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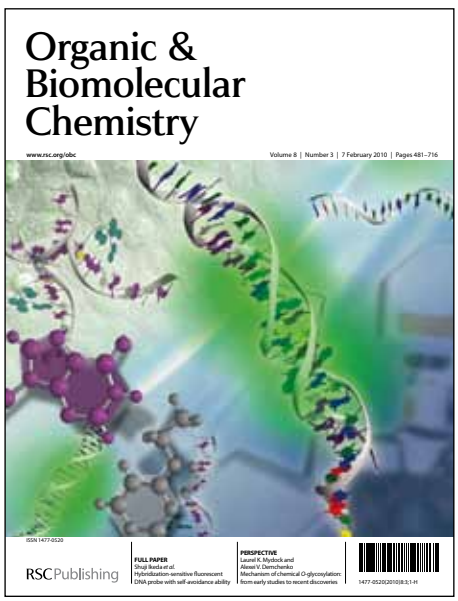

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ARTICLE TYPE

Palladium-Catalyzed Carbenoid Based N-H Bond Insertions: Application to the Synthesis of Chiral *α*-Amino Esters

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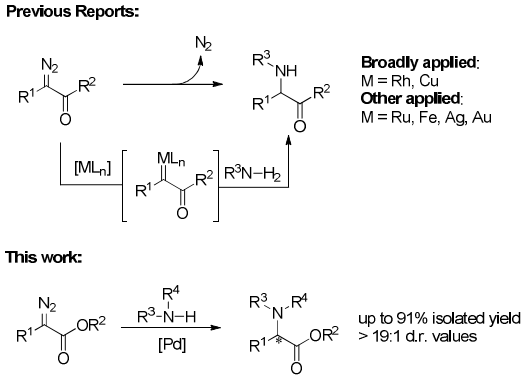
A highly efficient palladium-catalyzed carbenoid based N-H bond insertion has been developed. The *α*-amino esters were obtained in high isolated yields. Moreover, by choosing suitable chiral auxiliary, the stereoselective Pd-catalyzed N-H insertion has been realized. The chiral *α*-amino esters were obtained in high yields (up to 91%) and with excellent diastereoselectivities (d.r. > 19:1).

The C-N bond formation has been recognized as one of the most useful synthetic method in organic synthesis.[1] Moreover, the importance of aromatic C-N bond in pharmaceuticals and natural products attracted lots of interests to develop efficient approaches in this research area.[2] In addition, palladium catalyzed coupling reactions between amines and aryl iodides, bromides and triflates have been widely accepted as one of the most efficient methods to construct the C-N bond.[3] Besides this, the metal-catalyzed carbenoid insertion into N-H bond, is obviously a highly efficient C-N bond transformation by using diazo compounds as the precursors.[4] As reviewed by Gillingham,[4b] in the carbenoid insertions, a metal-carbenoid is typically generated *in situ* from a diazo precursor and then reacted with N-H bond to afford the insertion products. To date, the metal complex of Rh[5] and Cu,[6] have been broadly applied in the carbenoid based X-H (where X is any heteroatom such as nitrogen, oxygen or sulfur etc.) insertions. Other metal complex, such as Ru,[7] Ag[8], Fe[9] and Au,[10] also have been investigated in this reaction (Scheme 1).

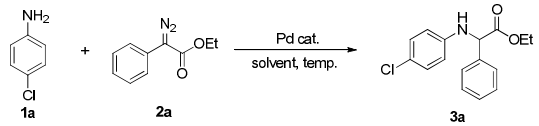


Scheme 1 Metal-catalyzed carbenoid based N-H insertion

During the past decade, palladium based carbenoid has been well studied in various transformations.[11] However, to our knowledge, the palladium based carbenoid has little or no use in the X-H insertion. Herein, we wish to report the successful palladium-catalyzed carbenoid based insertion into N-H bonds, which delivers the insertion products in high yields. Moreover, by choosing a suitable chiral auxiliary, the chiral *α*-amino esters were obtained in high yields and with excellent diastereoselectivities.

Initially, we examined the reaction of *p*-chloro-aniline with *α*-phenyl diazoacetate in the presence of various palladium resources at room temperature in dichloromethane. Within 12 hours, $PdCl_2$ gave the insertion product in moderate yield (Table 1, entry 1). $Pd(OAc)_2$, $Pd(TFA)_2$ and $Pd_2(dba)_3$ exhibited similar catalytic reactivity towards this reaction and gave the insertion products in nearly 30% yield (Table 1, entries 2 to 4). However, $Pd(PPh_3)_4$ and $Pd(dppf)Cl_2$ did not work in this insertion at all, which means the presence of phosphorus ligands thoroughly stop the reaction (Table 1, entries 5 and 6). Solvent screen showed 1,2-dicholoroethane (DCE) is the best one (Table 1, entry 12). Higher reaction temperature resulted in a decreased yield (Table 1, entry 13). High reaction temperature resulted in lots of side products (Table 1, entry 13). Finally, we found when the reaction stirred at room temperature for 3 hours then at 40°C for 6 hours, the insertion product was obtained cleanly in 85% isolated yield (Table 1, entry 14). This phenomenon probably can be explained with the fact that the first step is more selective at lower reaction temperatures while one of the latter step requires higher reaction temperatures. In addition, low catalyst loading resulted in a decreased isolated yield (Table 1, entry 15).

Table 1 Pd-catalyzed carbenoid based N-H bond insertion: Optimization of reaction conditions[a]



1a 2a 3a

Entry	Palladium complex	Solvent	Yield (%)[b]
1	$PdCl_2$	CH_2Cl_2	45
2	$Pd(OAc)_2$	CH_2Cl_2	38
3	$Pd(TFA)_2$	CH_2Cl_2	30
4	$Pd_2(dba)_3$	CH_2Cl_2	30
5	$Pd(PPh_3)_4$	CH_2Cl_2	0
6	$Pd(dppf)Cl_2$	CH_2Cl_2	0
7	$PdCl_2$	DCE	61
8	$PdCl_2$	THF	27
9	$PdCl_2$	DMF	42
10	$PdCl_2$	DMSO	38
11	$PdCl_2$	toluene	40

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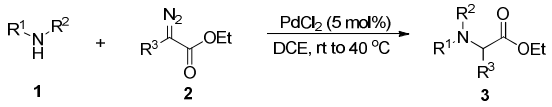
12	$PdCl_2$	DCE	51
13[c]	$PdCl_2$	DCE	20
14[d]	$PdCl_2$	DCE	85
15[e]	$PdCl_2$	DCE	52

[a]Unless otherwise noted, all reactions were carried out with *p*-chloroaniline (1.1 mmol), α-phenyl-diazoacetate (1 mmol), Pd complex (0.05 mmol) in 3 mL solvent at room temperature for 12 hours under nitrogen; [b]Isolated yields based on α-phenyl-diazoacetate; [c]The reaction was performed at 40°C; [d]The reaction was performed at room temperature for 3 hours, then 40°C for 6 hours.; [e]2 mol% $PdCl_2$ was used.

Upon the above results, we then investigated the substrate scope under the optimized conditions (5 mol% $PdCl_2$ in DCE at r.t for 3 hours then 40°C for 6 hours). The results were summarized in table 2. As observed, for the same diazo substrate, the *para*-substituted anilines with electron-withdrawing groups afforded the insertion products in higher yields (Table 2, entry 1 to entry 12) and *p*-nitroaniline gave the highest isolated yield (Table 2, entry 3). The substituted anilines with electron-withdrawing groups at the *ortho* or *meta* position, high yields were also obtained. *N*-methyl aniline also gave the insertion products in high yield (Table 2, entry 13). When α-benzyl diazoacetate was used, high yield was observed when reacted with **1a** (Table 2, entry 16). However, alkyl amine did not work in this case (Table 2, entries 17 and 18). As mentioned by Van Vranken in the palladium-catalyzed three-component coupling between α-diazoesters, vinyl-halides and amines, they did not find any N-H insertion products.[11c,11d] Also, for the 2-aminomethyl aniline, under this reaction conditions, the reaction did not work too, which means the aniline N-H insertion was inhibited in the presence of alkyl amine groups (Table 2, entry 19).

Table 2 Substrate scope[a]



1 **2** **3**

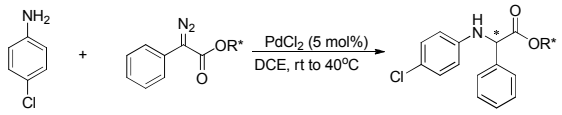
Entry	R^1	R^2	R^3	Yield (%)[b]
1	*p*-Cl-Ph	H	Ph	85
2	Ph	H	Ph	82
3	*p*-NO_2-Ph	H	Ph	93
4	*p*-Br-Ph	H	Ph	90
5	*p*-MeO-Ph	H	Ph	84
6	*p*-Me-Ph	H	Ph	74
7	*o*-Br-Ph	H	Ph	78
8	*o*-I-Ph	H	Ph	84
9	*o*-Me-Ph	H	Ph	78
10	*m*-Cl-Ph	H	Ph	87
11	*m*-Br-Ph	H	Ph	85
12	*m*-Me-Ph	H	Ph	82
13	Ph	Me	Ph	86
14	*p*-NO_2-Ph	H	*p*-Me-Ph	88
15	*p*-Cl-Ph	H	*p*-NO_2-Ph	84
16	*p*-Cl-Ph	H	benzyl	82
17	Benzyl	H	Ph	-
18	Piperidine	H	Ph	-
19	2-aminomethyl	H	Ph	-

[a]All reactions were carried out with substituted anilines or amine (1.1 mmol), α-phenyl-diazoacetates (1 mmol), $PdCl_2$ (0.05 mmol), in DCE (3 mL). All reactions were stirred at room temperature for 3 hours then 40°C for 6 hours. [b]Isolated yield.

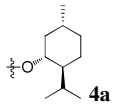
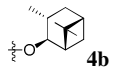
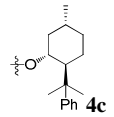
The diastereoselective/enantioselective insertion of α-diazocarbonyl compounds into N-H bond represents an attractive approach to obtain optically pure α-amino acid derivatives.[12] Zhou[13], Fu[14] and Feng[15] reported copper-catalyzed highly enantioselective N-H bonds insertions. However, as described by Zhou and Feng, for α-aryl diazo substrates, low to moderate enantioselectivities were observed. Also, Miyairi reported the cinchona alkaloids catalyzed asymmetric N-H insertions in moderate enantioselectivities.[16]

Based on the former results, we next investigated the use of chiral α-aryl diazoesters as the substrates in the stereoselective N-H insertions. As showed in table 3, solvent screen still showed DCE is the best one. When **4b** was selected as the chiral auxiliary (Table 3, entry 5), low d.r. value was observed. The (-)-menthol derived chiral diazoester gave 5:1 d.r. value (Table 3, entry 4). To our delight, excellent diastereoselectivity of the insertion product was obtained when (-)-phenyl-menthol[17] was used (Table 3, entry 6).

Table 3 $PdCl_2$-catalyzed stereoselective N-H insertion: Optimization of the reaction conditions[a, b]



1a **4** **5a** to **5c**

Entry	-OR*	Solvent	Yield (%)[b]	d.r. (%)[c]
1	 **4a**	CH_2Cl_2	72	3:1
2		CH_3CN	82	4:1
3		toluene	58	4:1
4		DCE	78	5:1
5	 **4b**	DCE	93	1.2:1
6	 **4c**	DCE	89	>19:1

[a]All reactions were carried out with *p*-chloroaniline (1.1 mmol), α-phenyl-diazoacetate (1 mmol), $PdCl_2$ (0.05 mmol), in DCE (3 mL). All reactions were stirred at room temperature for 3 hours then 40°C for 6 hours; [b]Isolated yield; [c]D.r. values were determined by NMR analysis of crude products.

Under optimized reaction conditions, we next use chiral diazoester **4c** as the standard substrate for further investigation. As shown in table 4, all of the reactions proceeded smoothly and furnished the chiral α-amino esters in moderate to high yields and with moderate to excellent diastereoselectivities (up to 91% yield and >19:1 d.r. value). The insertion products of electron-withdrawing substituted anilines gave better diastereoselectivities than the electron-donating substituted anilines. It is worth noting that the *N*-methyl-aniline gave the inverse chiral center compared with others (Table 4, **5g**).[18]

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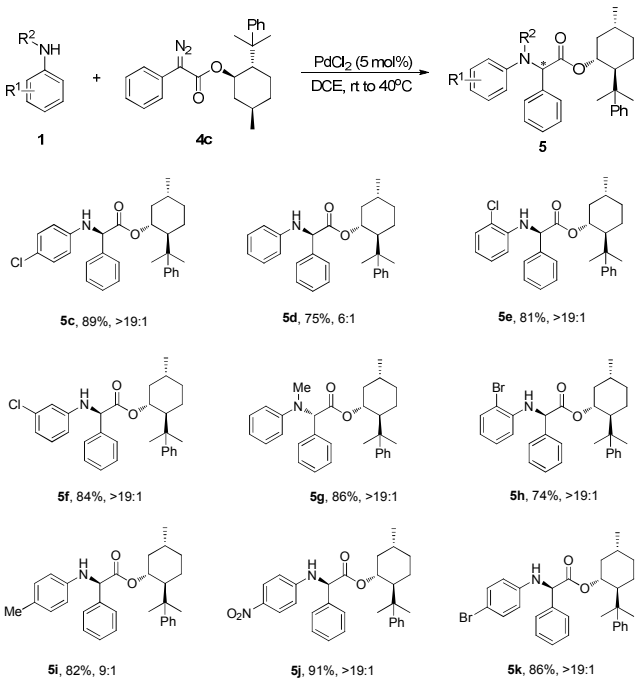
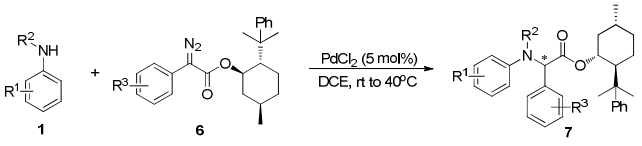
Table 4 $PdCl_2$-catalyzed stereoselective N-H insertion: Substrate scope[a, b, c]

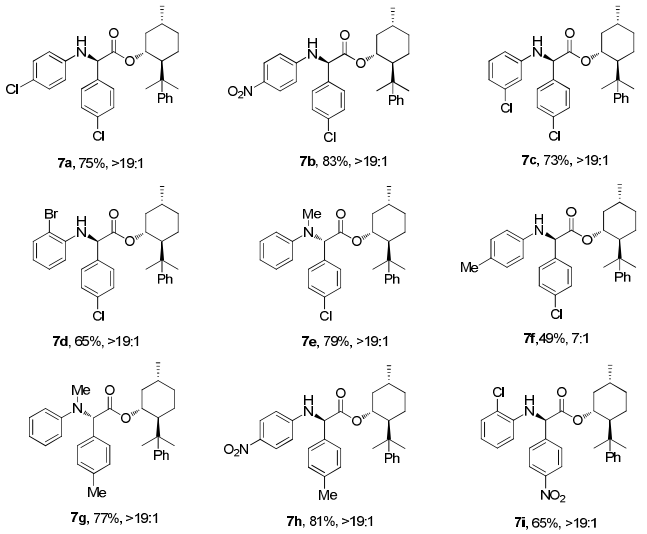


[a]All reactions were carried out with aniline (1.1 mmol), α-diazoester (1 mmol), $PdCl_2$ (0.05 mmol) in DCE (3 mL) at room temperature for 3 hours then 40°C for 6 hours; [b]Isolated yields; [c]D.r. values were determined by NMR analysis of crude products; The absolute configurations were determined by X-ray of **7h** or by analogy.

We then continue to investigate the substrate scope upon the variation of the diazo substrates and the anilines at the same time. For most cases, the chiral *α*-amino esters were obtained in high yields and with excellent diasteroselectivities except **7f** (Table 5, **7f**). As observed the same phenomenon with the former reaction, the *N*-methyl-aniline still gave the inverse chiral centers in (*S*) configuration when reacted with different diazo esters (Table 5, **7e** and **7g**).[18]

Table 5 Substrate scope[a, b, c]





[a]All reactions were carried out with aniline (1.1 mmol), α-diazoester (1 mmol), $PdCl_2$ (0.05 mmol) in DCE (3 mL) at room temperature for 3 hours then 40°C for 6 hours; [b]Isolated yields; [c]D.r. values were determined by NMR analysis of crude products; The absolute configurations were determined by X-ray of **7h** or by analogy.

The absolute and relative configurations of **5** and **7** were unambiguously assigned by X-ray crystallographic analysis of the optically pure compound **7h**, which was obtained by recrystallization from a mixture of dichloromethane. The structure enabled the (*R*) assignment of the newly formed stereogenic center in **7h** (Figure 1). The configurations of others (**5** and **7**) were then assigned by analogy can compared with literature.[18]

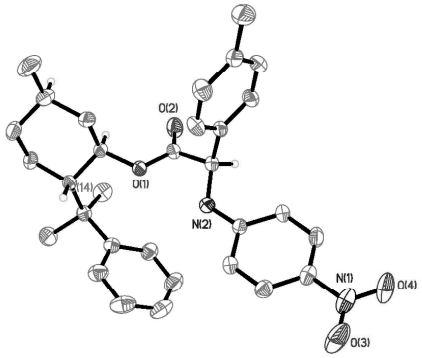


Fig 1 X-ray crystal structure of **7h.**

For the possible reaction mechanism and stereoselectivity (Figure 2), we concluded that the combination of $PdCl_2$ with *α*-phenyl diazoester gave the Pd-diazo intermediate **a**. Since higher reaction temperature resulted in messy products, we thought low temperature was essential for the carbene formation. Following by loss of N_2 delivers the Pd-carbenoid **b**. Nuclephilic attacked by aniline rendering the intermediate **c**. The asymmetric induction step was controlled by the steric factor of the chiral auxiliary, in which the bulky *ortho* group made the addition of aniline prone to attack from the less steric side. Then the migration of hydrogen from nitrogen to carbon and the leaving of palladium resulted in the formation of chiral *α*-amino ester.

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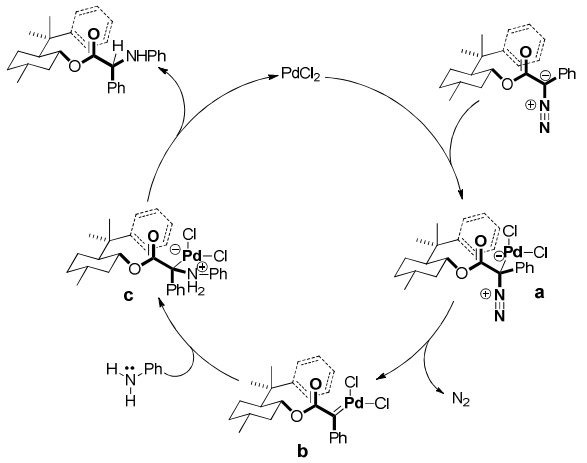

Fig 2 Proposed reaction mechanism and possible explanation of the observed stereochemistry

In conclusion, an efficient Pd-catalyzed carbenoid based N-H insertion has been developed. Furthermore, using (-)-phenylmenthol as chiral auxiliary, the insertion products have been obtained in high yields and with excellent diastereoselectivities (>19:1). Currently, we are investigating other Pd-catalyzed carbenoid based X-H insertions and their further applications.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of experiment procedures, NMR and HRMS for new compounds. CCDC 939059 for **7h**]. See DOI: 10.1039/b000000x/

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