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A Highly Tunable Stereoselective Olefination of Semistabilized Triphenylphosphonium Ylides with *N*-Sulfonyl Imines

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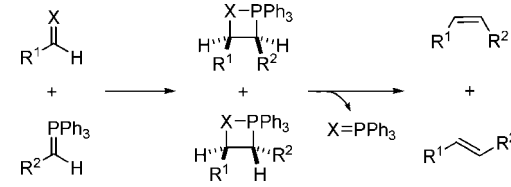
Geometrically defined alkenes not only are ubiquitous structural motifs in biologically relevant molecules but also serve as a foundation for a broad range of chemical transformations. A plethora of chemical methods have been invented for the convergent synthesis of stereodefined alkenes, which defines a pillar of modern synthetic chemistry.[1] While no single method provides a universal solution to stereoselective alkene synthesis, the Wittig reaction involving direct olefination of 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.[1,2]

Triphenylphosphonium ylides ($Ph_3P{=}CHR$) have been employed most frequently in the Wittig reaction because they are readily prepared through the reaction of triphenylphosphine, an inexpensive and air-stable phosphine, with alkyl halides followed by treatment of the resulting phosphonium salts with bases. In general, the Wittig reaction yields preferentially *Z*-alkenes for nonstabilized triphenylphosphonium ylides (R = alkyl) and *E*-alkenes for stabilized triphenylphosphonium ylides (R = alkoxycarbonyl, acyl, or cyano) but mixtures of *Z*- and *E*-alkenes for semistabilized triphenylphosphonium ylides (R = aryl or vinyl).[2,3] Although a number of efforts have been devoted to the modification of semistabilized triphenylphosphonium ylides by replacing the phenyl group with a substituted aryl group,[4] a heteroaryl group,[5] an alkyl group,[6] a dialkylamino group,[7] or an alkoxy group,[3,8,9] limited successes have been achieved in improving the stereoselectivity for the synthesis of conjugated alkenes, and furthermore, most of these procedures are costly, laborious, and time-consuming.

In sharp contrast to the modification of semistabilized triphenylphosphonium ylides, it is surprising that little has been done with the electrophiles in the Wittig reaction to improve the stereoselectivity for alkene synthesis. As early as 1963, Bestmann and Seng disclosed an olefination reaction of semistabilized triphenylphosphonium ylides with *N*-phenyl imines at 150−180 °C (or 190−200 °C) to yield (*E*)-stilbene and (1*E*,3*E*)-1,4-diphenyl-1,3-butadiene.[10] However, this protocol has not been improved toward a practical stereoselective synthesis of conjugated alkenes probably owing to the high reaction temperature and inconvenient operation. Nevertheless, the fact that imines possess distinct electronic and steric properties relative to aldehydes, together with our interest in stereoselective alkene synthesis,[11] prompted us to develop a tunable stereoselective synthesis of conjugated alkenes through an olefination reaction of semistabilized triphenylphosphonium ylides with appropriate imines instead of the aldehydes used in the Wittig reaction.

We planned to employ an electron-withdrawing group to activate an imine and facilitate subsequent carbon−nitrogen bond cleavage for the stereoselective olefination of a semistabilized triphenylphosphonium ylide. The use of a more reactive imine would require lower temperature relative to the reaction with an *N*-phenyl imine. Moreover, the electron-withdrawing group could serve as a handle to tune the stereoselectivity. As proposed by Bestmann and Seng, the olefination of a triphenylphosphonium ylide with an imine could potentially proceed through a Wittig-type reaction pathway involving formal [2 + 2] cycloaddition to generate a 1,2-azaphosphetane intermediate[12] followed by elimination of an iminophosphorane yielding an alkene (Scheme 1, X = N-EWG).[10] The *Z*/*E* ratio of an alkene product would rely totally on the stereoselectivity for the formation of the 1,2-azaphosphetane intermediate, during which an additional electron-withdrawing group could interact with the phenyl group, the R^1 group, and/or the R^2 group to tune the stereoselectivity when compared to a 1,2-oxaphosphetane intermediate generated in the Wittig reaction (Scheme 1, X = O).

Scheme 1. Olefinations of Semistabilized Triphenylphosphonium Ylides with Aldehydes (a) or Imines (b)[a]



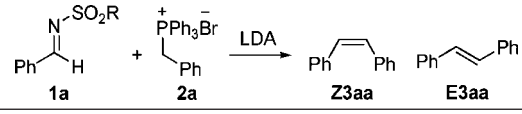
[a] R^1 = general hydrocarbon group; R^2 = aryl, vinyl; EWG = electron-withdrawing group. (a) The Wittig reaction: X = O, with low stereoselectivity. (b) Our approach: X = N-EWG; EWG facilitates the carbon−nitrogen bond cleavage and tunes the stereoselectivity for alkene synthesis.

We have recently demonstrated that a sulfonyl group is one of the most effective electron-withdrawing groups in activating imines and in facilitating carbon−nitrogen bond cleavage under mild reaction conditions.[13] In addition, *N*-sulfonyl imines are reasonably stable in the air at room temperature and are easily prepared through the condensation reaction of aldehydes with primary sulfonamides.[14] Thus, a number of sulfonyl groups were evaluated with regard to their ability to activate an imine and affect the stereoselectivity in the model reaction of benzylidenetriphenylphosphorane $Ph_3P{=}CHPh$, prepared in situ from phosphonium salt **2a** and lithium diisopropylamide (LDA), with *N*-benzylidene sulfonamide **1a** in tetrahydrofuran at −78 °C to room temperature (Table 1).[15] As demonstrated by the results summarized in Table 1, a sulfonyl group could significantly affect the yield and stereoselectivity for the synthesis of stilbene. To our great delight, the use of a *p*-toluenesulfonyl group to activate the imine resulted in the formation of (*Z*)-stilbene (**Z3aa**) with greater than 99:1 stereoselectivity (Table 1, entry 1),[16] and moreover, (*E*)-stilbene (**E3aa**) was also obtained with the same level of stereoselectivity when an *n*-hexadecanesulfonyl group was employed (Table 1, entry 11).

A broad range of *p*-toluenesulfonyl-activated aromatic or heteroaromatic imines underwent olefination reaction with various benzylidenetriphenylphosphoranes to afford structurally diversified (*Z*)-stilbene derivatives in good to excellent yields and with greater than 99:1 stereoselectivity (Table 2, entries 1−7 and 11−18). In

10.1021/ja910238f

Table 1. Survey of the Sulfonyl Groups[a]



1a **2a** **Z3aa** **E3aa**

entry	imine	R	yield (%)[b]	*Z*/*E*[c]
1	**1aa**	4-MeC_6H_4	79	>**99:1**
2	**1ab**	4-$MeOC_6H_4$	59	>99:1
3	**1ac**	4-$O_2NC_6H_4$	61	>99:1
4	**1ad**	2-$O_2NC_6H_4$	63	50:50
5	**1ae**	2,6-$Cl_2C_6H_3$	64	50:50
6	**1af**	2,4,6-$Me_3C_6H_2$	53	23:77
7	**1ag**	1-naphthyl	79	78:22
8	**1ah**	2-naphthyl	43	98:2
9	**1ai**	2-thienyl	69	>99:1
10	**1aj**	Me	47	50:50
11	**1ak**	*n*-$C_{16}H_{33}$	81	<**1:99**
12	**1al**	$PhCH_2$	58	28:72

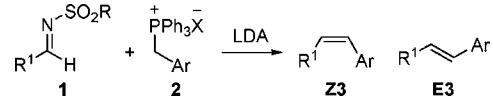
[a] Reaction conditions: phosphonium salt **2a** (0.60 mmol), LDA (0.65 mmol), THF (1.0 mL), −78 °C, 1 h; then imine **1a** (0.50 mmol), THF (1.0 mL), −78 °C to rt. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis.

the case of an *ortho*-substituted aromatic imine, an *o*-nitrobenzenesulfonyl group was needed for the olefination reaction to exhibit exclusive *Z* selectivity (Table 2, entries 8−10). It is noteworthy that either an electron-withdrawing or an electron-donating group was introduced into (*Z*)-stilbene by employing either an imine or an ylide bearing such a group on the aromatic ring. The exclusive *Z* selective olefination reaction was successfully extended to a range of α,*β*-unsaturated and aliphatic imines activated by a 2,6-dichlorobenzenesulfonyl group and a 1-naphthenesulfonyl group, respectively (Table 2, entries 19−23). Further switching of the electronic and steric properties of the sulfonyl groups allowed us to obtain exclusive *E* selectivity from the olefination reaction of benzylidenetriphenylphosphoranes with *N*-sulfonyl imines. An *n*-hexadecanesulfonyl group, a 2-naphthenesulfonyl group, and a 2,6-dichlorobenzenesulfonyl group were able to activate a broad range of aromatic, α,*β*-unsaturated, and aliphatic imines to yield various conjugated *E*-alkenes with greater than 99:1 stereoselectivity, respectively (Table 2, entries 24−35). These results demonstrate that a right match of the R^1 group and the sulfonyl group is essential for the olefination of imine **1** with a benzylidenetriphenylphosphorane to exhibit high *Z* or *E* selectivity.[17]

Next, we examined the olefination reaction of allylidenetriphenylphosphoranes with *N*-sulfonyl imines for the stereoselective synthesis of conjugated dienes and trienes (Table 3), which exhibited extremely high stereoselectivity with regard to the newly formed carbon−carbon double bonds when appropriate sulfonyl groups were employed. As summarized in Table 3, exclusive *E* selectivity was obtained from the reaction with a range of *p*-toluenesulfonyl- or methanesulfonyl-activated aromatic, α,*β*-unsaturated, and aliphatic imines (Table 3, entries 1−14), and furthermore, the use of 2,6-dichlorobenzenesulfonyl-activated aromatic, α,*β*-unsaturated, and aliphatic imines resulted in exclusive *Z* selectivity (Table 3, entries 15−20). It is noteworthy that the geometric configuration of the carbon−carbon double bond in either an imine or ylide was completely preserved in this olefination reaction (Table 3, entries 6−20).

Finally, the efficiency of this new process has been demonstrated in the highly stereoselective synthesis of two anticancer agents, DMU-212 (**E6**) and its isomer **Z6** (Scheme 2). DMU-212 (**E6**) shows high activity and selectivity against several cancer cell types,[18] and alkene **Z6** is potent in inducing rapid perinuclear

Table 2. Tunable Stereoselective Olefination of Benzylidenetriphenylphosphoranes with *N*-Sulfonyl Imines[a]



1 **2** **Z3** **E3**

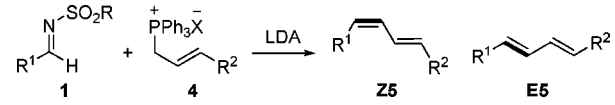
entry	R^1	Ar	R	product	yield (%)[b]	*Z*/*E*[c]
1	Ph	Ph	4-MeC_6H_4	**Z3aa**	79	>99:1
2	4-ClC_6H_4	Ph	4-MeC_6H_4	**Z3ba**	73	>99:1
3	4-NCC_6H_4	Ph	4-MeC_6H_4	**Z3ca**	73	>99:1
4	4-$MeO_2CC_6H_4$	Ph	4-MeC_6H_4	**Z3da**	86	>99:1
5	4-$O_2NC_6H_4$	Ph	4-MeC_6H_4	**Z3ea**	77	>99:1
6	4-$MeOC_6H_4$	Ph	4-MeC_6H_4	**Z3fa**	71	>99:1
7	3-ClC_6H_4	Ph	4-MeC_6H_4	**Z3ga**	79	>99:1
8	2-ClC_6H_4	Ph	2-$O_2NC_6H_4$	**Z3ha**	73	>99:1
9	2-$O_2NC_6H_4$	Ph	2-$O_2NC_6H_4$	**Z3ia**	79	>99:1
10	2-MeC_6H_4	Ph	2-$O_2NC_6H_4$	**Z3ja**	67	>99:1
11	2-naphthyl	Ph	4-MeC_6H_4	**Z3ka**	81	>99:1
12	3-pyridyl	Ph	4-MeC_6H_4	**Z3la**	78	>99:1
13	2-pyridyl	Ph	4-MeC_6H_4	**Z3ma**	89	>99:1
14	Ph	4-NCC_6H_4	4-MeC_6H_4	**Z3ca**	73	>99:1
15	Ph	4-$MeOC_6H_4$	4-MeC_6H_4	**Z3fa**	77	>99:1
16	Ph	2-naphthyl	4-MeC_6H_4	**Z3ka**	71	>99:1
17	4-ClC_6H_4	4-$MeOC_6H_4$	4-MeC_6H_4	**Z3bc**	74	>99:1
18	4-$MeOC_6H_4$	4-NCC_6H_4	4-MeC_6H_4	**Z3fb**	82	>99:1
19	(*E*)-PhCH=CH	Ph	2,6-$Cl_2C_6H_3$	**Z3na**	76	>99:1
20	(*E*)-PhCH=CH	2-naphthyl	2,6-$Cl_2C_6H_3$	**Z3nd**	77	>99:1
21	*n*-C_6H_{13}	Ph	1-naphthyl	**Z3oa**	77	>99:1
22	Me_2CH	Ph	1-naphthyl	**Z3pa**	69	>99:1
23	cyclohexyl	Ph	1-naphthyl	**Z3qa**	76	>99:1
24	Ph	Ph	*n*-$C_{16}H_{33}$	**E3aa**	81	<1:99
25	4-ClC_6H_4	Ph	*n*-$C_{16}H_{33}$	**E3ba**	79	<1:99
26	4-NCC_6H_4	Ph	*n*-$C_{16}H_{33}$	**E3ca**	73	<1:99
27	4-$MeOC_6H_4$	Ph	*n*-$C_{16}H_{33}$	**E3fa**	68	<1:99
28	3-ClC_6H_4	Ph	*n*-$C_{16}H_{33}$	**E3ga**	69	<1:99
29	2-naphthyl	Ph	*n*-$C_{16}H_{33}$	**E3ka**	71	<1:99
30	4-ClC_6H_4	4-$MeOC_6H_4$	*n*-$C_{16}H_{33}$	**E3bc**	75	<1:99
31	4-$MeOC_6H_4$	4-NCC_6H_4	*n*-$C_{16}H_{33}$	**E3fb**	78	<1:99
32	(*E*)-PhCH=CH	Ph	2-naphthyl	**E3na**	61	<1:99
33	*n*-C_6H_{13}	Ph	2,6-$Cl_2C_6H_3$	**E3oa**	63	<1:99
34	Me_2CH	Ph	2,6-$Cl_2C_6H_3$	**E3pa**	65	<1:99
35	cyclohexyl	Ph	2,6-$Cl_2C_6H_3$	**E3qa**	67	<1:99

[a] Reaction conditions: phosphonium salt **2** (0.60 mmol), X = Br (For entries 15, 17, and 30, X = Cl), LDA (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] Isolated yield. [c] Determined by ^{1}H NMR analysis.

mitochondrial clustering and p53-independent apoptosis in cancer cells but not normal cells.[19] While several routes have been disclosed for the synthesis of DMU-212 (**E6**), many of them suffer from low stereoselectivity and/or lengthy synthetic sequences.[6a,20] By contrast, a highly stereoselective synthesis of alkene **Z6** has not been reported. Our tunable protocol allowed the synthesis of both DMU-212 (**E6**) and its isomer **Z6** in a highly stereoselective manner. Treatment of 4-methoxybenzylidenetriphenylphosphorane with *N*-(*n*-hexadecanesulfonyl) imine **1rk** afforded DMU-212 (**E6**) in 74% yield and with greater than 99:1 stereoselectivity, and similar treatment with *N*-(*p*-toluenesulfonyl) imine **1ra** afforded alkene **Z6** in 69% yield and with greater than 99:1 stereoselectivity. In addition, a gram-scale synthesis of alkene **Z6** was successfully performed according to our protocol without deterioration in both yield and stereoselectivity (74% yield, > 99:1 *Z*/*E*).

In summary, we have developed a simple and efficient protocol to improve the stereoselectivity significantly for the olefination reaction of semistabilized triphenylphosphonium ylides by replacing the aldehydes used in the Wittig reaction with *N*-sulfonyl imines, which possess distinct electronic and steric properties relative to aldehydes. A broad range of aromatic, α,*β*-unsaturated, and aliphatic

Table 3. Tunable Stereoselective Olefination of Allylidenetriphenylphosphoranes with *N*-Sulfonyl Imines[a]

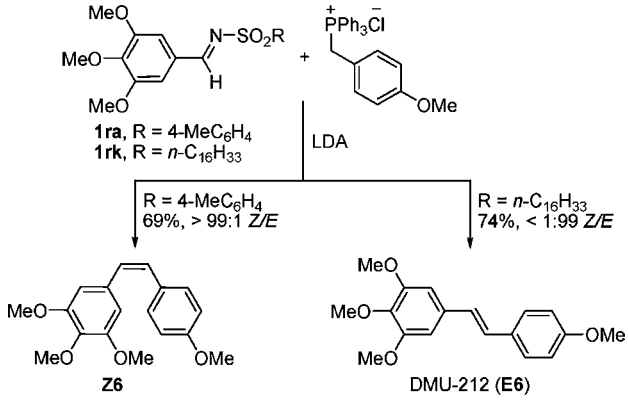


1 **4** **Z5** **E5**

entry	R^1	R^2	R	product	yield (%)[b]	*Z*/*E*[c]
1	Ph	H	4-MeC_6H_4	**E5aa**	77	<1:99
2	4-ClC_6H_4	H	4-MeC_6H_4	**E5ba**	88	<1:99
3	4-$O_2NC_6H_4$	H	4-MeC_6H_4	**E5ea**	76	<1:99
4	4-$MeOC_6H_4$	H	4-MeC_6H_4	**E5fa**	90	<1:99
5	2-pyridyl	H	4-MeC_6H_4	**E5ma**	71	<1:99
6	Ph	Ph	Me	**E3na**	78	<1:99
7	4-ClC_6H_4	Ph	Me	**E5bb**	78	<1:99
8	4-$MeOC_6H_4$	Ph	Me	**E5fb**	74	<1:99
9	2-ClC_6H_4	Ph	Me	**E5hb**	73	<1:99
10	2-pyridyl	Ph	Me	**E5mb**	77	<1:99
11	2-naphthyl	Ph	Me	**E3nd**	82	<1:99
12	(*E*)-PhCH=CH	Ph	Me	**E5nb**	87	<1:99
13	*n*-C_6H_{13}	Ph	Me	**E5ob**	64	<1:99
14	cyclohexyl	Ph	Me	**E5qb**	69	<1:99
15	Ph	Ph	2,6-$Cl_2C_6H_3$	**Z3na**	71	>99:1
16	2-pyridyl	Ph	2,6-$Cl_2C_6H_3$	**Z5mb**	68	>99:1
17	2-naphthyl	Ph	2,6-$Cl_2C_6H_3$	**Z3nd**	77	>99:1
18	(*E*)-PhCH=CH	Ph	2,6-$Cl_2C_6H_3$	**Z5nb**	74	>99:1
19	*n*-C_6H_{13}	Ph	2,6-$Cl_2C_6H_3$	**Z5ob**	69	>99:1
20	cyclohexyl	Ph	2,6-$Cl_2C_6H_3$	**Z5qb**	73	>99:1

[a] Reaction conditions: phosphonium salt **4** (0.60 mmol), *X* = Br (For entries 6−20, *X* = Cl), LDA (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] Isolated yield. [c] Determined by ^{1}H NMR analysis.

Scheme 2. Stereoselective Synthesis of DMU-212 (**E6**) and Its Isomer **Z6**



imines bearing appropriate *N*-sulfonyl groups smoothly undergo olefination reaction with various benzylidenetriphenylphosphoranes or allylidenetriphenylphosphoranes under mild reaction conditions to afford an array of both *Z*- and *E*-isomers of conjugated alkenes in good to excellent yields and with greater than 99:1 stereoselectivity. Moreover, this tunable protocol has been successfully applied to the highly stereoselective synthesis of two anticancer agents, DMU-212 and its *Z*-isomer.

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Supporting Information Available: General information, experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) A stepwise process involving initial carbon−carbon bond formation leading to a betaine intermediate was proposed for the formal [2+2] cycloaddition. Alternatively, the 1,2-azaphosphetane intermediate can be generated directly through a four-center transition state analogous to that suggested for the Wittig reaction (see refs 2b, c, and 3).

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(15) The reaction was quenched with water upon completion, and byproduct iminophosphorane was decomposed by water to give triphenylphosphine oxide and a primary sulfonamide.

(16) The *Z*/*E* ratios of the alkene products were determined by ^{1}H NMR analysis within 3 days owing to the isomerization of (*Z*)-alkenes under the influence of light and air at room temperature. For a relevant study, see: Ren, Y.; Che, Y.; Ma, W.; Zhang, X.; Shen, T.; Zhao, J. *New J. Chem.* **2004**, *28*, 1464.

(17) According to the proposed mechanism depicted in Scheme 1, the interactions of the sulfonyl group, phenyl group, R^1 group, and Ar group contribute to the stereoselectivity for the formation of the 1,2-azaphosphetane intermediate leading to an alkene product. Since the electronic and steric properties of an aryl group, alkenyl group, and alkyl group are significantly different from each other, it is plausible that each type of imine shown in Table 2 needs a different *N*-sulfonyl group to control the stereoselectivity synergically in its olefination reaction with a benzylidenetriphenylphosphorane.

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