CHEMISTRY

Enantio- and *Z*-selective synthesis of functionalized alkenes bearing tertiary allylic stereogenic center

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Olefins are ubiquitous in biologically active molecules and frequently used as building blocks in chemical transformations. However, although many strategies exist for the synthesis of stereodefined *E*-olefines, their thermodynamically less stable *Z* counterparts are substantially more demanding, while access to those bearing an allylic stereocenter with an adjacent reactive functionality remains unsolved altogether. Even the classic Wittig reaction, arguably the most versatile and widely used approach to construct *Z*-alkenes, falls short for the synthesis of these particularly challenging yet highly useful structural motives. Here, we report a general methodology for *Z*-selective synthesis of functionalized chiral alkenes that establishes readily available alkene-derived phosphines as an alternative to alkylating reagents in Wittig olefination, thus offering previously unidentified retrosynthetic disconnections for the formation of functionalized disubstituted alkenes. We demonstrate the potential of this method by structural diversification of several bioactive molecules.

INTRODUCTION

Significant effort has been spent to develop methods that produce stereodefined olefins, as these are essential functional groups in organic chemistry, both as feedstocks for further chemical transformations and as synthetic targets (*1*, *2*). As a result, various strategies exist to access both *E* and *Z* stereoisomers of olefins. Access to the thermodynamically more stable *E*-alkenes is especially well established, while synthetic access to the thermodynamically less stable *Z*-alkenes is substantially more difficult (*3*). In particular, stereodefined *Z*-alkenes that bear a tertiary allylic stereogenic center with a reactive functionality adjacent to it, e.g., an electron-withdrawing group (EWG), present major issues. These structural motifs are not only common in natural and biologically active compounds but also serve as very attractive chiral building blocks because the reactive functional groups allow for rapid further transformations (*4*–*7*). Unfortunately, they are also challenging to synthesize as this requires delicate control of both the double bond geometry and the allylic stereocenter. Among all of the strategies developed for the synthesis of different *Z*-alkenes (*8*–*19*), the Wittig reaction (*20*–*22*) is arguably the most versatile and widely used approach, because it is highly *Z*-selective, reliable, general in scope, requires readily available commercial reagents, and can be applied to complex molecules (Fig. 1A). However, even the classic Wittig reaction falls short for the synthesis of these particularly challenging structural motifs.

In the Wittig olefination, two organic fragments are coupled through the reaction between a carbonyl and a phosphorus ylide (Fig. 1A) (*20*, *21*). The latter is accessible by in situ deprotonation of the parent phosphonium salt, obtained in turn by alkylation of a phosphine. *Z*-configured alkenes with a tertiary allylic stereocenter and an EWG pose a serious synthetic problem for this and other olefination methods. Out of the two possible retrosynthetic disconnections when considering the Wittig reaction, the most feasible one (Fig. 1B, disconnection 2) is the one leading to phosphonium salt, which would require a multistep synthesis, is configurationally unstable, and is prone to 1,2-elimination (Fig. 1B).

The latter two issues result from the increased acidity of the hydrogen atom at the stereogenic center neighboring the EWG (H_β), which can lead to racemization of the phosphonium salt or elimination of triphenyl phosphine (PPh_3) in the presence of the base that is needed to deprotonate H_α to form the ylide for the Wittig olefination. A general strategy based on Wittig olefination to access these synthetically demanding but very useful structural motives in good yields while also offering full control over the stereochemistry of the generated double bond and the chemo- and stereoselectivity of the reaction is synthetically very appealing.

To address this challenge, we thought of a different strategy for Wittig olefination using functionalized phosphonium salts, where the difference in the acidity between the corresponding α- and β-hydrogens can easily be tuned. We hypothesized that accessing phosphonium salts through heteroarylation of tertiary alkyl(diphenyl)phosphines would offer an opportunity to tune the acidity of the H_α hydrogen next to the phosphonium moiety by adjusting the electronic properties of the heteroaryl substituent (Fig. 1C). This will allow the undesired 1,2-elimination path discussed above to be outcompeted and make the racemization in the case of phosphonium salts less likely. Furthermore, tertiary alkyl(diphenyl)phosphines are often used either as Lewis base catalysts (*23*) or as ligands (*24*) in homogeneous catalysis, but their potential as organic precursors for Wittig olefination are unexplored. However, a large structural diversity of alkyl(diphenyl)phosphines (including chiral versions) is available because they are commonly derived via hydrophosphination of terminal alkenes (*25*–*32*), which are readily available, relatively stable, and common functional groups in organic chemistry. Thus, if transformed to phosphonium salts, these compounds are potentially excellent candidates to access a structural variety of phosphonium ylides for Wittig olefination (Fig. 1C).

Here, we report the successful realization of the outlined strategy that solves the challenges that so far have hindered the selective

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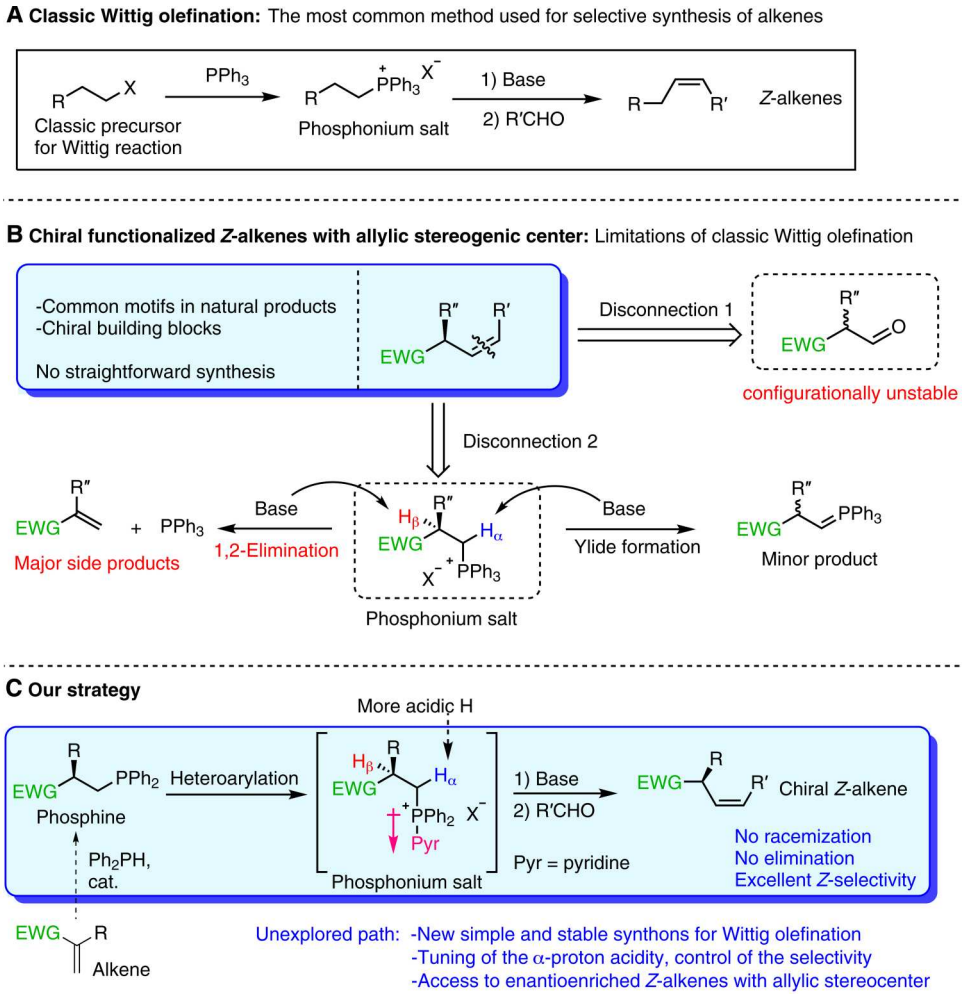

Fig. 1. State of the art and our work. (**A**) Steps involved in classic Wittig olefination reactions starting from the main precursors: alkylating reagents and PPh_3. (**B**) *Z*-alkenes with tertiary allylic stereogenic center and an adjacent EWG. Their retrosynthesis via Wittig olefination leads to either chiral, configurationally unstable, enolizable carbonyl (disconnection 1), or to the corresponding phosphonium salt (disconnection 2), which is configurationally unstable and prone to undesired 1,2-elimination in the presence of a base: The cause of this is the increased acidity of H_β caused by the EWG, making it susceptible to deprotonation concurrently with the deprotonation of the desired H_α. (**C**) Our design for the synthesis of chiral functionalized *Z*-alkenes involves the use of alkene-derived phosphines that can be selectively substituted with an electron-poor heteroaryl moiety to form the corresponding phosphonium salts; the increased acidity of the H_α in these salts selectively promotes the Wittig olefination path.

synthesis of functionalized chiral *Z*-alkenes. At the same time, it establishes alkenes as a viable, convenient alternative to the alkylating reagents commonly used to prepare phosphonium salts for Wittig olefination, thus offering a new retrosynthetic disconnection for the formation of functionalized alkenes.

RESULTS AND DISCUSSION

We started our investigation by looking into options to use heteroarylation reactions to transform phosphines, derived from hydrophosphination of alkenes, into relatively electron-poor phosphonium salts. Few examples have been reported for arylations of phosphines in general, most of which are not suitable for our purposes (*33*, *34*). Our attention was drawn by a report from 1987 (*35*) describing the synthesis of C4-substituted phosphonium salts upon the reaction between pyridinium salts and PPh_3 as well as by S_NAr reactions between halopyridines and phosphine that yield the same products (*36*). We envisioned that alkyl(diphenyl) phosphine products derived from hydrophosphination of alkenes could be transformed into pyridylphosphonium salts using either of these two methods. Moreover, we anticipated that the pyridine moiety could serve the additional purpose of increasing the acidity of the hydrogens next to the phosphorus (H_α) atom with respect to the acidity of the H_β, thus favoring solely the Wittig reaction pathway.

We selected phosphine **1a** that can be easily obtained via catalytic asymmetric hydrophosphination of methacrylonitrile (*29*, *31*) as our model substrate (Fig. 2). When **1a** was subjected to the reaction with 4-iodo-pyridine in $CHCl_3$ at 70°C, the corresponding phosphonium salt **2a′** was obtained with yields that highly depended on the commercial source of the 4-iodo-pyridine. After some more investigations, we found that some samples of 4-iodo-pyridine contained traces of molecular iodine, capable of catalyzing the

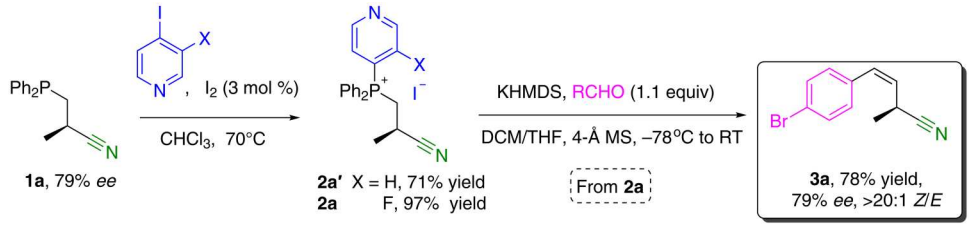

Fig. 2. Initial study. The synthesis of *Z*-configured alkene **3a**.

reaction. The addition of 3 mole percent (mol %) of I_2 at the start of the reaction made the results reproducible and allowed **2a′** to be obtained with 71% yield, requiring purification before further use. Fortunately, the introduction of a fluorine substituent at the 3-position of the pyridine afforded the corresponding phosphonium salt **2a** with nearly quantitative yield, allowing it to be used in the Wittig olefination without further purification.

With the successful synthesis of the salt in hands, we diverted our attention to the Wittig olefination, starting with common reaction conditions. Using tetrahydrofuran (THF) as the solvent, potassium bis(trimethylsilyl)amide (KHMDS) as the base, and an initial temperature of −78°C raising to room temperature (RT) after addition of the aldehyde, we were pleased to obtain the desired product **3a** with adjacent electron-withdrawing nitrile moiety, albeit with only 30% yield (table S1). The remaining compound was identified as the phosphine oxide derivative of **1a**, formed from the phosphonium salt in the presence of a base and traces of water. Phosphine oxide formation could be minimized by working with dry solvents and the addition of molecular sieves to the reaction mixture. Another cause for the low yield was the low solubility of the phosphonium salt in THF. Adding a small amount of dichloromethane (DCM) improved the solubility of the phosphonium salt and significantly increased the yield of the desired product. When using lithium diisopropylamide (LDA) or potassium tert-pentoxide (^{t}PentOK) as the base, a complex reaction mixture was obtained (table S1), most likely due to the additional issue of the reactivity between the nitrile moiety and the base. Upon optimization of various reaction parameters including solvent, bases, and temperature, we found that **3a** could be obtained in 78% isolated yield when using a solvent system of THF/DCM (3.3/1), KHMDS as base, and molecular sieved (4Å MS) as additive (Fig. 2). In the case of both phosphonium salts **2a** and **2a′**, no 1,2-elimination product was

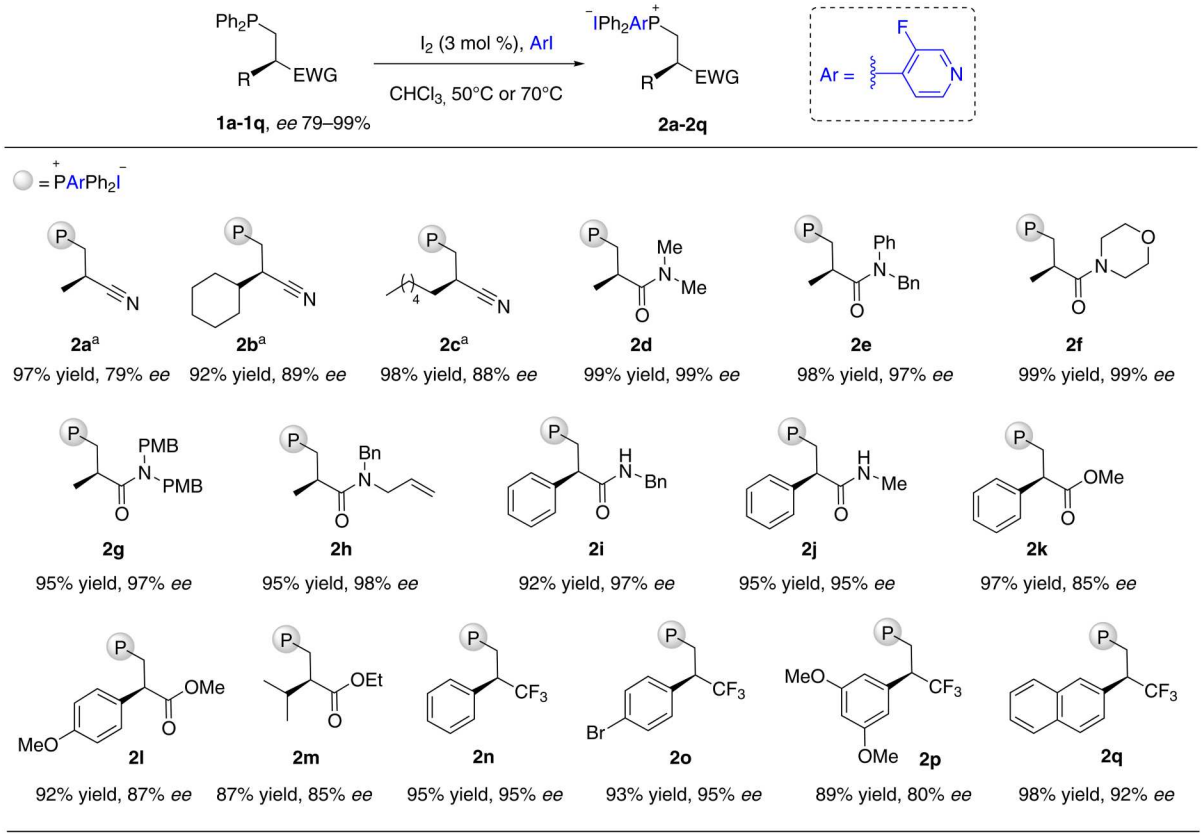

Fig. 3. Scope of the phosphonium salts. Isolated yields are reported. Absolute configurations determined by analogy with x-ray crystallography data of **1b** (*31*) and **1i**. Reaction conditions: compound **1a**-**1q** (1 mmol), 3-fluoro-4-iodopyridine (1 equivalent), and I_2 (3 mol %) in $CHCl_3$ (2 ml) at 50°C for 16 hours.

observed, and the original 79% enantiopurity of phosphine **1a** remained unchanged.

Encouraged by the high yield, excellent *Z*-selectivity, and retained enantiopurity of **3a**, we wanted to transform our new protocol into a general methodology by introducing various EWGs and substituents at the corresponding *Z*-alkene. Many hydrophosphination protocols have been reported that use styrene derivatives and Michael acceptors under various conditions (*25*–*28*) including examples of catalytic asymmetric synthesis of phosphines (*29*–*32*). To access enantioenriched phosphines bearing a variety of EWGs at the resulting stereogenic center, we used a slightly modified hydrophosphination methodology that we have developed recently (see the Supplementary Materials) (*31*). Next to phosphines bearing nitrile, secondary and tertiary carboxamide, and ester EWGs, we also prepared phosphines with a CF_3 substituent. The trifluoromethyl group is frequently introduced in medicinal chemistry to modulate the physicochemical properties and increase the binding affinity of drug molecules (*37*), thus rendering it attractive to extend our methodology to final alkenes with a neighboring trifluoromethyl substituent. Using the optimized heteroarylation protocol, all the enantioenriched phosphines were successfully subjected to the reaction with 3-fluoro-4-iodopyridine, affording the corresponding pyridylphosphonium salts **2** in excellent yields (87 to 99%), while retaining the original enantiopurity (Fig. 3).

With the variety of enantioenriched phosphonium salts in hand, their use in Wittig olefination was evaluated next (Fig. 4). At this stage, it is important to note that no purification is required for the phosphonium salts before their use in the Wittig olefination. The olefination reaction was evaluated for all phosphonium salts, using 4-bromobenzaldehyde as the model coupling partner. First, we concentrated on the nitrile-substituted phosphonium salts, finding that their corresponding *Z*-olefin products (**3a**-**3c**) could be obtained in good yields (78 to 91%) under the reaction conditions indicated above, while retaining enantiopurity. With the general reaction conditions established, we moved to the phosphonium salts with tertiary carboxamide substituents and found that ^{t}PentOK (table S2) is the most suitable base for this class of salts.

The corresponding carboxamide-substituted *Z*-alkenes (**3d**-**3h**) were afforded with good yields (60 to 81%) and 96 to 98% enantiomeric excess (*ee*). In the case of phosphonium salts **2i** and **2j** with a secondary carboxamide motif, the presence of the acidic amide hydrogen requires a large excess (1.9 equivalent) of the base to avoid obtaining only traces of the products. Although this excess of base could be detrimental for the reaction outcome and result in fully racemized alkene products, the enantioenriched products **3i** (*Z*/*E* = 13/1) and **3j** (exclusively *Z*) were obtained with good yields. Only a slight decrease in enantioselectivity was observed for **3j** (from 95 to 93% *ee*), while product **3i** was obtained with 87% *ee*, a 10% drop from the original value.

Subsequently, we explored the Wittig olefination of phosphonium salts with ester substituents next to the double bond. We expected these substrates to be more difficult because of the increased acidity of H_β compared to nitriles and carboxamides and because of the intrinsic reactivity of the ester functional group. As expected, complex reaction mixtures were obtained with bases such as KHMDS and sodium bis(trimethylsilyl)amide (NaHMDS) (table S4). Successful completion of the reaction was only achieved with LDA while maintaining the temperature at −78°C after the aldehyde addition, in which case the corresponding chiral products **3k**-**3m** were obtained with good yields (55 to 71%), with excellent *Z*-selectivity, and with the original enantiopurity retained. We believe that our protocol owes its compatibility with the ester functional group to the fluoro-pyridine moiety introduced in the structure of the phosphonium salt, which leads to an increased acidity of H_α. Last, the phosphonium salts containing a trifluoromethyl substituent were explored. The corresponding *Z*-alkene products **3n**-**3q** were obtained in good yields (62 to 85%) and once again retained the original enantiomeric excess (84 to 95%). The *E*-isomer could be observed in low amounts (*Z*/*E* ratio of 10/1 to >20/1) in the reaction crude, independently of the base used (table S5). In general, we found that the use of lithium bases tends to produce *E*-isomers, while the overall yields and isomer ratios are largely determined by the phosphonium salt. Having established the performance of various phosphonium salts in the Wittig olefination with the model aldehyde substrate, we set out to explore the scope of the aldehyde in the reaction with phosphonium salt **2d** derived from phosphine carboxamide **1d**. We were delighted to obtain excellent results with both aromatic and heteroaromatic aldehydes (**4a**-**4g**), with yields varying between 60 and 85%, with the enantiomeric excess of the phosphonium salt precursor retained in all cases, and with the *Z*/*E* ratio of the final alkene exceeding 20/1. α,β-Unsaturated aldehydes were also tolerated (36 to 87% yield), generating products **4h**, **4i**, and **4j** with high enantiopurities and *Z*-selectivities while the lower yield for **4j** can be attributed to phosphine oxide formation. Excellent stereoselectivity was observed for alkene products **4k** and **4l** obtained from the reaction with aliphatic aldehydes. This protocol also supports the use of paraformaldehyde, providing the corresponding products (**4m** and **4n**) with a terminal double bond in 70 and 65% yield and in 98 and 95% *ee*, respectively. These products are interesting chiral derivatives for potential synthetic transformations. To emphasize the compatibility of our protocol for late-stage functionalizations, more complex natural product derivatives or drug-like molecules with aldehyde functionality were explored. Specifically, the D-galactopyranose derivative **4o**, lithocholic acid derivative **4p**, indomethacin derivative **4q**, and fluvastatin derivative **4r** were successfully synthesized.

To demonstrate the potential application of our protocol, we performed the complete sequence from the achiral terminal alkene **5d** to the final chiral enantioenriched *Z*-alkene **3d** at a 10-fold scale-up. The corresponding product **3d** was obtained with a 71% total yield and 97% *ee* (Fig. 5A).

The procedure discussed above does not require purification of the corresponding phosphine and phosphonium salts and only requires solvent replacement (evaporation/refill), namely, from toluene to $CHCl_3$ after the hydrophosphination step and from $CHCl_3$ to THF before the reaction with aldehyde. However, to make the protocol even more user-friendly, we also explored a one-pot procedure using the same solvent and no purifications throughout the whole sequence. Catalytic asymmetric hydrophosphination of achiral **5d**, subsequent formation of the corresponding phosphonium salts, and, lastly, the Wittig olefination were accomplished by sequentially adding the necessary reagents to the same reaction flask (Fig. 5A). The final *Z*-alkene **3d** was obtained with 68% yield.

Last, we explored enantioenriched *Z*-alkenes as convenient building blocks for various transformations (Fig. 5B). With Oxone and $NaHCO_3$, **4a** was converted into epoxide derivative **6a** in 80% yield and in good enantiomeric excess (98% *ee*). Product **3f**

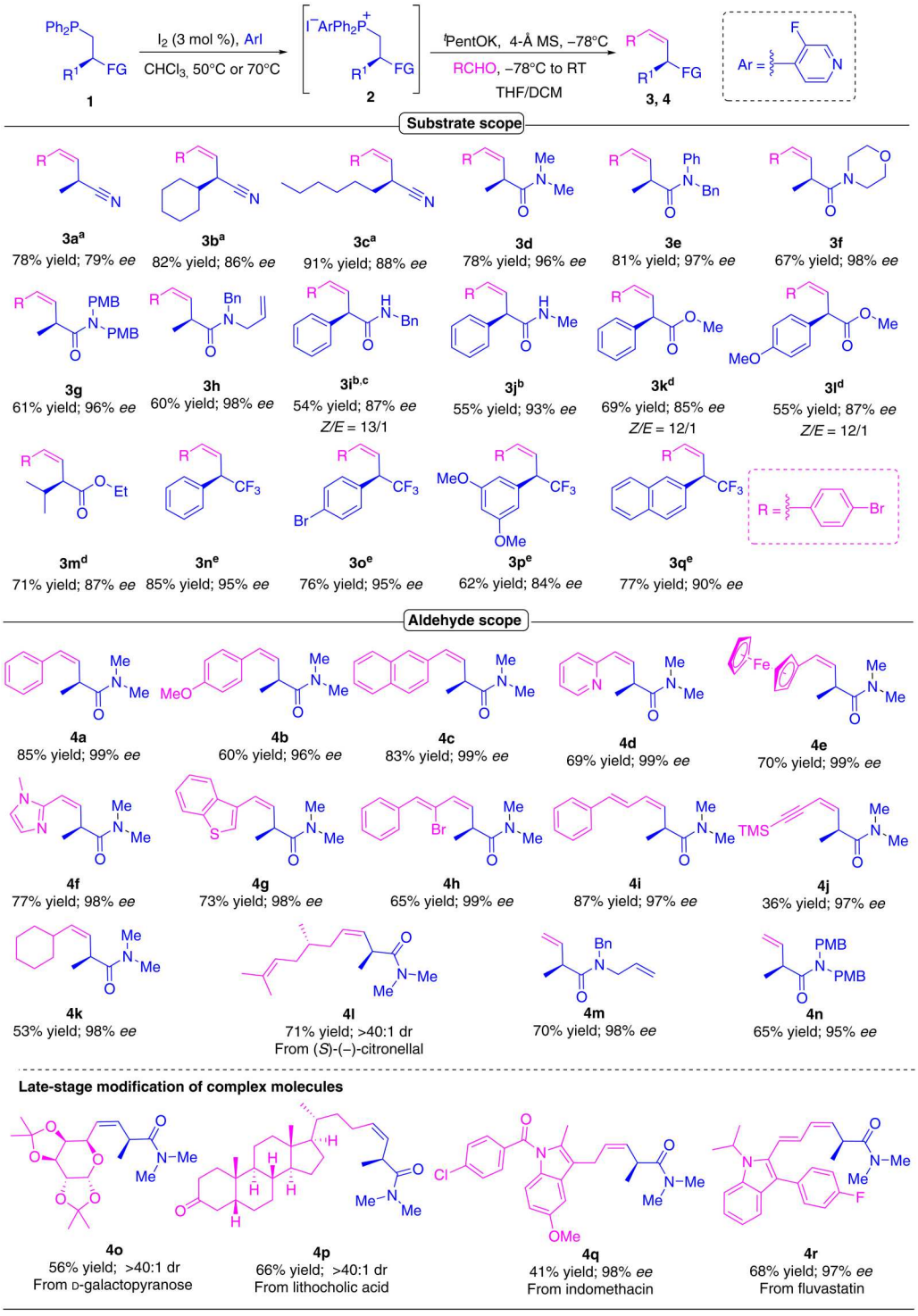

Fig. 4. Scope of the phosphonium salts and aldehydes used in the Wittig olefination. Isolated yields are reported, and full conversion was obtained in all cases. Ratios of *Z*/*E* are >20/1 unless stated otherwise. Reaction conditions: compound **2a**-**2q** (0.2 mmol, 1.0 equivalent), in THF/DCM (2.6 ml, 3.3/1), 300 mg of 4Å MS, ^{t}PentOK (1.1 equivalent) at −78°C for 30 min, and then aldehyde (1.0 equivalent) addition at −78°C to RT, overnight. [a]KHMDS (1.2 equivalent) was used as base and the salt in excess (1.2 equivalent) with respect to aldehyde (1.0 equivalent). [b]Reaction performed without 4-Å MS; LDA (1.9 equivalent) was used as base and stirred for 1 hour before the addition of aldehyde (2.0 equivalent), keeping the reaction at −78°C. [c]Reaction performed in THF (2 ml). [d]LDA (1.1 equivalent) was used as base, in THF (2 ml), and the reaction was kept at −78°C. [e]LiO^{t}Bu (1.1 equivalent) was used as base, in THF (2 ml).

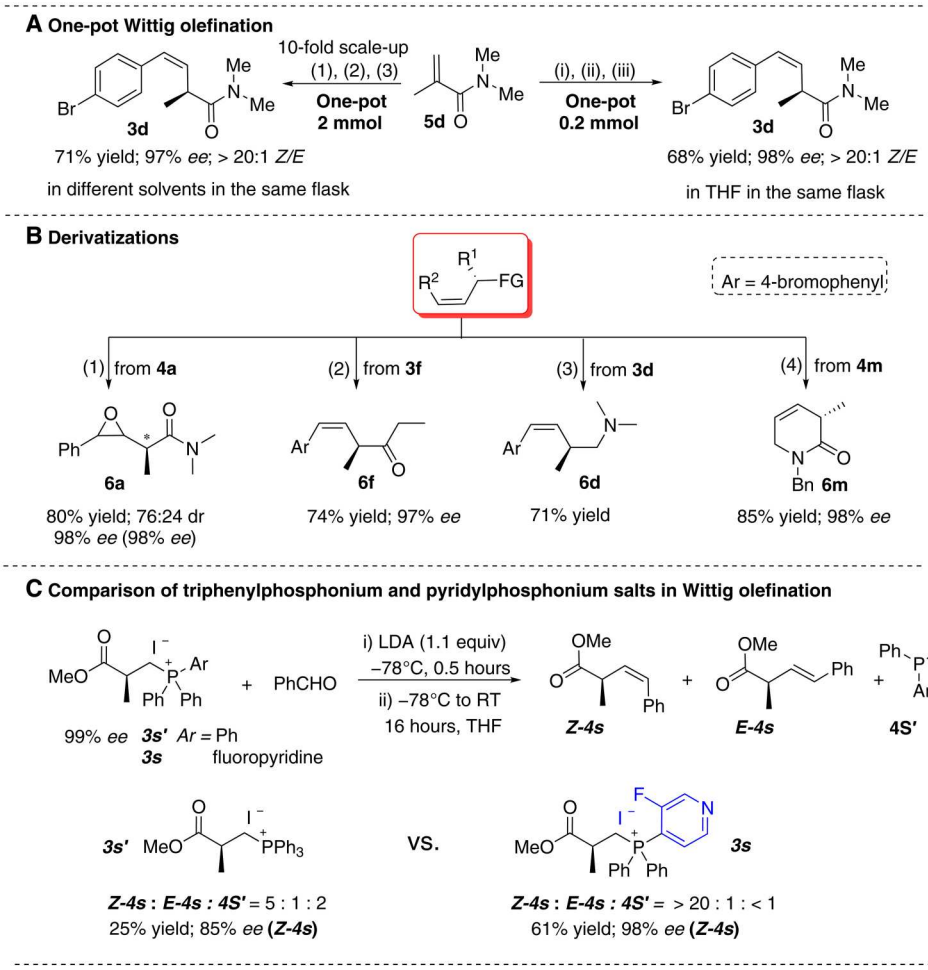

Fig. 5. One-pot procedure and the potential of the methodology. (**A**) One-pot protocol for the synthesis of functionalized chiral *Z*-alkene **3d** starting from achiral terminal alkene **5d**. (1) **5d** (2 mmol, 1.0 equivalent), Ph_2PH (1.0 equivalent), (R_C, S_P)-Clarke (1 mol %), ^{t}PentOK (2 mol %), and toluene (10 ml), RT, 16 hours (*31*); (2) 3-fluoro-4-iodopyridine (1.0 equivalent), I_2 (3 mol %), and $CHCl_3$ (4 ml), 50°C, 16 hours; (3) ^{t}PentOK (1.0 equivalent), 4-bromobenzaldehyde (1.1 equivalent), 4-Å MS (3 g), and DCM/THF (1/3.3, 26 ml), −78°C to RT, 16 hours. (i) **5d** (0.2 mmol, 1.0 equivalent), Ph_2PH (1.0 equivalent), (R_C, S_P)-Clarke (2 mol %), ^{t}PentOK (3 mol %), and THF (2 ml), RT, 16 hours; (ii) 3-fluoro-4-iodopyridine (1.0 equivalent) and I_2 (10 mol %), 50°C, 24 hours; (iii) ^{t}PentOK (1.0 equivalent), 4-bromobenzaldehyde (1.1 equivalent), and 4Å MS (300 mg), −78°C to RT, 16 hours. (**B**) Synthetic transformations of olefination products. (1) **4a** (0.1 mmol, 1.0 equivalent), Oxone (2.2 equivalent), $NaHCO_3$ (1 ml), and acetone/acetonitrile (1:1, 2 ml), 0°C, 2 hours; (2) **3f** (0.1 mmol), EtMgBr (2 equivalent), and DCM (1 ml), 0°C to RT, 16 hours; (3) **3d** (0.1 mmol, 1.0 equivalent), $LiAlH_4$ (2.0 equivalent), and THF (1 ml), 60°C, 16 hours; (4) **4m** (0.1 mmol, 1.0 equivalent), Grubbs II catalyst (10 mol %), and CH_2Cl_2 (1 ml), 40°C, 24 hours. (**C**) Comparison of classic triphenylphosphonium salts and our pyridylphosphonium salts in Wittig olefination.

with ethylmagnesiumbromide (EtMgBr) afforded the ketone product **6f** (74% yield), providing an alternative method for the synthesis of *Z*-olefins bearing a ketone motif. Reduction of the alkene carboxamide **3d** resulted in the corresponding chiral amine **6d**, while chiral piperidinone derivative **6m** was efficiently synthesized by ring-closing metathesis of **4m** (85% yield).

To demonstrate the key role of the fluoro-pyridine motif for the remarkable enantioretention observed in our reactions, we performed two control experiments (Fig. 5C). First, we synthesized the triphenylphosphonium salt **3s**′ with 99% *ee* in a few steps, starting from the commercially available enantiopure alcohol derivative, and subjected it to the standard olefination reaction with benzaldehyde. As expected, the resulting alkene *Z*-**4s** was obtained with only 85% *ee* due to base-promoted racemization (from 99 to 85% *ee*), a low *Z*/*E* ratio of 5:1, and a yield of 25%. It was accompanied with 10% of side product **4s**′ resulting from the competing base-promoted 1,2-elimination path. These results are in sharp contrast with the excellent *Z*/*E* ratio (>20:1), good yield, and full retention of enantiopurity (99%) obtained with our complete protocol with fluoropyridyl phosphonium salt. In our conditions, less than 1% of 1,2-elimination product was observed by ^{1}H nuclear magnetic resonance (NMR). Overall, these results underline the superior role of the fluoro-pyridine moiety installed in our phosphonium salt for the observed chemo-, enantio-, and stereoselectivities during the olefination step. Note that the fluoro-pyridyl phosphonium salt **3s** was prepared by alkylation of fluoro-pyridyl phosphine rather than from terminal alkenes. The increased reaction selectivities offered by the fluoro-pyridyl substituent in the phosphonium salt in Wittig olefination can also be achieved when preparing fluoro-

pyridyl phosphonium salts from the conventionally used alkyl halides.

Terminal alkenes are readily available functional groups that are commonly used in organic chemistry. Hydrophosphination of these alkenes is a well-established strategy to access a large structural variety of tertiary phosphines, including chiral versions via asymmetric catalysis. In this work, we transformed the phosphines prepared in this manner into the corresponding fluoro-pyridyl phosphonium salts and subsequently used these in Wittig olefination with various aldehydes. The power of this strategy has been demonstrated by establishing a general, *Z*-, chemo-, and enantioselective route to synthetically challenging chiral alkenes bearing a tertiary allylic stereocenter and an adjacent functional group such as a carboxamide, ester, nitrile, or trifluoromethyl. We expect the present study to pave the way for using readily available, simple alkenes and the corresponding phosphines as an attractive alternative for alkylating reagents as synthons for Wittig olefination, offering new retrosynthetic disconnections for the formation of functionalized alkenes.

MATERIALS AND METHODS

For the one-pot procedure with solvent change, all reactions using oxygen- and/or moisture-sensitive materials were carried out with anhydrous and deoxygenated solvents under a nitrogen atmosphere using oven-dried glassware and standard Schlenk techniques. Hydrophosphination and phosphonium salt formation reactions were carried out in the glovebox. (R_C,S_P)-Clarke manganese catalyst (*38*) (0.02 mmol, 1 mol %) was added to a heat gun–dried Schlenk tube equipped with a magnetic stirring bar. The Schlenk tube was placed into the glovebox, followed by the addition of dry, deoxygenated toluene (10 ml) and stirring for 1 min. Then, a commercially available solution of *t*PentOK at 1.7 M (0.04 mmol, 2 mol %; a higher amount of the base results in lower enantioselectivity) was added, and the mixture was stirred for 5 min, during which the catalyst was fully dissolved and the color of the solution changed from yellow to dark red. After 5 min, the substrate **5d** (2 mmol, 1.0 equivalent) was added at once, followed by the addition of $HPPh_2$ (2 mmol, 1.0 equivalent). For the hydrophosphination reaction to work, a high purity of the starting materials, catalyst, and solvents used is crucial. After 16 hours, the solvent was concentrated under reduced pressure. To the same Schlenk tube, 3-fluoro-4-iodopyridine (2 mmol, 1.0 equivalent) was added, after which the Schlenk tube was placed into the glovebox, followed by the addition of dry, deoxygenated $CHCl_3$ and I_2 (0.06 mmol, 3 mol %). The Schlenk tube was then taken out of the glovebox and put under a nitrogen flow. The mixture was heated to 50°C for 16 hours before the solvent was concentrated under reduced pressure. Subsequently, the same Schlenk tube was subjected to three cycles of vacuum/nitrogen backfill and cooled down to −78°C. Dry DCM (6 ml) and THF (20 ml) were added (dry solvents are of great importance to achieve a high yield), followed by the addition of heat gun–activated 4-Å molecular sieves (3 g) under a nitrogen flow. The mixture was stirred vigorously at −78°C for 5 min before the addition of the *t*PentOK solution (1.7 M in toluene) (2.0 mmol, 1.0 equivalent) through a syringe via the septum. The reaction mixture was then stirred for 1 hour at −78°C before the addition of the *p*-Br-benzaldehyde (2.2 mmol, 1.1 equivalent) and subsequent warm-up to RT for 16 hours. A saturated aqueous solution of NH_4Cl (25 ml) was then added, and the suspension was filtered over Celite and washed with DCM (10 ml × 3), after which the aqueous layer was extracted with DCM (10 ml × 3). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Last, the residue was purified by column chromatography to afford the product (*S*, *Z*)-**3d** (SiO_2; pentane:Et_2O = 0:1) (71% yield and 97% *ee*).

Supplementary Materials

This PDF file includes:

Supplementary Materials and Methods
Tables S1 to S6
Figs. S1 and S2
NMR spectra
References

View/request a protocol for this paper from *Bio-protocol*.

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