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Cross-Coupling of *N*-Allylic Sulfonimides with Organozinc Reagents at Room Temperature

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An efficient cross-coupling reaction of *N*-allylic sulfonimides with organozinc reagents has been developed. In the presence of 1 mol-% of $Pd_2(dba)_3$, a range of *N*-allylic sulfonimides smoothly couple with various organozinc reagents at room temperature to give the corresponding (*E*)-alkene products in moderate to excellent yields and with good to exclusive α-selectivity. It is noteworthy that allyl ether, benzyl ether, and ester are tolerated under the reaction conditions.

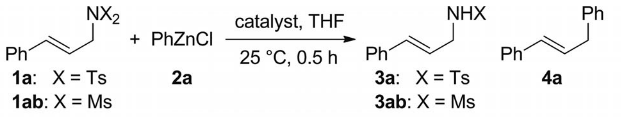
Introduction

Whereas primary allylic amines are widely employed as nitrogen nucleophiles in chemical synthesis, they rarely serve as useful carbon electrophiles due to the extremely poor leaving ability of their amino groups.[1] Previous studies show that the introduction of electron-withdrawing groups to the allylic amine nitrogen atoms can significantly activate sp^3 C–N bonds and consequently enhance the leaving ability of amino groups.[2] Particularly, doubly sulfonyl-activated allylic amines, *N*-allylic sulfonimides, can serve as unique carbon electrophiles under basic conditions to couple with carbon nucleophiles such as malonates,[3] organocuprates,[4] and Grignard reagents.[5,6] In the course of expanding the scope of carbon nucleophiles, we found that organozinc reagents could couple with *N*-allylic sulfonimides at room temperature through selective cleavage of the sp^3 C–N bonds rather than the N–S bonds. This study significantly extends the applications of primary allylic amine derivatives as allylic electrophiles in chemical synthesis.

Results and Discussion

The model reaction of *N*-allylic sulfonimide **1a** with PhZnCl (**2a**) was found to be very sluggish in dry tetrahydrofuran at room temperature (Table 1, Entry 1). Recognizing that palladium catalysts are frequently employed to activate allylic electrophiles through the generation of π-allylpalladium intermediates[7] and that they mediate a number of reactions with organozinc reagents,[8] we examined a few palladium sources (1–2 mol-%), most of which were effective in promoting the desired sp^3 C–N bond cleavage and minimizing the N–S bond cleavage (Table 1, Entries 2–7). $Pd_2(dba)_3$ was identified as the palladium source of choice, the use of which led to the formation of the desired product, alkene **4a**, in 92% yield (Table 1, Entry 2). A few nickel and copper sources were also examined, but they failed to promote the model reaction (Table 1, Entries 8–10). Replacing the *N*-*p*-toluenesulfonyl group in substrate **1a** with a methanesulfonyl group led to a lower yield (87%; Table 1, Entry 11).

Table 1. Optimization of the reaction conditions.[a]



Entry	X	Catalyst (mol-%)	Yield [%][b]	
			3a–ab	**4a**
1	Ts	none	trace	trace
2	Ts	$Pd_2(dba)_3$ (1)	trace	92
3	Ts	$Pd(PPh_3)_4$ (2)	4	78
4	Ts	$Pd(PPh_3)_2Cl_2$ (2)	trace	69
5	Ts	$Pd(dppf)_2Cl_2$ (2)	0	0
6	Ts	$Pd(OAc)_2$ (2)	3	71
7	Ts	$PdCl_2$ (2)	5	64
8	Ts	$Ni(PPh_3)_2Cl_2$ (2)	0	0
9	Ts	CuI (2)	0	0
10	Ts	$Cu(OTf)_2$ (2)	0	0
11	Ms	$Pd_2(dba)_3$ (1)	5	87

[a] Reaction conditions: sulfonimide **1a** or **1ab** (0.50 mmol), organozinc reagent **2a** (0.60 mmol), catalyst (1–2 mol-%), tetrahydrofuran (2.5 mL), 25 °C, 0.5 h. [b] Isolated yield. Ts = *p*-toluenesulfonyl, Ms = methanesulfonyl, dba = dibenzylideneacetone, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, Tf = trifluoromethanesulfonyl.

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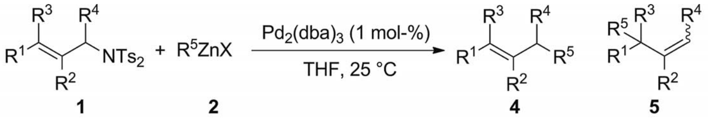
Table 2. Cross-coupling of *N*-allylic sulfonimides with organozinc reagents.[a]

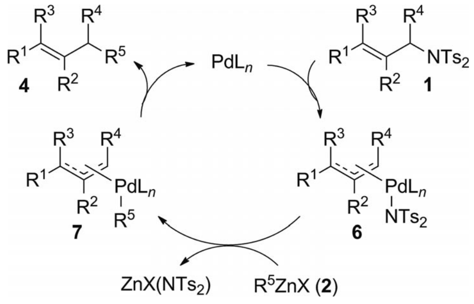


Entry	1	R^1	R^2	R^3	R^4	2	R^5	X	*t* [h]	Product	4/5[b]	Yield [%][c]	(*E*)/(*Z*)[b]
1	**1a**	Ph	H	H	H	**2a**	Ph	Cl	0.5	**4a**	>99:1	92	>99:1
2	**1b**	4-MeOC_6H_4	H	H	H	**2a**	Ph	Cl	0.5	**4b**	>99:1	95	>99:1
3	**1c**	4-ClC_6H_4	H	H	H	**2a**	Ph	Cl	0.5	**4c**	>99:1	93	>99:1
4	**1d**	2-furyl	H	H	H	**2a**	Ph	Cl	1	**4d**	>99:1	84	97:3
5	**1e**	2-thienyl	H	H	H	**2a**	Ph	Cl	1	**4e**	>99:1	91	98:2
6	**1f**	*n*-heptyl	H	H	H	**2a**	Ph	Cl	2	**4f**	85:15	72	95:5
7	**1g**	$BnOCH_2$	H	H	H	**2a**	Ph	Cl	2	**4g**	86:14	88	95:5
8	**1h**	cyclohexyl	H	H	H	**2a**	Ph	Cl	2	**4h**	97:3	70	96:4
9	**1i**	Ph	Me	H	H	**2a**	Ph	Cl	4	**4i**	>99:1	56	94:6
10	**1j**	$Me_2C{=}CH(CH_2)_2$	H	Me	H	**2b**	$2,4,6\text{-Me}_3C_6H_2$	Cl	2	**4j**	>99:1	84	>99:1
11	**1k**	H	H	$BnOCH_2$	H	**2a**	Ph	Cl	2	**4g**	86:14	72	85:15
12	**1l**	Ph	H	H	Me	**2a**	Ph	Cl	1	**4k**	>99:1	95	>99:1
13	**1m**	H	H	$R^3,R^4 = (CH_2)_3$		**2a**	Ph	Cl	4	**4l**		56	
14	**1a**	Ph	H	H	H	**2b**	$2,4,6\text{-Me}_3C_6H_2$	Cl	1	**4m**	>99:1	93	>99:1
15	**1a**	Ph	H	H	H	**2c**	$2,4,6\text{-}(i\text{Pr})_3C_6H_2$	Cl	1	**4n**	>99:1	94	>99:1
16	**1a**	Ph	H	H	H	**2d**	4-MeC_6H_4	Cl	1	**4o**	>99:1	95	>99:1
17	**1a**	Ph	H	H	H	**2e**	4-MeOC_6H_4	Cl	1	**4p**	>99:1	97	>99:1
18	**1a**	Ph	H	H	H	**2f**	2-MeOC_6H_4	Cl	1	**4q**	>99:1	98	>99:1
19	**1a**	Ph	H	H	H	**2g**	$4\text{-(EtO}_2\text{C)C}_6H_4$	I	4	**4r**	>99:1	41	>99:1
20	**1a**	Ph	H	H	H	**2h**	Me	Cl	1	**4s**	>99:1	67	>99:1

[a] Reaction conditions: sulfonimide **1** (0.50 mmol), organozinc reagent **2** (0.60 mmol), $Pd_2(dba)_3$ (1 mol-%), tetrahydrofuran (2.5 mL), 25 °C. [b] Determined by ^1H NMR spectroscopy. [c] Isolated yield.

In the presence of 1 mol-% of $Pd_2(dba)_3$, a range of *N*-allylic sulfonimides smoothly coupled with various organozinc reagents at room temperature to give the corresponding alkene products in moderate to excellent yields (Table 2). While the alkene geometry was retained in the reaction with (*E*)-*N*-allylic sulfonimides, it was mostly inverted in the reaction with (*Z*)-*N*-allylic sulfonimides (Table 2, Entry 11). The stereoconvergence could be attributable to the generation of a π-allylpalladium intermediate from the palladium catalyst and the *N*-allylic sulfonimide (vide infra),[7] and the reaction preferred to give (*E*)-alkenes under thermodynamic conditions. When the R^1 group in the sulfonimide was an aryl or a heteroaryl group, the reaction proceeded with exclusive α-selectivity probably due to the maintenance of a maximum degree of conjugation and the minimization of steric hindrance. In contrast, inferior α-selectivity was achieved in some cases wherein the R^1 group was an alkyl group (Table 2, Entries 6–8 and 11). It is noteworthy that allyl ether, benzyl ether, and ester were tolerated under our reaction conditions (Table 2, Entries 7, 11, and 19). In addition, bulky organozinc reagents proved to be suitable carbon nucleophiles to couple with *N*-allylic sulfonimides (Table 2, Entries 10, 14, and 15).

On the basis of our results and the general mechanism of palladium catalysis,[7,8] we propose the reaction pathway depicted in Scheme 1 for the cross-coupling of *N*-allylic sulfonimides with organozinc reagents. The allylic C–N bond of *N*-allylic sulfonamide **1** is cleaved through oxidative addition by the palladium(0) catalyst to give π-allylpalladium complex **6**, which undergoes transmetalation with organozinc reagent **2** followed by reductive elimination to give alkene **4**, which regenerates the palladium(0) catalyst. The generation of π-allylpalladium complex **6** as an intermediate during the reaction accounts for the stereoconvergence and the formation of alkene **5** as a minor product in some cases (Table 2, Entries 6–8 and 11).



Scheme 1. Proposed reaction pathway.

Conclusions

In conclusion, we have developed, for the first time, an efficient cross-coupling reaction of *N*-allylic sulfonimides with organozinc reagents. In the presence of 1 mol-% of $Pd_2(dba)_3$, a range of *N*-allylic sulfonimides smoothly couple with various organozinc reagents at room temperature to give the corresponding (*E*)-alkene products in moderate to excellent yields and with good to exclusive α-selectivity.

It is noteworthy that allyl ether, benzyl ether, and ester are tolerated under the reaction conditions.

Experimental Section

General Procedure for the Cross-Coupling of *N*-Allylic Sulfonimides with Organozinc Reagents: A Schlenk tube was charged with sulfonimide **1** (0.50 mmol), tetrahydrofuran (0.50 mL), and $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol, 1 mol-%). To the stirred mixture was added a solution of organozinc reagent **2** (0.30 M in THF, 2.0 mL, 0.60 mmol) by syringe. The reaction mixture was stirred under an atmosphere of nitrogen at room temperature until no further transformation was observed by TLC analysis. HCl (1.0 M, 5.0 mL) was added, and the mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried with anhydrous magnesium sulfate and concentrated. The residue was purified by preparative TLC, developing with petroleum ether, to afford compounds **4** and **5** (if any).

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

Acknowledgments

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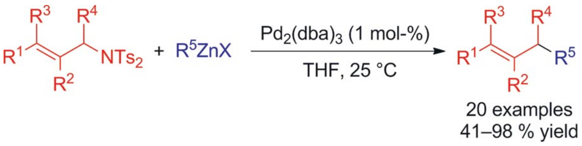
Cross-Coupling



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