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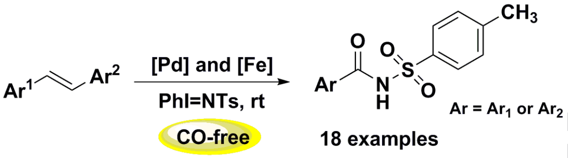

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Metal-catalyzed formal amidation of alkenes under CO-free condition

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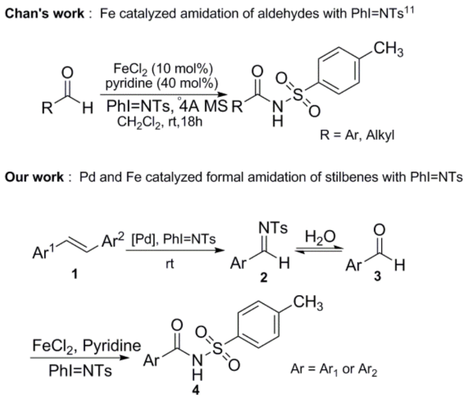
ABSTRACT

An effective procedure of synthesis of amides from alkenes and PhI=NTs via Pd and Fe catalysts under mild conditions is described. A series of benzamides containing various functional groups can be obtained in reasonable yield and the possible reaction pathway is proposed in this paper.

Amides as the important building blocks in natural products and the fundamental structural motifs of peptides play a crucial role in organic chemistry and pharmaceutical chemistry as well as biological chemistry.[1] Typically amides can be obtained by the coupling reaction of highly activative acid derivatives with corresponding amines via coupling reagents.[2] However, additional preparation and unstability of acid derivatives make the synthesis of amides more complicated. During the past decades, the highly efficient synthesis of amides has attracted considerable interest from chemists, such as oxidative amidation of alcohols and aldehydes[3], aminocarbonylation of organohalides[4], alkenes[5], and alkynes[6], oxidation of amines[7], rearrangement reaction[8], and so on.[9]

The transition-metal-catalyzed aminocarbonylation of simple alkenes with amines and CO is a straightforward method to convert a carbon-carbon double bond into an amide bond, which generally suffers from high temperature and air pressure.[5] To the best of our knowledge, only two examples reported CO-free oxidative amidation of terminal alkenes via oxidants TBHP or I_2.[10] Therefore it is still significant to develop new protocols for the amidation of alkenes under mild condition. During our studies, we have found that benzaldimines (**2**) and benzaldehydes (**3**) can be obtained from stilbenes (**1**) catalyzed by Pd with PhI=NTs as nitrogen donor. Recently, Chan[11] reported Fe-catalyzed amidation of aldehydes using the same iminoiodinane as nitrogen source.[12] Inspired by Chan's work, we proposed a sequential procedure catalyzed by palladium and iron respectively, using PhI=NTs as nitrogen transfer reagent at room temperature, which presented a formal amidation of alkenes (Scheme 1).

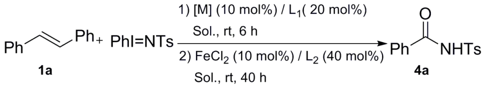


Scheme 1. Design of one-pot amidation of stilbenes.

Initially, trans-stilbene (**1a**), PhI=NTs, and Pd catalyst were stirred for 6 hours to generate benzaldimine (**2a**) which would be hydrolyzed to benzaldehyde (**3a**) in the presence of trace amounts of H_2O in air. Subsequently, $FeCl_2$ and Pyridine were added to the mixture, giving amide **4a** as the final product. The efficiency of the in situ process might be highly dependent on the balance among benzaldimine (**2a**) and benzaldehyde (**3a**) (Scheme 1). As shown in Table 1, various Pd catalysts were firstly screened in the reaction of trans-stilbene with PhI=NTs. Amide **4a** could be obtained in 52-60% yields catalyzed by Pd (0) such as, $Pd_2(dba)_3$, $Pd(dba)_2$, and $Pd(PPh_3)_4$ (entries 1-3, Table 1). Among Pd(II) catalysts, $PdCl_2$ gave the highest activity (62% yield) (entry 5, Table 1) while $PdBr_2$, $Pd(acac)_2$, and $(\eta^3\text{-}C_3H_5PdCl)_2$ catalyzed the cascaded reaction in similar efficiency (entries 6,7,and 9, Table 1). Lower product yields (26% and 31%) were found when $Pd(OAc)_2$ and $Pd(COD)Cl_2$ were used as catalysts (entries 4 and 8, Table 1). Several phosphite ligands were also screened in the Pd catalyzed process. However the reaction efficiency was obviously decreased (entries 10-13, Table 1). On the other hand, a series of nitrogen-containing ligands were applied in $FeCl_2$ catalyzed amidation of aldehydes, furnishing **4a** in 14-46% yields (entries 14-17, Table 1). Therefore pyridine was still the most suitable ligand for $FeCl_2$. Further optimization of reaction condition was carried out with $PdCl_2$ as catalyst. Different solvents were tested in the amidation of stilbene. Higher yields could be

Table 1

Optimization of reaction conditions[a]



Entry	Condition	Yield (%)[b]
1	$Pd_2(dba)_3$, L_2 = py, CH_2Cl_2	52
2	$Pd(dba)_2$, L_2 = py, CH_2Cl_2	56
3	$Pd(PPh_3)_4$, L_2 = py, CH_2Cl_2	60
4	$Pd(OAc)_2$, L_2 = py, CH_2Cl_2	26
5	$PdCl_2$, L_2 = py, CH_2Cl_2	62
6	$PdBr_2$, L_2 = py, CH_2Cl_2	53
7	$(\eta^3\text{-}C_3H_5PdCl)_2$, L_2 = py, CH_2Cl_2	53
8	$Pd(COD)Cl_2$, L_2 = py, CH_2Cl_2	31
9	$Pd(acac)_2$, L_2 = py, CH_2Cl_2	59
10	$PdCl_2$, L_1 = PPh_3, L_2 = py, CH_2Cl_2	25
11	$PdCl_2$, L_1 = dppf, L_2 = py, CH_2Cl_2	29
12	$PdCl_2$, L_1 = dppp, L_2 = py, CH_2Cl_2	28
13	$PdCl_2$, L_1 = dppe, L_2 = py, CH_2Cl_2	25
14	$PdCl_2$, L_2 = DMAP, CH_2Cl_2	32
15	$PdCl_2$, L_2 = 2-picolinic acid, CH_2Cl_2	35
16	$PdCl_2$, L_2 = Ph-pybox, CH_2Cl_2	46
17	$PdCl_2$, L_2 = 1,10-phenanthroline, CH_2Cl_2,	14
18	$PdCl_2$, L_2 = py, $CHCl_3$	66
19	$PdCl_2$, L_2 = py, $ClCH_2CH_2Cl$	54
20	$PdCl_2$, L_2 = py, Toluene	34
21	$PdCl_2$, L_2 = py, THF	40
22	$PdCl_2$, L_2 = py, DMF	12
23	$PdCl_2$, L_2 = py, 1,4-Dioxane	36
24[c]	$PdCl_2$, L_2 = py, MeOH	-
25[d]	$PdCl_2$, L_2 = py, $CHCl_3$	trace
26[c,e]	$PdCl_2$, L_2 = py, $CHCl_3$	-
27[f]	$PdCl_2$, L_2 = py, $CHCl_3$	16

[a] All reactions were carried out with trans-stilbene (0.50 mmol), PhI=NTs (2.0 mmol), Pd catalyst (0.050 mmol), L_1 (0.10 mmol), $FeCl_2$ (0.050 mmol), and L_2 (0.20 mmol) in solvent (2.0 mL) at rt.

[b] Isolated yield.

[c] The product amide **4a** was not dectected. [d] Reaction temperature was 40 °C.

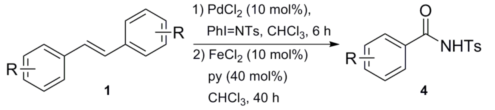
[e] Reaction temperature was 0 °C.

[d] PhI=NTs was replaced by $PhI(OAc)_2$ (2.0 mmol) and $TsNH_2$ (2.0 mmol).

obtained in haloalkanes (enties 18-19, Table 1), which were identical with chan's report[11]. In other solvents, imine **2a** was produced in small amounts and N-tosylbenzamide (**4a**) was afforded in 12-40% yields (enties 20-23, Table 1). No imine and corresponding amide could be detected by TLC using MeOH as a solvent (entry 24, Table 1). Higher temperature was negative for the $FeCl_2$-catalyzed second step, giving trace amide (entry 25, Table 1). On the other hand, imine **2a** could not be obtained at lower temperature, so no desired amide product was isolated when the reaction temperature was 0 °C (entry 26, Table 1). It is worth to mention that the amidation reaction with $PhI(OAc)_2$ and $TsNH_2$ as nitrogen source proceeded less effectively to furnish the product 4a in 16% yield (entry 27, Table 1).

Table 2

Scope of the substituted stilbenes of $PdCl_2$ and $FeCl_2$ catalyzed amidation.[a]



Entry	R	Product(**4**)	Yield (%)[b]
1	*p*-H	**4a**	66
2[c]	*p*-H (cis)	**4a**	64
3	*p*-CO_2Me	**4b**	51
4[c]	*p*-CO_2Me (cis)	**4b**	56
5	*p*-Ph	**4c**	49
6	*p*-Br	**4d**	62
7	*p*-OMe	**4e**	47
8	*o*-Me	**4f**	49
9	*m*-Me	**4g**	60
10	*p*-Me	**4h**	72
11	*p*-Et	**4i**	75
12	*p*-*n*Bu	**4j**	63
13	*p*-*i*Bu	**4k**	67
14	*p*-*n*Amyl	**4l**	71
15	*p*-*n*Hexyl	**4m**	68

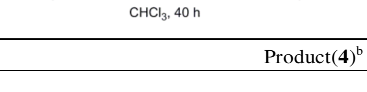
[a] All reactions were carried out with stilbenes (0.50 mmol), PhI=NTs (2.0 mmol), $PdCl_2$ (0.050 mmol), $FeCl_2$ (0.050 mmol), and pyridine (0.20 mmol) and in $CHCl_3$ (2.0 mL).
[b] Isolated yield.
[c] Cis olefin was used.

Under the optimal reaction conditions, the scope of $PdCl_2$ and $FeCl_2$ catalyzed amidation of substituted stilbenes was examined. As summarized in Table 2, the reaction could proceed smoothly with various substituted stilbenes affording the corresponding N-tosylbenzamides in 47-75% yields. The exploration of geometric isomers' activities indicated that there was no obvious distinction between trans and cis olefins (entries 1-4, Table 2). Stilbenes with electron-withdrawing functional groups at para position of the aromatic gave the amide products in 49-62% (entries 3-6, Table 2). The fact that 4-methoxybenzaldehyde was not an efficient substrate for the $FeCl_2$ catalyzed process[11] led to the low reactivity of the 4,4'- dimethoxyl stillbene (entry 7, Table 2). *Ortho* and *meta*-methyl substituted N-tosylbenzamides (**4f** and **4g**) were obtained in lower yields than the *para*-methyl substituted one (**4h**) which was perhaps due to the larger steric hinderance of stilbenes **1f** and **1g** (entries 8-10, Table 2). The substrates with alkyl groups were able to be nicely tolerated in the reaction, giving the desired amides **4i-m** in 63-75% yields (entries 11-15, Table 2).

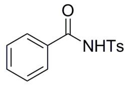
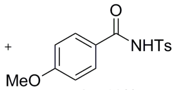
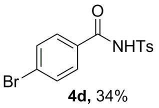
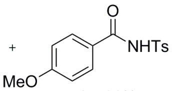
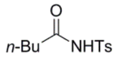
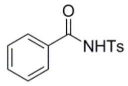
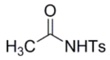
The amidation of stilbenes with different *para*-substituents on benzene ring was also examined, affording two corresponding imides (entries 1-2, Table 3). *P*-methoxylbenzamide **4e** could be obtained in lower product

Table 3

Scope of the substituted alkenes of $PdCl_2$ and $FeCl_2$ catalyzed amidation.[a]



Substrate(**1**)	Product(**4**)[b]

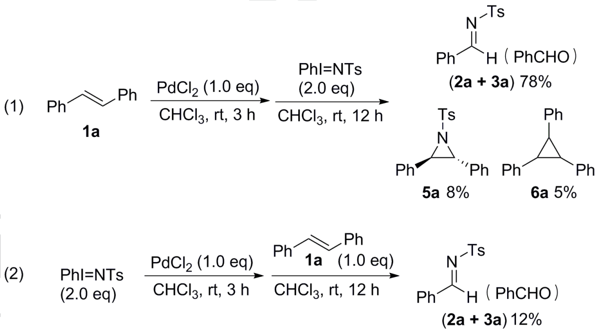
R^1 = Ph, R^2 = *p*-OMePh; (**1n**)	 **4a**, 39% +  **4e**, 18%
R^1 = *p*-BrPh, R^2 = *p*-OMePh; (**1o**)	 **4d**, 34% +  **4e**, 26%
R^1 = R^2 = *n*-Bu; (**1p**)	 0%
R^1 = Ph, R^2 = CH_3; (**1q**)	 **4a**, 39% +  0%

[a] All reactions were carried out with alkene (0.50 mmol), PhI=NTs (2.0 mmol), $PdCl_2$ (0.050 mmol), $FeCl_2$ (0.050 mmol), and pyridine (0.20 mmol) and in $CHCl_3$ (2.0 mL).

[b] Isolated yield.

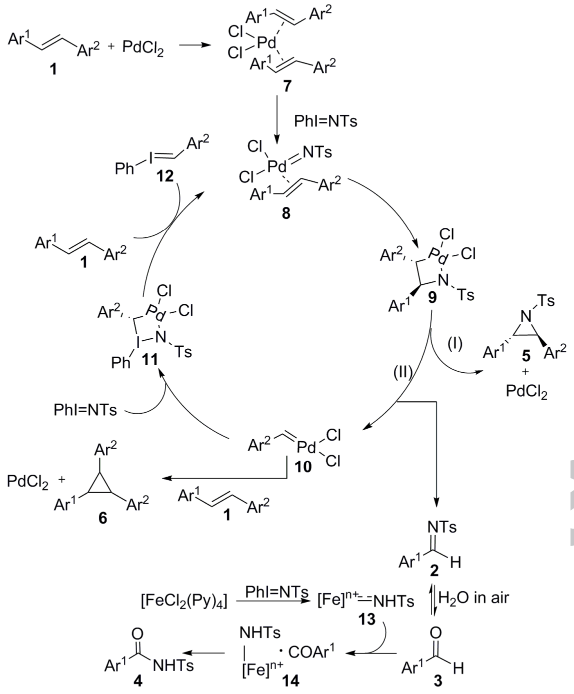
yield than benzamide **4a** and *p*-bromobenzamide **4d**. Unfortunately, under standard condition the amidation reaction couldn't proceed as aliphatic olefin was used (entry 3, Table 3), which was also supported by the fact that the benzamide **4a** was the only product in the amidation of phenylpropylene (**1n**) (entry 4, Table 3).

Some control experiments were carried out for the mechanistic study of the Pd-catalyzed cracking of alkenes (Scheme 2). Equivalent $PdCl_2$ was used respectively to react with stilbene (**1a**) or PhI=NTs for 3 hours before the other material was added. Under the same reaction conditions, the reaction (**1**) proceed smoothly, giving N-tosylbenzamides and benzaldehyde in 78% ^{1}H NMR yield as well as trace aziridine **5a** and triphenylcyclopropane **6a**, while the reaction (**2**) was inefficient with a large amount of remaining stilbene in the crude product mixture. Those experiments



Yields were determined by ^{1}H NMR of crude products with CH_2BrCH_2Br as standard

Scheme 2. Control experiments for mechanistic study.



Scheme 3. Proposed reaction pathway for the amidation of alkenes.

indicated that the Pd catalyst might firstly react with stilbene to generate metal-alkene complex which was likely necessary for the reaction. Furthermore, relatively electron-rich aliphatic olefin might be unable to coordinate with PdCl$_2$, so no amide product was obtained when 5-decene was used as the substrate (entry 3, Table 3).

Based on the aforementioned observations, a plausible reaction pathway for the PdCl$_2$ and FeCl$_2$ catalyzed amidation of alkenes is proposed in Scheme 3. Pd-alkene complex **7** reacts with PhI=NTs to generate Palladium-nitrogen species **8** which will form compound **9**. The four-membered ring **9** will undergo two types of ring-opening, affording aziridine **7**[13] or imine **2** (Scheme 2). Compound **10**, which can be captured by stilbene **1** to produce cyclopropane **6** (Scheme 2), as another product of elimination path (**II**) will react with PhI=NTs to regenerate Palladium-nitrogen species **8** with four-membered ring **11** as intermediate. The C-H bond of arylaldehyde **3** hydrolyzed from imine **2** in air is inserted by an iron-nitrenoid species **14** to furnish the amide product **4**.[11]

In summary, we have developed a novel CO-free formal amidation of alkenes catalyzed by palladium and iron with PhI=NTs as nitrogen source at room temperature. Benzamides with various functional groups can be afforded in moderate yield. The current method provides a straightforward and effective approach to synthesize arylamides from substituted stilbenes, which consist of palladium-catalyzed transformation of carbon-carbon double bond to carbon-nitrogen double bond and iron-catalyzed amidation of aldehydes. Further studies will be devoted to developing more effective catalytic systems to expand substrate scope as well as deeply exploring the reaction mechanism.

Acknowledgments

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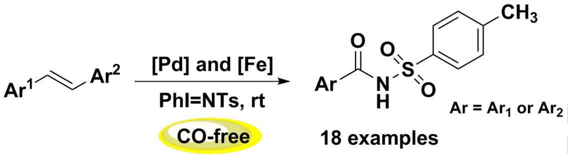

Manuscript Title: *Metal-Catalyzed Formal Amidation of Alkenes under CO-Free Condition.*

Author Name: *Yuanyuan Zhang, Wenjing Ye, Xue Leng, Ying He, Hui Zhang* and Xiao Xiao**

Highlights

- A novel metal-catalyzed formal amidation of alkenes without CO and oxidant is developed.
- A various of substituted benzamides can be synthesized in reasonable yield
- The cascaded reaction involves oxidative cleavage of alkenes and amidation of aldehydes.