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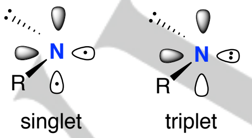
A novel catalyst-free synthesis of 2, 2-diaryl enamides from stilbenes via nitrene transfer reaction

Yuanyuan Zhang[a], Wenjing Ye[a], Hui Zhang[a], Xiao Xiao* [a,b]

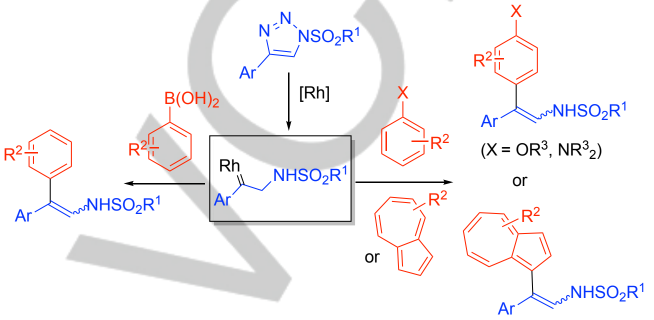
Abstract: A novel catalyst-free nitrene transfer reaction between stilbenes and iminoiodinanes was realized for the first time, which provides an efficient and environmentally friendly way to access variously substituted 2, 2-diaryl enamides under mild conditions. Mechanistic investigations suggested the reaction proceed via nitrene transfer and aromatic rearrangement. The iminoiodinane also acted as a Lewis acid, benefitting the ring-opening of intermediate aziridine.

Introduction

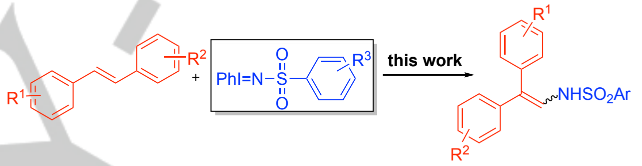
Nitrenes have been recognized as the important active intermediates in the synthesis of nitrogen-containing compounds that are ubiquitous in organisms and natural products as well as pharmaceuticals.[1] The four non-bonding valence electrons of a mono-valent nitrene are arranged such that one pair of electrons occupies one orbital, while the other two electrons may either be spin-antiparallel or spin-parallel, corresponding to an excited singlet or ground-state triplet, respectively (Scheme 1). In both states, nitrene is a highly reactive electrophilic reagent and can easily insert into C-H bond to form C-N bond.[2] Sulfonyliminoiodinanes ($RSO_2N{=}IPh$) are a class of nitrene precursors that were first synthesized and utilized by Abramovitch[3] and Yamada[4] in the 1970s, and further investigated by Breslow,[5] Mansuy,[6] Evans and Müller[7]. These species have been widely applied in nitrogen transfer reactions involving C-H amination and aziridination of alkenes. [8,9] The key role of organonitrogen compounds within many fields such as chemistry, medicine, biology, and materials, drives the development of new nitrene methodologies to achieve highly efficient synthesis of C-N bonds.



Scheme 1 Singlet and triplet states of nitrenes.



Rh-catalyzed arylation of azavinyl carbene ref. 14-16



Novel metal-free nitrene transfer reaction

Scheme 2 Synthesis of enamides via carbene/nitrene reagent

Enamides are among the most crucial synthetic tools for introducing nitrogen-containing functional groups.[10] Various useful N-containing molecular backbones in organic synthesis and medicinal chemistry can be afforded with enamides as substrates or intermediates.[11,12] The increasing interest in nitrogen-atom chemistry necessitates the development of synthetic approaches to enamides.[13] However, the example of 2, 2-diaryl enamide preparation from nitrene is rare. Recently, Fokin[14] reported an aryl boronic acid mediated Rh-catalyzed arylation of N-sulfonyl triazoles that generated azavinyl carbene by eliminating nitrogen gas, giving 2, 2-diaryl enamides as the products of C-C coupling. Similar processes have also been described by Anbarasan[15] and Lee[16] (Scheme 2). Herein, we would like to report an effective method to synthesize 2, 2-diaryl enamides directly from alkenes via nitrene transformation in the absence of metal catalyst.

Results and Discussion

Initially, (*E*)-1,2-di-*o*-tolylethene (**1a**) was used in the Pd/Fe catalyzed amidation[17] with *p*-bromobenzenesulfonyl iminoiodinane (PhI=NBs) as a nitrogen donor, forming 2, 2-di-*o*-tolyl enamide as an unexpected by-product in low yield (12% yield) at room temperature (Scheme 3). To start our investigation, the stilbene **1a** and PhI=NBs (**2a**) were chosen as standard substrates with $PdCl_2$ as a catalyst, for optimization studies. As shown in Table 1, the enamide **3a** was obtained in 45% yield with *o*-tolylimines (*o*-tolylC=NBs) and *o*-tolualdehyde as the main

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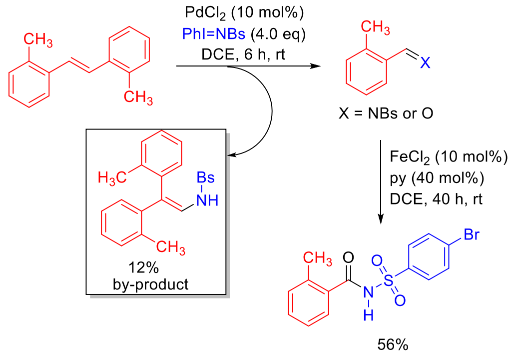
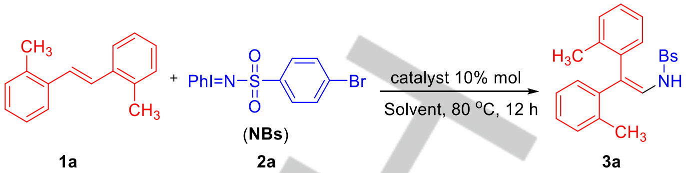
Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate)) competitive products, when the reaction performed in 1,2-dichloroethane (DCE) at 80 °C (entry 1, Table 1). Encouraged by the obtained result, other metals were further investigated in this nitrene transformation reaction. Increasing reactivity (51% yield) was observed when Pd$_2$(dba)$_3$ was used (entry 2, Table 1). Ru complexes such as RuCl$_2$(PPh$_3$)$_2$, and [Ru(*p*-cymene)Cl$_2$]$_2$ were also involved in the reaction (entries 3–4, Table 1). It was found that the yield was increased to 72%, when using the [Ru(*p*-cymene)Cl]$_2$ as a catalyst. Enamide **3a** could be obtained in moderate yield when AuCl$_3$ (entry 5, Table 1) was used as a catalyst. CuBr$_2$ was also tested, but the lower yield (31%) was observed (entry 6, Table 1). To our delight, the best results were obtained by using the catalyst-free condition and the designed product **3a** could be obtained in 75% yield, which indicated the iminoiodinane might work more efficiently than metal-nitrene intermediates in this process (entry 7, Table 1). Different solvents including toluene, ethanol, acetonitrile, 1,4-dioxane, and *N,N*-dimethyl formamide, were subsequently screened for the reaction (entries 8–12, Table 1). However, lower reactivity was observed in those solvents, indicating the 1,2-dichloroethane would be the best choice. A higher reaction temperature (150 °C) and a longer reaction time (48 hours) decreased the yields to 67% and 71%, respectively (entries 13-14, Table 1). The nitrene transfer reaction with PhI(OAc)$_2$ and NH$_2$Bs, which generated PhI=NBs in situ, afforded the enamide product in 38% yield (12 hours) and 36% yield (48 hours).



Scheme 3 Pd/Fe catalyzed formal amidation of stilbenes

Table 1 Optimization of reaction conditions[a]



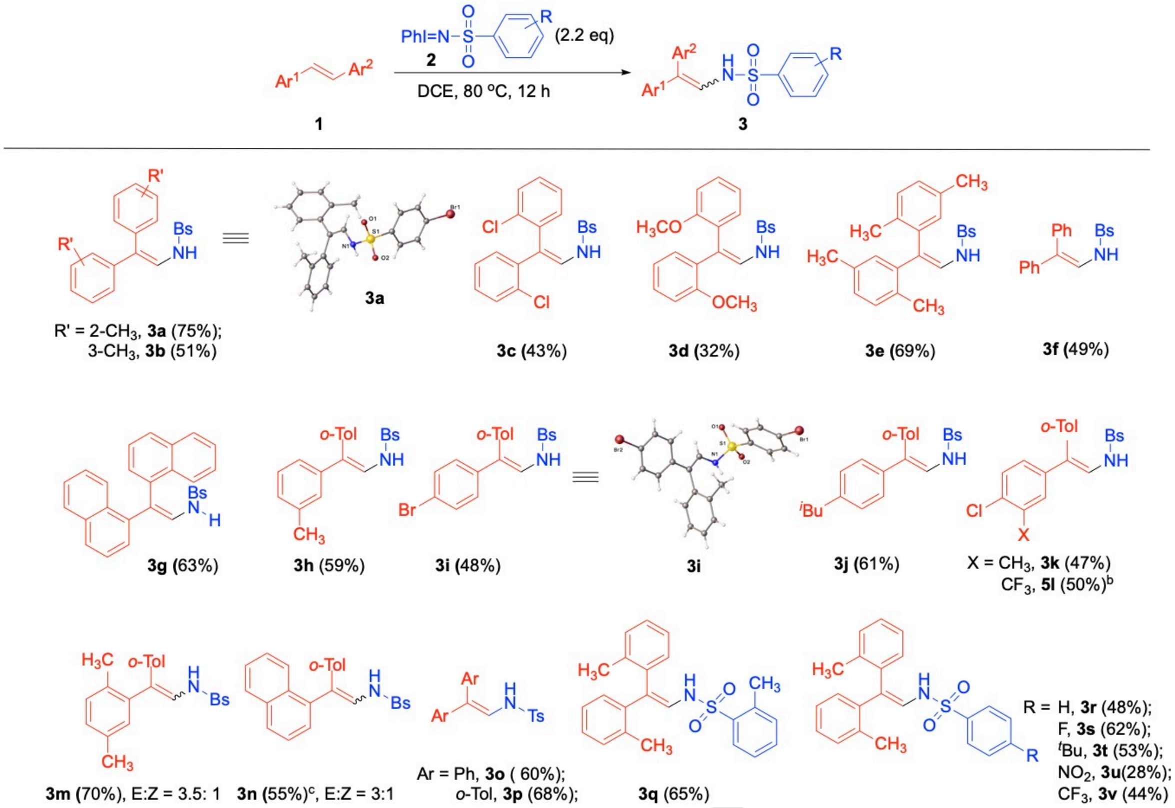
Entry	Catalyst	Solvent	Yield (%)[b]
1	PdCl$_2$	DCE	45
2	Pd$_2$(dba)$_3$	DCE	51
3	RuCl$_2$(PPh$_3$)$_2$	DCE	44
4	[Ru(*p*-cymene)Cl$_2$]$_2$	DCE	72
5	AuCl$_3$	DCE	61
6	CuBr$_2$	DCE	31
7	**--**	**DCE**	**75**
8	--	Toluene	53
9	--	EtOH	25
10	--	CH$_3$CN	66
11	--	1,4-	26
12	--	Dioxane	--
13[c]	--	DMF	67
14[d]	--	DCE	71
15[e]	--	DCE	38(36)[f]

[a] All reactions were carried out with stilbene **1a** (0.25 mmol), PhI=NBs (**2a**) (0.55 mmol), and catalyst (0.025 mmol), in solvent (0.5 mL) at 80 °C for 12 hours. [b] Isolated yield. [c] The reaction temperature was 150 °C. [d] The reaction time was 48 hours. [e] PhI=NBs was replaced by PhI(OAc)$_2$ (0.75 mmol) and NH$_2$Bs (0.75 mmol). [f] The mixture were stirred for 48 hours in the condition of entry 15

With optimal conditions in hand, the substrate scope of this catalyst-free nitrene transfer reaction was examined with various substituted trans-stilbenes **1** and iminoiodinanes **2**, affording a broad range of 2, 2-diaryl enamides **3** in 28–75% yields (Table 2). Firstly, stilbenes **1a-n** were subjected to the nitrene transformation using PhI=NBs (**2a**) as a nitrene reagent. Symmetrically substituted stilbenes containing 3-methyl, 2-chloro, 2-methoxyl, and 2, 5-dimethyl substituted aromatic groups afforded products **3b-e** in 32–69% yields. Besides the imine, complicated side-products were formed in the reaction mixture when highly activated stilbene **1d** was used, leading to **3d** in low yield. 2, 2-Diphenylethene underwent the optimized process to furnish the product **3f** in 49% yield. The 1,2-di(naphthalen-2-yl) ethene **1g** underwent the nitrene transfer reaction smoothly to yield the corresponding 2, 2-dinaphthyl enamides (**3g**) in 63% yield. To our delight, the nitrene transfer reaction of unsymmetrically substituted stilbenes **1h-k** was also tolerated, providing more sterically hindered 2-*o*-tol, 2-aryl cis-enamides (3'-methyl, 4'- bromo, 4'-isobutyl, and 3'-methyl-4'-chloro) in 47–61% yields with high stereoselectivity (**3h-k**). Aziridine, which was not observed in other examples, was isolated as the main product of the reaction of stilbene **1l** with PhI=NBs (**2a**). A mixture of *cis* and *trans* enamides were obtained in moderate to good activity when unsymmetrically alkene **1m** and **1n** were used. In this case, the existence of isomers might arise from the facial tautomerization to more stable *E*-enamides. It is worth noting that the nitrene transfer did not occur when stilbenes with *para*-CH$_3$, MeO, Br, substituents on both phenyl rings were used; these substrates underwent complicated reactions to afford some unknown mixture of products. Next, the substituted iminoiodinane **2** was studied with substrates **1a** and **1f**. Ortho- and para-toluene sulfonyliminoiodinanes (**2b** and **2c**) gave the enamide products **3o-q** in 60–68% yields. Iminoiodinanes containing activating groups (fluorine and *tert*-butyl) at the C4 position of phenylsulfonyl were more reactive than those bearing deactivating groups (trifluoromethyl and nitryl) (**3r-v**). The structure of products **3a** and **3i** were confirmed by the single-crystal X-ray analysis.[18]

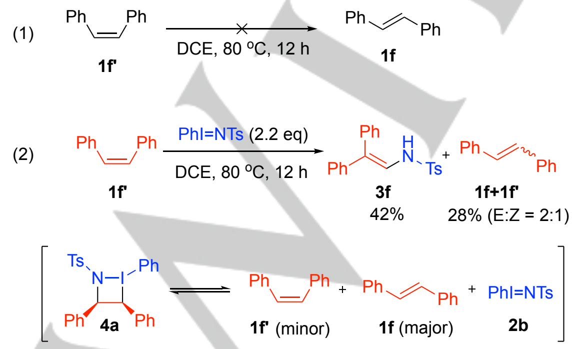
To identify the mechanism of the reaction, several control experiments were performed. Under the standard reaction condition, cis-stilbene **1f'** couldn't undergo tautomerization to give trans-stilbene **1f** (Scheme 4, eq 1). When *cis*-stilbene **1f'** and PhI=NTs (**2b**) were used as the substrates of nitrene transfer reaction under the standard condition, affording enamide **3f** in 42% yield and recovering 28% alkene mixture (*cis*/*trans* = 2/1) (Scheme 4, eq 2). That result suggested the existence of unstable four-membered ring intermediate **4a**[19]**,** which generated

Table 2 Substrate scope of the catalyst-free synthesis of 2, 2-diaryl enamides[a]

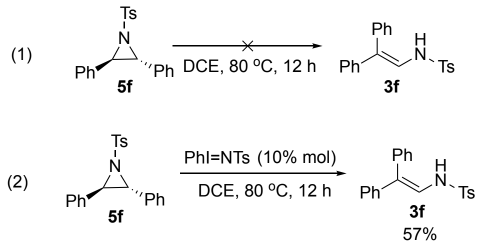


[a] All reactions were carried out with stilbenes **1** (0.50 mmol), iminoiodinane **2** (1.1 mmol), in DCE (1.0 mL) at 80 °C for 12 hours. The geometries of enamide products **3** were tentatively proposed by analogy with the X-ray structure of enamide **3a** and **3i**. [b] Corresponding aziridine **5l** was obtained instead of an enamide (see supporting information). [c] The isomer ratio of stilbene **1n** is 1.5 : 1 (E : Z).

thermodynamic stable *trans*-stilbene **1f** during the elimination of PhI=NTs from **4a**. In most cases, the aziridine, which is the general product of nitrogen transfer reaction between iminoiodinanes and alkenes[9], was not observed in this method except for product **5l**. As shown in Scheme 5, no enamide product was detected when aziridine **5a** was subjected to the standard conditions for 12 hours. To our surprise, when a catalytic amount PhI=NTs was used, it could promote the rearrangement of aziridine **5a**, giving enamide **3f** in 57% yield. These control experiments indicate that the iminoiodinane may act not only as a nitrogen donor in the formation of aziridine but also a Lewis acid which catalyzed the ring-opening and rearrangement of aziridine.[20] This result can also explain: 1) the corresponding aziridine intermediates of those para-substituted (4-methyl, 4-MeO, 4-Br) substrates might be too reactive and would rapidly decompose to complex mixtures, so no enamide products were obtained for these *para*-substituted stilbenes; 2) when most electron-deficient subtrate **1l** was used, the corresponding aziridine had relatively low reactivity of ring-opening, only giving aziridine **5l** as a final product.



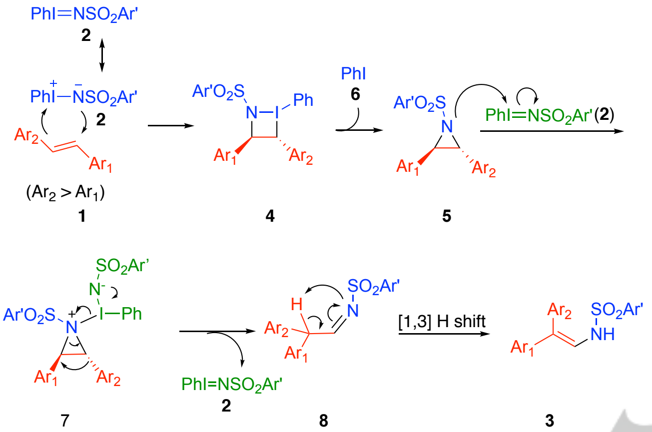
Scheme 4 Nitrene transfer reaction between *cis*-stilbene **1f**' and iminoiodinane **2b**.



Scheme 5 Control experiments

On the basis of the experimental results and previous reports[19,20], a plausible mechanism was proposed in scheme 6. We envisioned that the iminoiodinane might mediated the aryl [1, 2] migration of aziridine to form the enamide product

(Scheme 6). First, the [2+2] cyclization of stilbenes **1** with iminoiodinane **2** generates the four-membered ring intermediate **4**, followed by elimination of iodobenzene to give aziridine **5**. Sequentially, the iminoiodinane **2**, as a role of Lewis acid, interacts with aziridine **5**, forming the dinitrogen-ligands hypervalent iodine **7**[21]. Similar to an aza pinacol rearrangement[20a], the irreversibly facial-selective [1, 2] migration of the aromatic group might proceed through intermediate **7**, to give the 2, 2-diaromatic imine **8**. Compound **8** undergoes automerization to afford the final product enamide **3** with high stereoselectivity.



Scheme 6 Proposed mechanism

Conclusions

We have developed an effective and convenient synthesis strategy of 2, 2-diaryl enamide via catalyst-free nitrene transfer from sulfonyliminoiodinane to substituted stilbene. This method provides an unprecedented route to 2, 2-diaryl enamides, which have important synthetic utility. A probable reaction pathway was demonstrated involving nitrene insertion and aromatic group rearrangement of aziridine.

Experimental Section

Representative procedure of nitrene transfer reaction

To a oven-dried sealed tube charged with stilbene **1a** (0.104 g, 0.50 mmol) in DCE (1.0 mL) was added PhI=NBs (**2a**) (0.482 g, 1.1 mmol). Upon stirring at 80 °C for 12 h, the crude product was concentrated and purified by flash chromatography (silical gel, petroleum ether/EtOAc = 10: 1) to give enamide **3a** as a white solid.

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Keywords: catalyst-free • 2, 2-diaryl enamides • nitrene transfer reaction • iminoiodinanes

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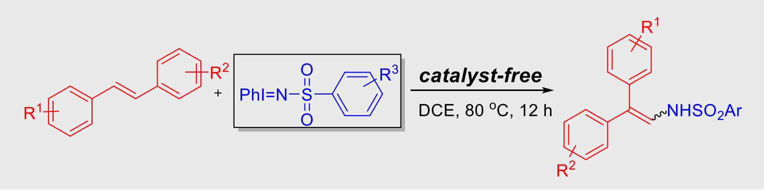
COMMUNICATION



An unexpected nitrene transfer from imioiodinane to stilbene in absence of catalyst has been described, directly giving a series of 2, 2-diaryl enamides in 28-75% yields. This reaction involved aziridination, ring-opening of aziridine, and aromatic rearrangement, in which iminoiodinane played a dual role.

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