or reduction were obtained. The only exception was the methylation with $(CH_3)_3In$, which gave the corresponding methyl derivative (*Z*)-**6f** in 88% yield (Scheme 3). Developed methodology enabled introduction of a hetaryl substituent, as demonstrated in the reaction of phosphate (*Z*)-**3b** with 2-thienylboronic acid, where the expected product (*Z*)-**5g** was prepared in 86% yield (Scheme 3).

With the series of stereodefined phosphates in hand, introduction of the third carbon group was required to complete the stereoselective synthesis of tetrasubstituted alkenes. The Pd-catalyzed reaction with boronic acids led to low conversion and/or decomposition, while Ni catalysts, which are particularly useful for the activation of unreactive C−O bonds, afforded a mixture of geometrical isomers. Therefore, we turned our attention to the Kumada coupling.[18] It was necessary to use DMAEE-complexed Grignard reagents and $PdCl_2$(XantPhos) as the catalyst in THF to prevent the formation of undesired byproducts and to achieve stereospecific coupling.[19] Under these conditions, no trace of alkene geometry erosion was observed. Thus, *p*-tolyl, phenyl, and benzylmagnesium chlorides afforded the corresponding tetrasubstituted alkenes in high yields as single isomers, which was confirmed by the preparation of each *E* and *Z* isomer of compound (*Z*)-**7a,b** and (*E*)-**7a,b** (Scheme 4). In contrast, the results with simple alkyl (ethyl, allyl) Grignard reagents were unsatisfactory. Therefore, cross-coupling with trialkylaluminums was used instead to install methyl, allyl, and benzyl groups on substrates (*E*)-**7d** and (*Z*)-**7e,f**. In addition, application of trialkylaluminums opens a route to stereoselective functionalization of enolphosphate **6** under mild conditions.



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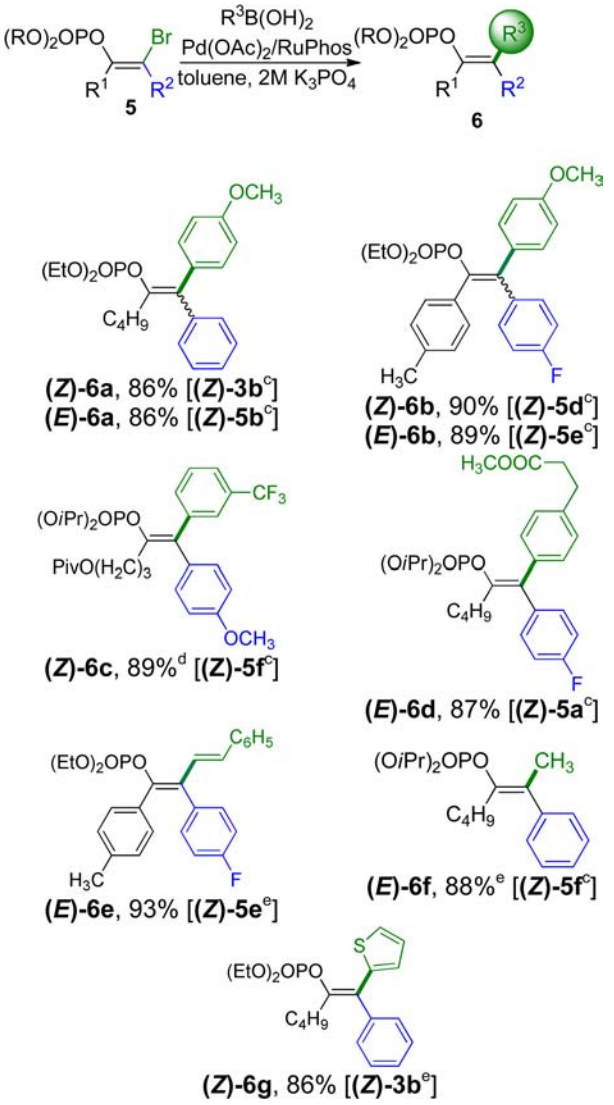
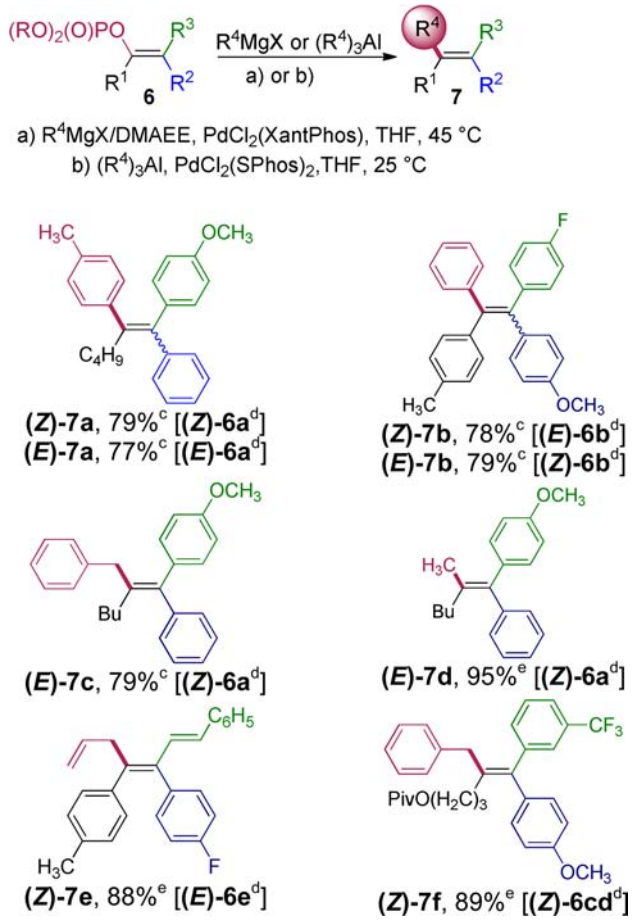
**Scheme 3. Preparation of Stereodefined Trisubstituted Enolphosphate 6 by the Cross-Coupling Reaction of Phosphates 5[a,b]**




[a]Isolated yield. [b]Alkenes were isolated as a single stereoisomers (>98% *Z* or *E*). [c]Starting compound. [d]Cross-coupling reaction of (*Z*)-**5f** with 3-$CF_3C_6H_4ZnCl$ catalyzed by $PdCl_2MeCN_2$; RuPhos was used. [e]Cross-coupling reaction of (*Z*)-**3b** with $(CH_3)_3In$ catalyzed by $PdCl_2(CH_3CN)_2$; RuPhos was used.

In summary, we have developed a new approach for the completely stereoselective synthesis of tetrasubstituted alkenes, allowing modular access to a wide variety of alkenes. The methodology is based on three consecutive cross-coupling reactions of enolphosphate templates with carbon nuclephiles, where the following features can be emphasized: First, chemo- and stereoselective cross-coupling reactions of enolphosphate dibromide with boronic acids proceeds at the terminal carbon at the *trans* position relative to the phosphate moiety under mild reaction conditions with complete selectivity. Second, RuPhos-derived Pd catalysts enabled substitution of the second bromine atom by reaction with organozinc reagents or boronic acids. Third, the cross-coupling reaction of trisubstituted enolphosphate with arylmagnesium halides catalyzed with $PdCl_2$(XantPhos) accomplished the stereoselective synthesis of tetrasubstituted alkenes. Further extension of the developed methodology for the synthesis of functionalized and more complex molecules as well as bioactive substances is underway in our laboratory.

**Scheme 4. Preparation of Tetrasubstituted Alkenes via Cross-Coupling Reaction of Enolphosphate 6 with Grignard or Organoaluminum Reagents[a,b]**




[a]Isolated yield. [b]Alkenes were isolated as the single stereoisomer (>98% *Z* or *E*). [c]The compound was prepared by cross-coupling reaction with Grignard reagent $R^4MgX$. [d]Starting compound. [e]The compound was prepared by cross-coupling reaction with $R^4{}_3Al$.

## ■ ASSOCIATED CONTENT

### Supporting Information

Detailed experimental procedures, characterization of all compounds, and copies of $^1H$ and $^{13}C$ NMR and selected NOE spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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