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Stereoselective Olefination of *N*-Sulfonyl Imines with Stabilized Phosphonium Ylides for the Synthesis of Electron-Deficient Alkenes

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An unprecedented protocol has been developed for the stereoselective synthesis of structurally diverse electron-deficient alkenes in moderate to excellent yields from readily accessible *N*-sulfonyl imines and stabilized phosphonium ylides. Significantly, the olefination reaction of *N*-sulfonyl imines with nitrile-stabilized phosphonium ylides affords an array of α,β-unsaturated nitriles with high *Z* selectivity, and the reactions with ester-, amide-, and ketone-stabilized phosphonium ylides afford α,β-unsaturated esters, amides, and ketones with high *E* selectivity, respectively. Spectroscopic analysis of the reaction mixtures and trapping of the intermediates allow plausible mechanisms to be proposed. Initial imine/ylide addition leads to the formation of betaines that cyclize to form 1,2-azaphosphetanes that subsequently eliminate iminophosphoranes to yield alkenes. For the synthesis of electron-deficient 1,2-disubstituted alkenes, the presence of an electron-withdrawing group in the betaine allows rapid interconversion between its two diastereomers through proton transfer. The *Z*/*E* selectivity for alkene synthesis is determined by the different rates at which the two betaine diastereomers form the corresponding 1,2-azaphosphetane diastereomers. In contrast, the *Z*/*E* selectivity for the synthesis of electron-deficient trisubstituted alkenes originates from the diastereoselective addition of stabilized phosphonium ylides to *N*-sulfonyl imines.

Introduction

Electron-deficient alkenes are not only present in many natural products of biological significance,[1] but also serve as useful electrophilic species in a broad range of chemical transformations, such as Michael addition, cycloaddition, and cross-coupling reactions.[2] In this context, a plethora of chemical methods have been developed for the synthesis of electron-deficient alkenes that mainly focus on the issue of stereoselectivity. Carbonyl olefination, alkyne addition, alkenylation, and elimination are all effective methods that are widely employed in the stereoselective synthesis of electron-deficient alkenes.[3] Particularly noteworthy is the olefination reaction of aldehydes with carbon nucleophiles that are stabilized by heteroatoms such as phosphorus (the Wittig and Horner–Wadsworth–Emmons reactions), silicon (the Peterson reaction), and sulfur (the Julia olefination). In each case, the aldehyde/carbon nucleophile addition step is followed by an elimination to form a carbon–carbon double bond.

The Wittig reaction of stabilized phosphonium ylides with aldehydes has enjoyed widespread prominence and recognition owing to its simplicity, convenience, complete positional selectivity, and generally high levels of geometrical control.[4] Stabilized triphenylphosphonium ylides have been employed most frequently because they are readily accessible by the reaction of triphenylphosphane, which is an inexpensive and air-stable phosphane, with α-halo carbonyl compounds or nitriles, followed by treatment of the resulting phosphonium salts with appropriate bases. In general, the Wittig reaction yields electron-deficient (*E*)-alkenes with high stereoselectivity for ester-, ketone-, and amide-stabilized triphenylphosphonium ylides,[4,5] but with low stereoselectivity for nitrile-stabilized triphenylphosphonium ylides.[6] Efforts to improve the stereoselective synthesis of electron-deficient alkenes have focused on replacing the stabilized triphenylphosphonium ylides in the Wittig reaction with other phosphorus-,[7] sulfur-,[8] silicon-,[9] arsenic-,[10] or tellurium-stabilized[11] carbon nucleophiles.[3] However, only limited successes have been achieved and many of the modified olefination reactions suffer from inconvenient access to heteroatom-stabilized carbon nucleophiles, narrow substrate scope, and inconvenient operations.

In sharp contrast, little attention has been paid to the replacement of aldehydes with other carbon electrophiles in the Wittig reaction of stabilized phosphonium ylides. In 2004, Abdou and co-workers developed the reaction of *N*-aryl imines with stabilized phosphonium ylides in chloroform heated under reflux to afford α,β-unsaturated nitriles, esters, and ketones with exclusive *E* selectivity, albeit in only about 20% yield; see Equation (1).[12] Four years later, Chen and co-workers reported that an *N*-*tert*-butoxycarbonyl

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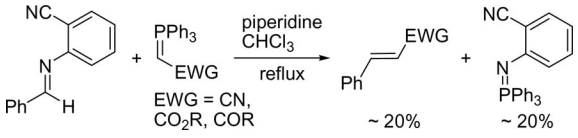
(Boc) imine reacted with a stabilized phosphonium ylide in toluene in the presence of molecular sieves (MS) at 0 °C to yield the corresponding imine/ylide adduct; see Equation (2).[13] Although these reactions are not useful for the stereoselective synthesis of electron-deficient alkenes, they prompted us to hypothesize that the employment of more reactive imines might enhance the yields for the formation of electron-deficient alkenes. In addition, switching the electronic and steric properties of the group on the imine nitrogen might improve or switch the stereoselectivity for alkene synthesis when compared to the corresponding Wittig reaction with aldehydes.



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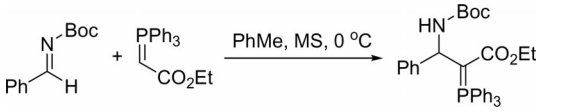
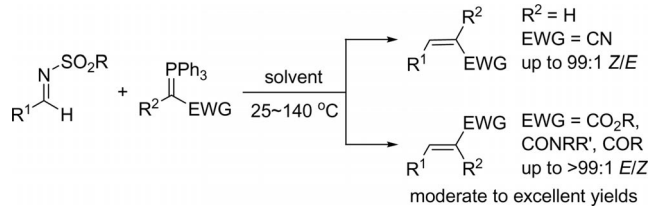


(2)

In the course of applying carbon–nitrogen bond cleavage to selective organic synthesis,[14] together with our interest in stereoselective alkene synthesis,[15] we recently discovered a highly tunable, stereoselective olefination of *N*-sulfonyl imines with semistabilized phosphonium ylides.[16] To extent this chemistry to the stereoselective synthesis of electron-deficient alkenes, we investigated the reaction of *N*-sulfonyl imines with a wide variety of stabilized phosphonium ylides, and synthesized structurally diverse electron-deficient alkenes in moderate to excellent yields. Importantly, these unprecedented reactions provided α,β-unsaturated nitriles with high *Z* selectivity, and α,β-unsaturated esters, amides, and ketones with high *E* selectivity (Scheme 1). Furthermore, spectroscopic analysis of the reaction mixtures and trapping of the intermediates allowed us to propose plausible mechanisms to account for the stereoselective formation of electron-deficient alkenes.



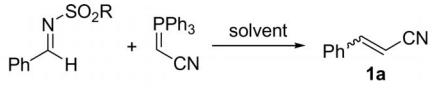
Scheme 1. Stereoselective olefination of *N*-sulfonyl imines with stabilized phosphonium ylides.

Results and Discussion

Stereoselective Olefination of *N*-Sulfonyl Imines with Nitrile-Stabilized Phosphonium Ylides

The Wittig reaction of nitrile-stabilized phosphonium ylides with aldehydes has been reported to yield (*E*)-α,β-unsaturated nitriles with low stereoselectivity.[6] To improve or switch the stereoselectivity for the synthesis of α,β-unsaturated nitriles, we replaced the aldehydes in the Wittig reaction with *N*-sulfonyl imines, which are reasonably stable in air at room temperature and are easily prepared through the condensation reaction of aldehydes with primary sulfonamides.[17] To our delight, the model reaction of (cyanomethylene)triphenylphosphorane with *N*-benzylidene-*p*-toluenesulfonamide proceeded smoothly in a number of common organic solvents at room temperature to afford α,β-unsaturated nitrile **1a** in moderate to excellent yields and with modest to excellent *Z* selectivity (Table 1, entries 1–8). Acetonitrile was identified as the solvent of choice; under these conditions the reaction afforded α,β-unsaturated nitrile **1a** in 95% yield and with a *Z*/*E* selectivity of 95:5 (Table 1, entry 5). For comparison, we carried out the Wittig reaction of benzaldehyde with (cyanomethylene)triphenylphosphorane under the same reaction conditions and obtained α,β-unsaturated nitrile **1a** with a *Z*/*E* selectivity of 23:77.[18] Whereas elevated temperature enhanced the yield, it decreased the stereoselectivity significantly (Table 1, entry 9). We further examined many other *N*-benzylidene sulfonamides in acetonitrile at room temperature and found that the *N*-sulfonyl group significantly affected the yield and stereoselectivity of the formation of α,β-unsaturated nitrile **1a** (Table 1, entries 10–18).[19] However, the stereoselectivity was not enhanced or switched by employing *N*-sulfonyl groups that possess distinct electronic and steric properties.

Table 1. Optimization of reaction conditions.[a]

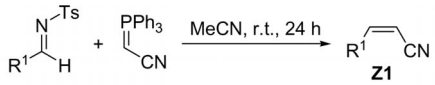


Entry	R	Solvent	*T* [°C]	Yield[b] [%]	*Z*/*E*[c]
1	4-MeC_6H_4	PhMe	25	53	59:41
2	4-MeC_6H_4	$CHCl_3$	25	77	93:7
3	4-MeC_6H_4	EtOAc	25	79	88:12
4	4-MeC_6H_4	THF	25	68	88:12
5	4-MeC_6H_4	MeCN	25	95	95:5
6	4-MeC_6H_4	DMF	25	87	92:8
7	4-MeC_6H_4	DMSO	25	85	86:14
8	4-MeC_6H_4	MeOH	25	42	75:25
9	4-MeC_6H_4	MeCN	60	98	85:15
10	4-MeOC_6H_4	MeCN	25	59	90:10
11	4-$O_2NC_6H_4$	MeCN	25	68	88:12
12	2-$O_2NC_6H_4$	MeCN	25	87	97:3
13	2,6-$Cl_2C_6H_3$	MeCN	25	65	84:16
14	2-naphthyl	MeCN	25	81	93:7
15	1-naphthyl	MeCN	25	63	81:19
16	2-thienyl	MeCN	25	76	94:6
17	Me	MeCN	25	61	77:23
18	*n*$C_{16}H_{33}$	MeCN	25	52	54:46

[a] Reaction conditions: *N*-sulfonyl imine (0.25 mmol), phosphonium ylide (0.30 mmol), solvent (0.50 mL), 25 or 60 °C, 24 h. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis. Tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO).

A broad range of *N*-(*p*-tolylsulfonyl) aromatic and heteroaromatic imines smoothly underwent olefination reactions with (cyanomethylene)triphenylphosphorane to afford structurally diverse (*Z*)-α,β-unsaturated nitriles in good to excellent yields and with excellent stereoselectivity (Table 2, entries 1–11). It is noteworthy that both electron-withdrawing and electron-donating groups could be introduced into the (*Z*)-α,β-unsaturated nitrile by employing a suitable imine bearing such a group on the aromatic ring. This *Z* selective olefination reaction was successfully extended to a range of *N*-(*p*-tolylsulfonyl) α,β-unsaturated imines, and various α,β,γ,δ-unsaturated nitriles were synthesized with excellent stereoselectivity (Table 2, entries 12–15). The geometric configuration of the carbon–carbon double bond in the *N*-sulfonyl imine was completely preserved in the olefination reaction. By contrast, the reaction with an *N*-(*p*-tolylsulfonyl) aliphatic imine proceeded slowly to afford the corresponding electron-deficient alkene with good *Z* selectivity (Table 2, entry 16).

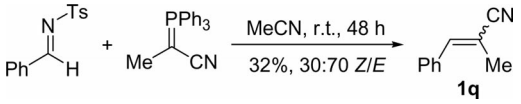
Table 2. Stereoselective olefination of *N*-sulfonyl imines with nitrile-stabilized phosphonium ylides.[a]



Entry	R^1	Z1	Yield[b] [%]	*Z*/*E*[c]
1	Ph	**Z1a**	97	95:5
2	4-$MeOC_6H_4$	**Z1b**	82	99:1
3	4-FC_6H_4	**Z1c**	84	95:5
4	2-MeC_6H_4	**Z1d**	98	94:6
5	2-$MeOC_6H_4$	**Z1e**	90	99:1
6	2-$O_2NC_6H_4$	**Z1f**	98	99:1
7	2,6-$Cl_2C_6H_3$	**Z1g**	83	97:3
8	3,4,5-$(MeO)_3C_6H_2$	**Z1h**	76	93:7
9	1-naphthyl	**Z1i**	99	98:2
10	2-furyl	**Z1j**	83	98:2
11	2-thienyl	**Z1k**	62	95:5
12	(*E*)-PhCH=CH	**Z1l**	78	93:7
13	(*E*)-4-$MeOC_6H_4CH$=CH	**Z1m**	73	93:7
14	(*E*)-2-$MeOC_6H_4CH$=CH	**Z1n**	99	97:3
15	(*E*)-2-$O_2NC_6H_4CH$=CH	**Z1o**	83	96:4
16[d]	cyclohexyl	**Z1p**	80	85:15

[a] Reaction conditions: *N*-(*p*-tolylsulfonyl) imine (0.25 mmol), phosphonium ylide (0.30 mmol), acetonitrile (1.0 mL), room temp., 24 h. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] The reaction was run for 48 h. Ts = *p*-tolylsulfonyl.

Poor reactivity and low stereoselectivity were observed in the olefination reaction with a nitrile-stabilized phosphonium ylide with greater steric demand. For example, the olefination reaction of (α-cyanoethylidene)triphenylphosphorane with *N*-benzylidene-*p*-toluenesulfonamide proceeded at room temperature for 48 h to afford trisubstituted α,β-unsaturated nitrile **1q** in only 32% yield; see Equation (3). Moreover, this reaction exhibited moderate *E* selectivity (30:70 *Z*/*E*), which is contrary to the stereoselectivity trend for the synthesis of α,β-disubstituted α,β-unsaturated nitriles shown in Table 2.

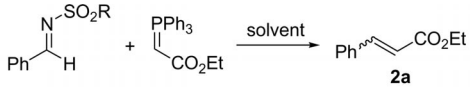


(3)

Stereoselective Olefination of *N*-Sulfonyl Imines with Ester-Stabilized Phosphonium Ylides

In contrast to (cyanomethylene)triphenylphosphorane, the olefination reaction of (ethoxycarbonylmethylene)triphenylphosphorane with *N*-benzylidene-*p*-toluenesulfonamide proceeded very slowly in a number of common organic solvents at room temperature and exhibited moderate to very good *E* selectivity (Table 3, entries 1–5). Replacement of the *p*-tolylsulfonyl group on the imine nitrogen with another sulfonyl group did not enhance the yield or stereoselectivity (Table 3, entries 6–9). We further examined the olefination reaction in *p*-xylene at an elevated temperature (Table 3, entries 10–12), and, to our delight, α,β-unsaturated ester **2a** was obtained in 74% yield with an *E*/*Z* selectivity of 98:2 when a methylsulfonyl group was employed to activate the imine (Table 3, entry 12).

Table 3. Optimization of reaction conditions.[a]

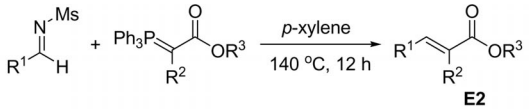


Entry	R	Solvent	*T* [°C]	Yield[b] [%]	*E*/*Z*[c]
1	4-MeC_6H_4	PhMe	25	27	91:9
2	4-MeC_6H_4	CH_2Cl_2	25	23	92:8
3	4-MeC_6H_4	EtOAc	25	32	90:10
4	4-MeC_6H_4	DMF	25	32	90:10
5	4-MeC_6H_4	EtOH	25	45	75:25
6	4-$MeOC_6H_4$	CH_2Cl_2	25	27	95:5
7	4-$O_2NC_6H_4$	CH_2Cl_2	25	38	88:12
8	2-$O_2NC_6H_4$	CH_2Cl_2	25	38	88:12
9	Me	CH_2Cl_2	25	31	91:9
10	4-MeC_6H_4	*p*-xylene	140	52	93:7
11	4-$MeOC_6H_4$	*p*-xylene	140	62	95:5
12	Me	*p*-xylene	140	74	98:2

[a] Reaction conditions: *N*-sulfonyl imine (0.25 mmol), phosphonium ylide (0.30 mmol), solvent (0.25 mL), 25 or 140 °C, 12 h. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis.

Under the optimized reaction conditions, (ethoxycarbonylmethylene)triphenylphosphorane reacted with various *N*-methylsulfonyl aromatic or heteroaromatic imines to afford the corresponding (*E*)-α,β-unsaturated esters in good yields and with excellent stereoselectivity (Table 4, entries 1–6). In contrast, very sluggish reactions were observed with *N*-methylsulfonyl α,β-unsaturated or aliphatic imines. To our delight, the olefination reaction worked well with a few other ester-stabilized phosphonium ylides having greater steric demands, and a range of trisubstituted α,β-unsaturated esters were synthesized in good yields and with excellent *E* selectivity from the corresponding *N*-methylsulfonyl imines and (α-alkoxycarbonylalkylidene)triphenylphosphoranes (Table 4, entries 7–11).

Table 4. Stereoselective olefination of *N*-sulfonyl imines with ester-stabilized phosphonium ylides.[a]



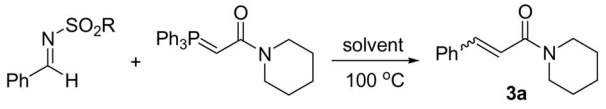
Entry	R^1	R^2	R^3	**E2**	Yield[b] [%]	*E*/*Z*[c]
1	Ph	H	Et	**E2a**	74	98:2
2	4-$MeOC_6H_4$	H	Et	**E2b**	75	95:5
3	4-ClC_6H_4	H	Et	**E2c**	65	>99:1
4	4-$O_2NC_6H_4$	H	Et	**E2d**	54	98:2
5	2-pyridyl	H	Et	**E2e**	66	>99:1
6	2-naphthyl	H	Et	**E2f**	70	99:1
7	Ph	Me	Et	**E2g**	77	98:2
8	4-$MeOC_6H_4$	Me	Et	**E2h**	63	96:4
9	2-$MeOC_6H_4$	Me	Et	**E2i**	62	>99:1
10	1-naphthyl	Me	Et	**E2j**	65	96:4
11	Ph	R^2, R^3 = CH_2CH_2		**E2k**	57	97:3

[a] Reaction conditions: *N*-methylsulfonyl imine (0.25 mmol), phosphonium ylide (0.30 mmol), *p*-xylene (0.25 mL), 140 °C, 12 h. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis, Ms = methylsulfonyl.

Stereoselective Olefination of *N*-Sulfonyl Imines with Amide-Stabilized Phosphonium Ylides

Elevated temperature was also needed to accelerate the olefination reaction of *N*-sulfonyl imines with amide-stabilized phosphonium ylides. A number of solvents were assessed in the model reaction of (1-piperidinylcarbonylmethylene)triphenylphosphorane with *N*-benzylidene-*p*-toluenesulfonamide at 100 °C (Table 5, entries 1–4), and it was found that dimethyl sulfoxide was the solvent of choice; under these conditions α,β-unsaturated amide **3a** was produced in 91% yield with an *E*/*Z* selectivity of 98:2 (Table 5, entry 3). Replacement of the *p*-tolylsulfonyl group on the imine nitrogen with other sulfonyl groups did not switch the stereoselectivity (Table 5, entries 5–9).

Table 5. Optimization of reaction conditions.[a]

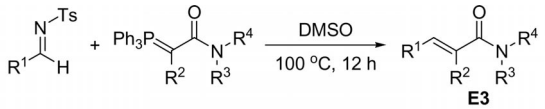


Entry	R	Solvent	Yield[b] [%]	*E*/*Z*[c]
1	4-MeC_6H_4	PhMe	67	83:17
2	4-MeC_6H_4	DMF	67	88:12
3	4-MeC_6H_4	DMSO	91	98:2
4	4-MeC_6H_4	H_2O	63	93:7
5	4-$O_2NC_6H_4$	DMSO	88	98:2
6	2-MeC_6H_4	DMSO	56	98:2
7	2-$O_2NC_6H_4$	DMSO	68	98:2
8	2-thienyl	DMSO	63	97:3
9	Me	DMSO	57	97:3

[a] Reaction conditions: *N*-sulfonyl imine (0.25 mmol), phosphonium ylide (0.30 mmol), solvent (0.25 mL), 100 °C, 12 h. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis.

Various *N*-(*p*-tolylsulfonyl) aromatic and heteroaromatic imines underwent olefination reactions with (1-piperidinylcarbonylmethylene)triphenylphosphorane to afford the corresponding (*E*)-α,β-unsaturated amides in good to excellent yields and with excellent stereoselectivity (Table 6, entries 1–5). In contrast, a moderate yield was obtained from the relatively slow reaction with an *N*-(*p*-tolylsulfonyl) aliphatic imine (Table 6, entry 6). To our delight, the olefination reaction worked well with a range of other amide-stabilized phosphonium ylides bearing structurally diverse substituents on the amide nitrogen atoms, and various di- and trisubstituted α,β-unsaturated amides were synthesized in good to excellent yields and with excellent *E* selectivity (Table 6, entries 7–12).

Table 6. Stereoselective olefination of *N*-sulfonyl imines with amide-stabilized phosphonium ylides.[a]



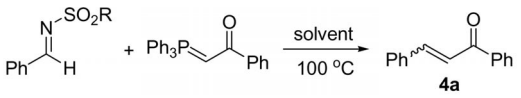
Entry	R^1	R^2	R^3	R^4	**E3**	Yield[b] [%]	*E*/*Z*[c]
1	Ph	H	R^3, R^4 = $(CH_2)_5$		**E3a**	91	98:2
2	4-$MeOC_6H_4$	H	R^3, R^4 = $(CH_2)_5$		**E3b**	62	97:3
3	4-ClC_6H_4	H	R^3, R^4 = $(CH_2)_5$		**E3c**	90	>99:1
4	2-thienyl	H	R^3, R^4 = $(CH_2)_5$		**E3d**	59	>99:1
5	1-naphthyl	H	R^3, R^4 = $(CH_2)_5$		**E3e**	88	>99:1
6[d]	cyclohexyl	H	R^3, R^4 = $(CH_2)_5$		**E3f**	45	95:5
7	Ph	H	R^3, R^4 = $(CH_2)_4$		**E3g**	62	98:2
8	Ph	H	R^3, R^4 = $(CH_2)_6$		**E3h**	59	98:2
9	Ph	H	R^3, R^4 = $O[(CH_2)_2]_2$		**E3i**	99	>99:1
10	Ph	H	*n*Bu	*n*Bu	**E3j**	80	>99:1
11	Ph	H	Me	OMe	**E3k**	90	95:5
12	Ph	Me	Me	OMe	**E3l**	60	>99:1

[a] Reaction conditions: *N*-(*p*-tolylsulfonyl) imine (0.25 mmol), phosphonium ylide (0.30 mmol), DMSO (0.25 mL), 100 °C, 12 h. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] The reaction was run for 72 h.

Stereoselective Olefination of *N*-Sulfonyl Imines with Ketone-Stabilized Phosphonium Ylides

A similar strategy was employed to optimize the reaction conditions for ketone-stabilized phosphonium ylides, and dimethyl sulfoxide was identified as the solvent of choice (Table 7, entries 1–4). The model reaction of (benzoylmethylene)triphenylphosphorane with *N*-benzylidene-*p*-toluenesulfonamide proceeded in dimethyl sulfoxide at 100 °C to afford α,β-unsaturated ketone **4a** in 98% yield, with an *E*/*Z* selectivity of 99:1 (Table 7, entry 3). Further investigations revealed that the sulfonyl group on the imine nitrogen atom only marginally affected the stereoselectivity in the alkene synthesis (Table 7, entries 5–9).

Table 7. Optimization of reaction conditions.[a]

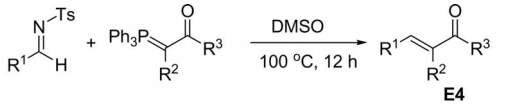


Entry	R	Solvent	Yield[b] [%]	*E*/*Z*[c]
1	4-MeC_6H_4	PhMe	27	97:3
2	4-MeC_6H_4	DMF	51	98:2
3	4-MeC_6H_4	DMSO	98	99:1
4	4-MeC_6H_4	H_2O	49	99:1
5	4-$O_2NC_6H_4$	DMSO	99	96:4
6	2-MeC_6H_4	DMSO	99	99:1
7	2,6-$Cl_2C_6H_3$	DMSO	99	96:4
8	2-thienyl	DMSO	61	98:2
9	Me	DMSO	82	98:2

[a] Reaction conditions: *N*-sulfonyl imine (0.25 mmol), phosphonium ylide (0.30 mmol), solvent (0.25 mL), 100 °C, 12 h. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis.

A broad range of *N*-(*p*-tolylsulfonyl) aromatic, α,β-unsaturated, and aliphatic imines served as suitable carbon electrophiles; these underwent olefination reactions with a wide variety of ketone-stabilized phosphonium ylides (Table 8). Significantly, an array of di- and trisubstituted α,β-unsaturated ketones were synthesized in moderate to excellent yields and with excellent *E* selectivity.

Table 8. Stereoselective olefination of *N*-sulfonyl imines with ketone-stabilized phosphonium ylides.[a]



Entry	R^1	R^2	R^3	**E4**	Yield[b] [%]	*E*/*Z*[c]
1	Ph	H	Ph	**E4a**	98	99:1
2	4-$MeOC_6H_4$	H	Ph	**E4b**	78	>99:1
3	4-FC_6H_4	H	Ph	**E4c**	89	99:1
4	2-$MeOC_6H_4$	H	Ph	**E4d**	70	97:3
5	1-naphthyl	H	Ph	**E4e**	76	99:1
6	Ph	H	4-$MeOC_6H_4$	**E4f**	58	>99:1
7	Ph	H	4-$O_2NC_6H_4$	**E4g**	89	99:1
8	Ph	H	CMe_3	**E4h**	86	95:5
9	Ph	H	Me	**E4i**	99	>99:1
10	(*E*)-PhCH=CH	H	Me	**E4j**	46	>99:1
11[d]	cyclohexyl	H	Me	**E4k**	77	>99:1
12	Ph	Me	Me	**E4l**	89	>99:1

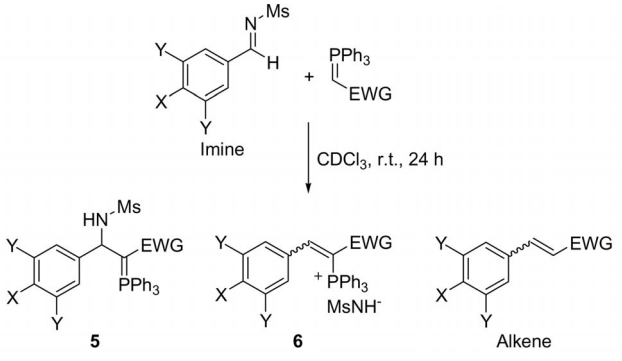
[a] Reaction conditions: *N*-(*p*-tolylsulfonyl) imine (0.25 mmol), phosphonium ylide (0.30 mmol), DMSO (0.25 mL), 100 °C, 12 h. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] The reaction was run for 24 h.

Mechanistic Studies

As demonstrated by the results summarized in Tables 2, 4, 6, and 8, the olefination reaction of *N*-sulfonyl imines with stabilized phosphonium ylides affords α,β-unsaturated nitriles with high *Z* selectivity, and α,β-unsaturated esters, amides, and ketones with high *E* selectivity. Whereas the stereoselectivity is highly tunable in the olefination reaction of *N*-sulfonyl imines with semistabilized phosphonium ylides,[16] it is difficult to tune the stereoselectivity for the corresponding reaction with stabilized phosphonium ylides simply by switching the electronic and steric properties of the sulfonyl groups on the imine nitrogen atoms. To gain insights into the reaction mechanism, we carried out spectroscopic analyses of the reaction mixtures and attempted to trap the possible intermediates.

In contrast to semistabilized phosphonium ylides, which are prepared in situ, stabilized phosphonium ylides are sufficiently stable to be purified before use. Importantly, employing pure stabilized phosphonium ylides and *N*-sulfonyl imines in the reaction greatly facilitated the spectroscopic analyses of the reaction mixtures. A nitrile-stabilized and an ester-stabilized phosphonium ylide were submitted to the olefination reaction with two representative *N*-methylsulfonyl imines in deuterated chloroform at room temperature, and, after 24 hours, each of the reaction mixtures was subjected to ^{1}H NMR spectroscopic analysis. As summarized in Table 9, significant amounts of imine/ylide adducts **5a**–**d** and vinylphosphonium salts **6a** and **6b** were identified as intermediates, the generation of which was substantially supported by ^{31}P NMR spectroscopic analysis of the reaction mixtures.[20] Moreover, vinylphosphonium salts **6a**–**d** were unambiguously detected in these reaction mixtures by ESI-HRMS (electron spray ionization high-resolution mass spectrometry) analysis. It is clear that only trace amounts of intermediates **6c** and **6d** were generated in the reactions with an ester-stabilized phosphonium ylide (Table 9, entries 3 and 4).

Table 9. Spectroscopic analysis of the reaction mixtures.[a]

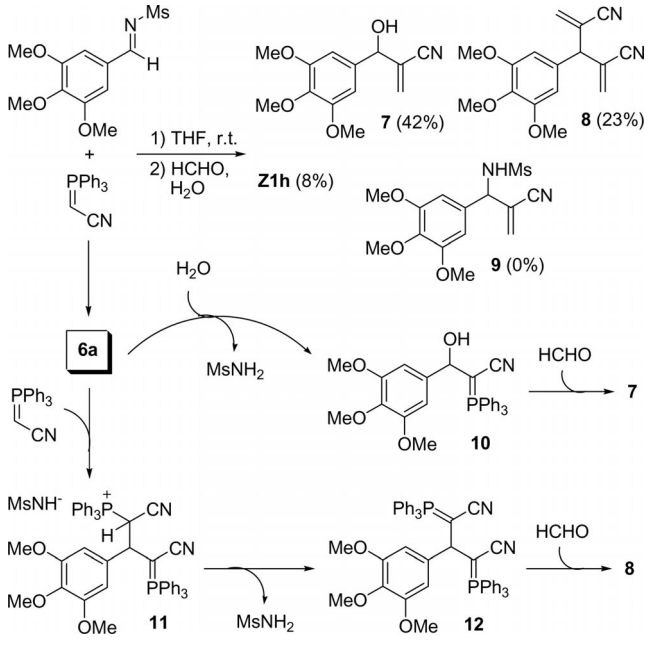


Entry	X	Y	EWG	**5**	**6**	Imine:**5**:**6**:Alkene[b]	*E*/*Z*[b,c]
1	OMe	OMe	CN	**5a**	**6a**	51:18:23:8	80:20
2	NO_2	H	CN	**5b**	**6b**	15:50:27:8	56:44
3	OMe	OMe	CO_2Me	**5c**	**6c**	55:36:--:9	3:97
4	NO_2	H	CO_2Me	**5d**	**6d**	16:75:--:9	8:92

[a] Reaction conditions: *N*-methylsulfonyl imine (0.125 mmol), phosphonium ylide (0.125 mmol), deuterated chloroform (0.50 mL), room temp., 24 h. [b] Determined by ^{1}H NMR spectroscopic analysis. [c] For electron-deficient alkenes.

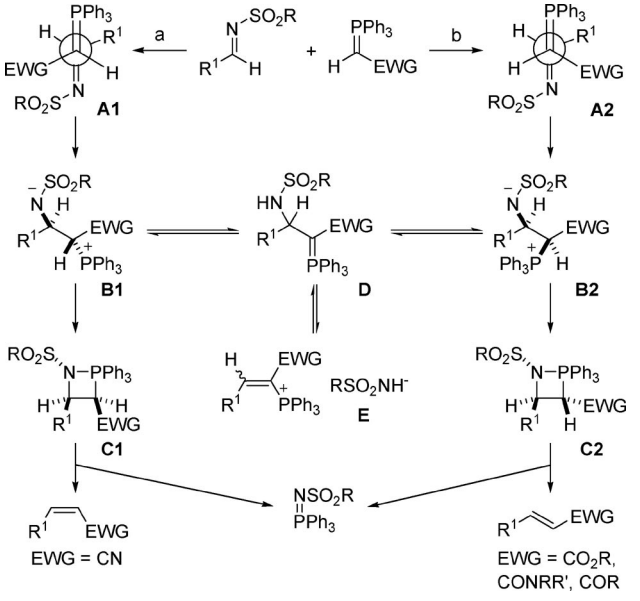
It is noteworthy that imine/ylide adduct **5d** was isolated with 95% purity (contaminated by the corresponding *N*-sulfonyl imine) by filtration after the reaction mixture was treated with petroleum ether and ethyl acetate (3:1) at room temperature. However, such a purification procedure did not allow the isolation of imine/ylide adducts **5a**–**c** and vinylphosphonium salts **6a**–**d** owing to their decomposition at room temperature to yield the corresponding electron-deficient alkenes.

Interestingly, treatment of the reaction mixture with formalin resulted in the trapping of vinylphosphonium salts **6** rather than imine/ylide adducts **5**. For example, when formalin was added after 1 h to the reaction of (cyanomethylene)triphenylphosphorane with *N*-(3,4,5-trimethoxy)benzylidenemethanesulfonamide in tetrahydrofuran at room temperature, allylic alcohol **7**, 1,4-diene **8**, and alkene **Z1h** (88:12 *Z*/*E*) were obtained (Scheme 2). In contrast, allylic amine derivative **9** was not obtained at all through the methylenation of intermediate **5a**, probably due to its rapid decomposition to yield alkene **Z1h** and/or intermediate **6a** under the reaction conditions. Tentatively, allylic alcohol **7** and 1,4-diene **8** are thought to be generated via intermediate **6a**, which was identified by the aforementioned NMR spectroscopic analysis (Table 9). The Michael addition of water to intermediate **6a** results in the formation of ylide **10**, which undergoes methylenation with formaldehyde to afford allylic alcohol **7**. Alternatively, the Michael addition of (cyanomethylene)triphenylphosphorane to intermediate **6a** followed by deprotonation leads to the formation of 1,3-diylide **12**, which undergoes double methylenation with formaldehyde to afford 1,4-diene **8**.



Scheme 2. Treatment of the reaction mixture with formalin.

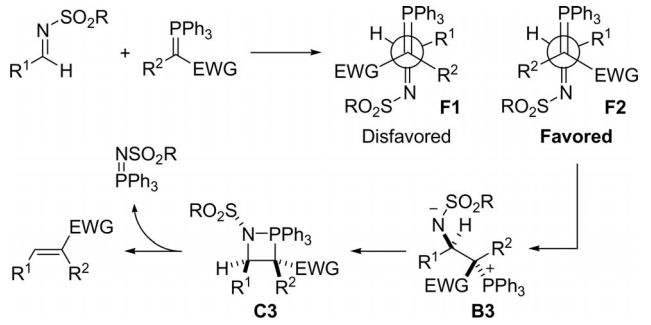
On the basis of our results and on previous studies reported in literature,[12,13,21] we propose the following mechanism to account for the stereoselectivity for the synthesis of electron-deficient 1,2-disubstituted alkenes from *N*-sulfonyl imines and stabilized phosphonium ylides (Scheme 3). The diastereoselective addition of a stabilized phosphonium ylide to an *N*-sulfonyl imine results in the formation of betaine **B** (as a mixture of *anti*-isomer **B1** and *syn*-isomer **B2**), which cyclizes to form 1,2-azaphosphetane **C** (as a mixture of *cis*-isomer **C1** and *trans*-isomer **C2**) and subsequently eliminates an iminophosphorane to yield an alkene.[22] Owing to the presence of the electron-withdrawing group, proton transfer occurs readily to result in isomerization between **B1** and **B2** via ylide **D**,[23] which reversibly loses a sulfonamide group to yield vinylphosphonium salt **E**. The large abundance of ylide **D** (and in some cases vinylphosphonium salt **E**) in the reaction mixture, as revealed by the examples shown in Table 9, suggests that the conversion of betaine **B** into 1,2-azaphosphetane **C** is much slower than the interconversion between betaine diastereomers **B1** and **B2**. Thus, it is reasonable to conclude that the *Z*/*E* selectivity for alkene synthesis does not parallel the diastereoselectivity for the initial addition of a stabilized phosphonium ylide to an *N*-sulfonyl imine. Instead, the *Z*/*E* selectivity for alkene synthesis is determined by the different rates for the transformations of **B1** and **B2** into **C1** and **C2**, respectively. When the total interactions of the *N*-sulfonyl group, the R^1 group, the *P*-phenyl group, and the EWG group that develop in the formation of **C2** are greater than that in the formation of **C1**, the olefination reaction prefers to afford a (*Z*)-alkene (EWG = CN), otherwise, an (*E*)-alkene is produced predominantly (EWG = CO_2R, CONRR′, COR).



Scheme 3. Proposed mechanism for the stereoselective synthesis of electron-deficient 1,2-disubstituted alkenes from *N*-sulfonyl imines and stabilized phosphonium ylides.

For the synthesis of an electron-deficient trisubstituted alkene, no intermediate was observed by ^{1}H NMR, ^{31}P NMR, or ESI-MS analysis of the reaction mixture. Of course, it is unlikely that the reaction would generate intermediates analogous to **D** and **E** when the α-hydrogen in a stabilized phosphonium ylide is replaced with an alkyl (R^2)

group (Scheme 4). Thus, we propose that the diastereoselective addition of a stabilized phosphonium ylide to an *N*-sulfonyl imine preferentially results in the formation of betaine **B3**, which cyclizes to form 1,2-azaphosphetane **C3** and subsequently eliminates an iminophosphorane to yield an electron-deficient (*E*)-trisubstituted alkene. The stereoselectivity for alkene synthesis is determined by the total interactions of the *N*-sulfonyl group, the R^1 group, the Ph_3P group, the EWG group, and the R^2 group that develop as the ylide and imine approach one another, and the favorable formation of betaine **B3** accounts for the *E* selectivity exhibited in the synthesis of an electron-deficient trisubstituted alkene.



Scheme 4. Proposed mechanism for the stereoselective synthesis of electron-deficient trisubstituted alkenes from *N*-sulfonyl imines and stabilized phosphonium ylides.

Conclusions

In conclusion, we have developed an unprecedented protocol for the stereoselective synthesis of structurally diverse electron-deficient alkenes in moderate to excellent yields from readily accessible *N*-sulfonyl imines and stabilized phosphonium ylides. Significantly, the olefination reaction of *N*-sulfonyl imines with nitrile-stabilized phosphonium ylides affords an array of α,β-unsaturated nitriles with high *Z* selectivity, and the reactions with ester-, amide-, and ketone-stabilized phosphonium ylides afford α,β-unsaturated esters, amides, and ketones with high *E* selectivity, respectively.

On the basis of spectroscopic analyses of reaction mixtures and the trapping of intermediates, plausible mechanisms have been proposed that account for the stereoselectivity of alkene synthesis. The diastereoselective addition of a stabilized phosphonium ylide to an *N*-sulfonyl imine results in the formation of a betaine, which cyclizes to form a 1,2-azaphosphetane and subsequently eliminates an iminophosphorane to yield an alkene. For the synthesis of an electron-deficient 1,2-disubstituted alkene, the presence of an electron-withdrawing group in the betaine allows rapid interconversion between its two diastereomers through proton transfer, and the *Z*/*E* selectivity for alkene synthesis is determined by the different rates at which the two betaine diastereomers form the corresponding 1,2-azaphosphetane diastereomers. In contrast, the *Z*/*E* selectivity for the synthesis of an electron-deficient trisubstituted alkene originates from the diastereoselective addition of a stabilized phosphonium ylide to an *N*-sulfonyl imine.

Experimental Section

General Procedure for the Stereoselective Olefination of *N*-Sulfonyl Imines with Nitrile-Stabilized Phosphonium Ylides: (Table 2): To a solution of *N*-(*p*-tolylsulfonyl) imine (0.25 mmol) in acetonitrile (1.0 mL) under nitrogen at room temperature was added the corresponding nitrile-stabilized phosphonium ylide (0.30 mmol). The mixture was stirred at room temperature for 24 h, and purified by flash column chromatography on silica gel or by preparative thin layer chromatography (TLC), eluting or developing with petroleum ether/ethyl acetate (10:1 to 3:1), to give α,β-unsaturated nitrile **Z1**.

General Procedure for the Stereoselective Olefination of *N*-Sulfonyl Imines with Ester-Stabilized Phosphonium Ylides: (Table 4): To a solution of *N*-(methylsulfonyl) imine (0.25 mmol) in *p*-xylene (0.25 mL) under nitrogen was added the corresponding ester-stabilized phosphonium ylides (0.30 mmol). The mixture was stirred at 140 °C for 12 h, purified by flash column chromatography on silica gel or by preparative TLC, eluting or developing with petroleum ether/ethyl acetate (10:1 to 3:1), to give α,β-unsaturated ester **E2**.

General Procedure for the Stereoselective Olefination of *N*-Sulfonyl Imines with Amide- or Ketone-Stabilized Phosphonium Ylides: (Tables 6 and 8): To a solution of *N*-(*p*-tolylsulfonyl) imine (0.25 mmol) in dimethyl sulfoxide (0.25 mL) under nitrogen was added the corresponding amide- or ketone-stabilized phosphonium ylide (0.30 mmol). The mixture was stirred at 100 °C for 12 h, and purified by flash column chromatography on silica gel or by preparative TLC, eluting or developing with petroleum ether/ethyl acetate (10:1 to 3:1), to give α,β-unsaturated amide **E3** or α,β-unsaturated ketone **E4**.

Supporting Information (see footnote on the first page of this article): General information, experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra for products.

Acknowledgments

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[18] Similar results have been reported in the literature, see ref.[6a,6b]

[19] The reaction of $PhCH{=}NPO(OPh)_2$ with (cyanomethylene)triphenylphosphorane was also performed in acetonitrile at room temperature; under these conditions, α,β-unsaturated nitrile **1a** was obtained in 70% yield with a *Z*/*E* selectivity of 58:42.

[20] For details, see the Supporting Information.

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[22] It is noteworthy that Ph_3PO, rather than an iminophosphorane, was detected as a byproduct by ^{31}P NMR spectroscopic analysis of the reaction mixture (Table 9) owing to the rapid decomposition of the iminophosphorane caused by a trace amount of water. The formation of an iminophosphorane as a primary byproduct was substantially confirmed by the fact that $Ph_3P^{18}O$ was generated in the reaction of *N*-benzylidene-*p*-toluenesulfonamide with (cyanomethylene)triphenylphosphorane in the presence of $H_2{}^{18}O$ (2.0 equiv.). For details, see the Supporting Information.

[23] Analogues of ylide **D**, prepared from triphenylphosphane, dialkyl acetylenedicarboxylates, and arylsulfonamides, have been proposed to decompose to give alkenes and iminophosphoranes via the corresponding betaines and 1,2-azaphosphetanes; see ref.[21]

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