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Tunable stereoselective alkene synthesis by treatment of activated imines with nonstabilized phosphonium ylides†

De-Jun Dong, Yuan Li, Jie-Qi Wang and Shi-Kai Tian*

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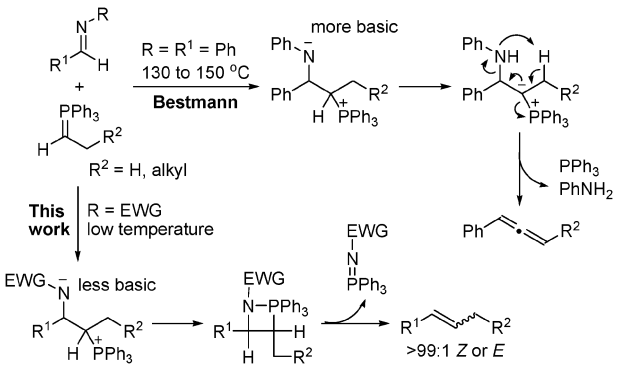
A broad range of readily accessible *N*-sulfonyl imines undergo olefination reaction with nonstabilized phosphonium ylides under mild conditions to afford an array of both *Z*- and *E*-isomers of 1,2-disubstituted alkenes, allylic alcohols, and allylic amines in good yields and with greater than 99 : 1 stereoselectivity.

A plethora of chemical methods have been invented for the convergent synthesis of geometrically defined alkenes owing to their application in a broad range of chemical transformations. Carbonyl olefination, alkyne addition, alkenylation, and elimination are the effective methods widely employed for the synthesis of stereodefined alkenes.[1] While no single method provides a universal solution to stereoselective alkene synthesis, the Wittig reaction involving direct olefination of nonstabilized phosphonium ylides with aldehydes has enjoyed widespread prominence and recognition owing to its simplicity, convenience, complete positional selectivity, and generally high levels of *Z* selectivity.[2] Moreover, the Schlosser modification of the Wittig reaction allows stereoselective synthesis of (*E*)-alkenes.[3] However, there remains room for improvement with respect to the stereoselectivity and substrate scope, and it is very desirable for the development of a tunable olefination reaction of nonstabilized phosphonium ylides to prepare both (*Z*)- and (*E*)-alkenes with extremely high stereoselectivity.

In the course of exploring the synthetic applications of carbon–nitrogen bond cleavage,[4] together with our interest in stereoselective alkene synthesis,[5] we discovered recently a highly tunable olefination reaction of imines with semistabilized phosphonium ylides.[6] To extent this chemistry to the tunable stereoselective synthesis of other types of 1,2-disubstituted alkenes, we initiated the study on the reaction of imines with nonstabilized phosphonium ylides. Notably, Bestmann and Seng disclosed in 1963 that treatment of *N*-benzylideneaniline with nonstabilized phosphonium ylides at 130–150 °C afforded allenes in moderate to good yields (Scheme 1).[7] Two years later they proposed a reaction pathway involving initial carbon–carbon bond formation leading to a betaine followed by proton transfer and fragmentation to release an allene.[8] Nevertheless, we envisioned an alternative reaction pathway by replacing the phenyl group on the imine nitrogen with an electron-withdrawing group (EWG), which would require much lower temperature for the addition of the imine to a nonstabilized phosphonium ylide. Hopefully, the basicity of the resulting betaine would be sufficiently reduced to terminate the proton transfer toward the formation of an allene. Instead, the betaine could cyclize to form a 1,2-azaphosphetane and subsequently eliminates an iminophosphorane to yield an alkene (Scheme 1). Herein, we report a highly tunable stereoselective alkene synthesis from readily accessible *N*-sulfonyl imines and nonstabilized phosphonium ylides. Significantly, this protocol provides a convenient access to an array of both (*Z*)- and (*E*)-isomers of 1,2-disubstituted alkenes, allylic alcohols, and allylic amines with greater than 99 : 1 stereoselectivity.



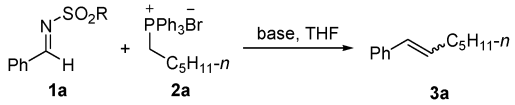
Scheme 1 Reactions of imines with nonstabilized phosphonium ylides.

Simply applying our previous reaction conditions[6] allowed us to obtain 1,2-disubstituted alkenes in good yields from *N*-sulfonyl imines and nonstabilized phosphonium ylides. Nevertheless, the geometrical control is far from satisfying. As demonstrated by the model reaction of *n*-hexylidenetriphenylphosphorane, prepared *in situ* from phosphonium salt **2a** and lithium diisopropylamide (LDA), with *N*-benzylidene sulfonamide **1a** in tetrahydrofuran at −78 °C to room temperature, alkene **3a** was obtained as a 92 : 8 mixture of *Z*/*E* isomers when using a methanesulfonyl group to activate the imine (Table 1, entry 1). However, it is disappointing that replacing the methanesulfonyl group on the imine nitrogen with another electron-withdrawing group proved fruitless to enhance or switch the

Joint Laboratory of Green Synthetic Chemistry, Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China. E-mail: tiansk@ustc.edu.cn; Fax: +86 551-360-1592; Tel: +86 551-360-0871

† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for products. See DOI: 10.1039/c0cc04739b

Table 1 Optimization of reaction conditions[a]



Entry	Imine	R	Base	Yield[b] (%)	Z/E[c]
1	**1aa**	Me	LDA	83	92 : 8
2	**1aa**	Me	NaHMDS	87	80 : 20
3	**1aa**	Me	*n*-BuLi	79	> **99** : **1**
4	**1ab**	*n*-$C_{16}H_{33}$	*n*-BuLi	57	66 : 34
5	**1ac**	4-MeC_6H_4	*n*-BuLi	79	84 : 16
6	**1ad**	4-$MeOC_6H_4$	*n*-BuLi	69	73 : 27
7	**1ae**	4-$O_2NC_6H_4$	*n*-BuLi	71	86 : 14
8	**1af**	2-$O_2NC_6H_4$	*n*-BuLi	72	80 : 20
9	**1ag**	2-MeC_6H_4	*n*-BuLi	81	< **1** : **99**
10	**1ah**	2,4,6-$Me_3C_6H_2$	*n*-BuLi	71	15 : 85
11	**1ai**	2-Naphthyl	*n*-BuLi	77	82 : 18
12	**1aj**	2-Thienyl	*n*-BuLi	81	84 : 16

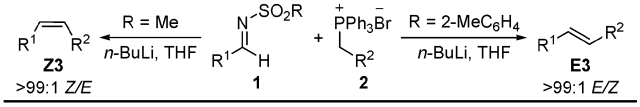
[a] Reaction conditions: phosphonium salt **2a** (0.60 mmol), base (0.65 mmol), THF (1.0 mL), −78 °C, 1 h; then imine **1a** (0.50 mmol), THF (1.0 mL), −78 °C to rt. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis.

stereoselectivity for the synthesis of alkene **3a**. Gratifyingly, the stereoselectivity was found to be significantly affected by the base used in the reaction, and the employment of *n*-butyl lithium to prepare *n*-hexylidenetriphenylphosphorane from phosphonium salt **2a** improved the *Z* selectivity up to greater than 99 : 1 (Table 1, entry 3).[9] Further investigation revealed that the employment of an *o*-toluenesulfonyl group to activate the imine completely switched the stereoselectivity to exhibit exclusive *E* selectivity (Table 1, entry 9).

A broad range of *N*-methanesulfonyl aromatic, heteroaromatic, α,β-unsaturated, and aliphatic imines smoothly underwent olefination reaction with *n*-hexylidenetriphenylphosphorane to afford various (*Z*)-alkenes in good yields and with greater than 99 : 1 stereoselectivity, and moreover, the corresponding (*E*)-alkenes were obtained with the same level of stereoselectivity when an *o*-toluenesulfonyl group was employed to activate the imines (Table 2, entries 1–16). Either an electron-withdrawing group or an electron-donating group could be introduced by employing an imine bearing such a group on the aromatic ring. In addition, a gram-scale synthesis of alkene **Z3a** was successfully performed according to this protocol without deteriorating stereoselectivity (1.34 g, 77% yield, > 99 : 1 *Z*/*E*). To our delight, some other alkylidenetriphenylphosphoranes and functionalized nonstabilized phosphonium ylides served as suitable substrates for the olefination reaction of *N*-methanesulfonyl and *N*-(*o*-toluenesulfonyl) imines to afford structurally diverse (*Z*)- and (*E*)-alkenes with greater than 99 : 1 stereoselectivity, respectively (Table 2, entries 17–24). It is particularly noteworthy that this protocol provides a convenient access to both (*Z*)- and (*E*)-allylic alcohols and amines with extremely high stereoselectivity (Table 2, entries 20–24).[10]

While the reaction of *N*-benzylideneaniline with ethylidenetriphenylphosphorane was reported to yield an isolable betaine intermediate that would require high temperature for decomposition (190 °C at about 15 mmHg),[8b] ^{31}P NMR analysis of the reaction mixture of *N*-sulfonyl imine **1aa** and *n*-hexylidenetriphenylphosphorane (Table 1, entry 3) indicated

Table 2 Tunable stereoselective olefination of *N*-sulfonyl imines with nonstabilized phosphonium ylides[a,b]



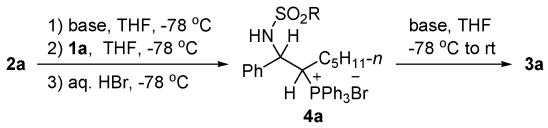
			R = Me		R = 2-MeC_6H_4	
Entry	R^1	R^2	**Z3**	Yield[c] (%)	**E3**	Yield[c] (%)
1	Ph	*n*-C_5H_{11}	**Z3a**	79	**E3a**	81
2	4-$MeOC_6H_4$	*n*-C_5H_{11}	**Z3b**	76	**E3b**	79
3	4-ClC_6H_4	*n*-C_5H_{11}	**Z3c**	71	**E3c**	75
4	4-$O_2NC_6H_4$	*n*-C_5H_{11}	**Z3d**	66	**E3d**	73
5	3-$O_2NC_6H_4$	*n*-C_5H_{11}	**Z3e**	70	**E3e**	76
6	2-MeC_6H_4	*n*-C_5H_{11}	**Z3f**	83	**E3f**	77
7	2-ClC_6H_4	*n*-C_5H_{11}	**Z3g**	71	**E3g**	82
8	1-Naphthyl	*n*-C_5H_{11}	**Z3h**	79	**E3h**	71
9	2-Pyridyl	*n*-C_5H_{11}	**Z3i**	81	**E3i**	75
10	2-Furyl	*n*-C_5H_{11}	**Z3j**	78	**E3j**	81
11	2-Thienyl	*n*-C_5H_{11}	**Z3k**	71	**E3k**	71
12	(*E*)-PhCH=CH	*n*-C_5H_{11}	**Z3l**	81	**E3l**	81
13	(*E*)-MeCH=CH	*n*-C_5H_{11}	**Z3m**	77	**E3m**	71
14	*n*-C_6H_{13}	*n*-C_5H_{11}	**Z3n**	82	**E3n**	74
15	$PhCH_2CH_2$	*n*-C_5H_{11}	**Z3o**	60	**E3o**	69
16	Cyclohexyl	*n*-C_5H_{11}	**Z3p**	66	**E3p**	63
17	2-Naphthyl	Me	**Z3q**	81	**E3q**	73
18	(*E*)-PhCH=CH	Me	**Z3r**	77	**E3r**	81
19	2-Naphthyl	$CHMe_2$	**Z3s**	74	**E3s**	71
20	Ph	CH_2NMe_2	**Z3t**	75	**E3t**	72
21	(*E*)-PhCH=CH	CH_2NMe_2	**Z3u**	72	**E3u**	79
22[d]	Ph	CH_2OH	**Z3v**	84	**E3v**	66
23[d]	(*E*)-PhCH=CH	CH_2OH	**Z3w**	76	**E3w**	81
24[d]	Cyclohexyl	CH_2OH	**Z3x**	63	**E3x**	60

[a] Reaction conditions: phosphonium salt **2** (0.60 mmol), *n*-BuLi (0.65 mmol), THF (1.0 mL), −78 °C, 1 h; then imine **1** (0.50 mmol), THF (1.0 mL), −78 °C to rt. [b] The stereoselectivity was determined by ^{1}H NMR analysis. [c] Isolated yield. [d] 1.3 mmol of *n*-BuLi was used.

that the corresponding betaine intermediate, characterized by a signal at δ 25.0 ppm relative to external 85% phosphoric acid, decomposed smoothly at room temperature.[11,12] The employment of HBr to quench the reaction mixture of *n*-hexylidenetriphenylphosphorane and *N*-benzylidene sulfonamide **1a** at −78 °C allowed us to isolate a salt form of the betaine intermediate, phosphonium salt **4a**, which was subsequently treated with a base to afford alkene **3a** in moderate to good yields (Table 3).[13] As demonstrated by the data summarized in Table 3, the diastereomeric ratios of phosphonium salt **4a** exactly parallel the *Z*/*E* ratios of alkene **3a**. Significantly, both series of data parallel the *Z*/*E* ratios obtained from the corresponding olefination reaction of *N*-sulfonyl imines with nonstabilized phosphonium ylides that were prepared with either *n*-BuLi or LDA (Tables 1 and 3).

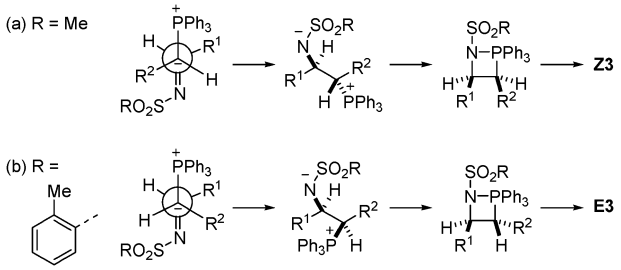
These results suggest that the *Z*/*E* selectivity for alkene synthesis originates from the diastereoselective addition of nonstabilized phosphonium ylides to *N*-sulfonyl imines,[14] wherein the stereoselectivity is finely tuned by the total interactions of the *N*-sulfonyl group, the R^1 group, the R^2 group, and the Ph_3P group that develop as the ylide and imine approach one another (Scheme 2).[15,16] When the R^2 group suffers greater steric repulsion from the R^1 group than that from the *N*-sulfonyl group, the reaction prefers to generate *anti*-betaines that decompose to yield (*Z*)-alkenes *via cis*-1,2-azaphosphetanes. Otherwise, (*E*)-alkenes are produced predominantly.

Table 3 Formation and conversion of phosphonium salt **4a**



Entry	1a	R	Base	4a	4a, dr[a]	3a, Z/E[a]
1	**1aa**	Me	*n*-BuLi	**4aa**	> 99 : 1	> 99 : 1
2	**1aa**	Me	LDA	**4aa**	90 : 10	90 : 10
3	**1ac**	4-MeC_6H_4	*n*-BuLi	**4ac**	84 : 16	84 : 16
4	**1ag**	2-MeC_6H_4	*n*-BuLi	**4ag**	< 1 : 99	< 1 : 99
5[b]	**1ag**	2-MeC_6H_4	LDA	**4ag**	41 : 59	41 : 59

[a] Determined by ^{1}H NMR analysis. [b] The reaction of imine **1ag** with phosphonium salt **2a** in the presence of LDA afforded alkene **3a** as a 41 : 59 mixture of Z/E isomers.



Scheme 2 Proposed mechanism for the tunable stereoselective olefination of *N*-sulfonyl imines with nonstabilized phosphonium ylides.

In summary, we have developed a highly tunable stereoselective alkene synthesis from readily accessible *N*-sulfonyl imines and nonstabilized phosphonium ylides. A broad range of *N*-sulfonyl aromatic, heteroaromatic, α,β-unsaturated, and aliphatic imines react with various nonstabilized phosphonium ylides to afford an array of both (*Z*)- and (*E*)-isomers of 1,2-disubstituted alkenes, allylic alcohols, and allylic amines in good yields and with greater than 99 : 1 stereoselectivity. The Z/E selectivity for alkene synthesis has been demonstrated to originate from the diastereoselective addition of nonstabilized phosphonium ylides to *N*-sulfonyl imines, wherein the *N*-sulfonyl groups serve as powerful handles to finely tune stereoselectivity.

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9 By contrast, under the same reaction conditions the Wittig reaction of benzaldehyde with *n*-hexylidenetriphenylphosphorane afforded alkene **3a** as a 90 : 10 mixture of Z/E isomers.

10 We also performed the reaction of $PhCH_2CH_2CH{=}NMs$ with $[Me_2NCH_2CH_2PPh_3]^+Br^-$ in the presence of *n*-BuLi, but did not obtain the desired allylic amine.

11 About 0.5 mL of the reaction mixture at −78 °C was injected into an NMR tube and immediately subjected to ^{31}P NMR (162 M) analysis (at room temperature). When the reaction mixture was allowed to stand at room temperature, the signal at δ 25.0 ppm, assigned to the betaine intermediate, was found to decrease and disappear completely in 3 h. The assignment of the betaine intermediate was substantially supported by ^{31}P NMR analysis of its HBr salt, phosphonium salt **4aa** (Table 3, entry 1), which shows a signal at δ 25.0 ppm. For details, see the ESI†.

12 It is noteworthy that Ph_3PO rather than an iminophosphorane was detected as a byproduct by ^{31}P NMR analysis owing to the rapid decomposition of the latter by a trace amount of water. The formation of iminophosphorane as a primary byproduct was substantially confirmed by the fact that $Ph_3P^{18}O$ was generated after the reaction mixture was worked up with $H_2{}^{18}O$. For details, see the ESI†.

13 Phosphonium salts **4a** were obtained in 63–73% yields, and alkene **3a** was obtained in 51–89% yields. For details, see the ESI†.

14 For an example on the addition of ester-stabilized phosphonium ylides to *N*-Boc imines, see: Y. Zhang, Y.-K. Liu, T.-R. Kang, Z.-K. Hu and Y.-C. Chen, *J. Am. Chem. Soc.*, 2008, **130**, 2456.

15 The dramatic influenceof a base on the stereoselectivity (Table 1) suggests an effective coordination between lithium cation and an *N*-sulfonyl imine.

16 The formation of the betaine intermediate is suggested to be irreversible by the following experiment. Treatment of phosphonium salt **4aa** (> 99 : 1 dr, Table 3, entry 1) successively with *n*-BuLi and 4-Me$OC_6H_4CH{=}NMs$ at −78 °C to room temperature led to no formation of alkene **Z3b** (Table 2, entry 2).

