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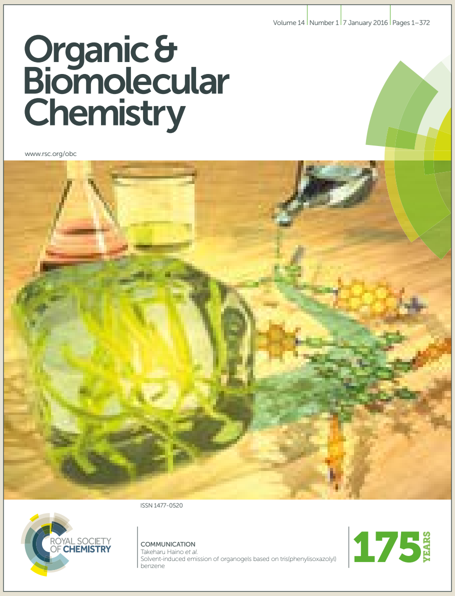

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Iridium Catalyzed Acceptor/Acceptor Carbene Insertion into the N−H Bond in Water Medium

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ABSTRACT:

The chemistry of **A** and **D**/**A** carbenes (**D** and **A** are donor and acceptor groups respectively) are known to the great extent in the literature, nevertheless the chemistry of **A/A** class of carbenes are less explored although **A/A** class of carbenes are more important in the natural product synthesis. Known catalysts for **A/A** carbene chemistry is also less in number and found to be efficient only in typical organic solvents. These limitations prompted us to search for new catalysts and environmentally benign reaction conditions for **A/A** class of carbenes. The present study revealed that the [(COD)IrCl]$_2$ is found to be an efficient catalyst for **A/A** and Pd$_2$(dba)$_3$ for **D**/**A** class of carbenes for insertion into N−H bond in water medium under mild reaction conditions. Reactivity comparison study with different class of carbenes revealed that the silver based catalysts can be the right choice for **D/D** class of carbenes insertion into N−H bond in water medium. A large number of α-amino malonates and amino esters which are important for the synthesis of heterocycles and several natural products have been synthesized by following current methodology and characterized using standard analytical and spectroscopic techniques.

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Introduction:

Metal complexes mediated carbene reactions have been an important tool in the synthetic organic chemistry owing to their potential applications.[1,2] In general different carbenes are generated from their corresponding diazo compounds mediated by transition metal complexes as catalysts (nevertheless majority of NHC class of carbenes are synthesized by other methods).[3] Typical carbene related reactions are carbene insertion into X−H (X= NR, O, S, CR_3, SiR_3 or $BR_{2)}$ bond and cyclization etc.[4,5] These typical carbene reactions provide practically viable route for the construction of new C−C and C−X (X=hetero atom) bonds under mild reaction conditions.[6] Carbene reaction with olefin provides an easy way to the construction of strained three membered rings (carbene cyclization with olefin), which are serving as key intermediates for synthesis of drug molecules and natural products in pharmaceuticals.[7–9]

Based on the nature of α-substituents (donor (**D**), acceptor (**A**)), the carbene precursors namely diazo compounds can be classified as donor/donor (**D/D**), donor/acceptor (**D/A**), and acceptor/acceptor (**A/A**) (Scheme 1) as they display different reactivity pattern.[10,11] Among these three class of diazo compounds, so far only **D/A** diazo compounds have been intensely studied owing to their more reactivity and moderate thermal stability. These diazo compounds (**D/A**) react with suitable substrates under mild reaction conditions with excellent chemoselectivity[12–15] and enantioselectivity.[16–20] However carbenes having **A/A** substituents are very important owing to their immense applications in the total synthesis including heterocycles.[21–24] Nevertheless the chemistry of carbenes having **A/A** and **D/D** substituents has not been explored owing to their high thermal stability and low reactivity of **A/A** carbene source and low thermal stability and high reactivity of **D/D** carbene source (Scheme 1).[10] Among these **A/A** and **D/D** carbenes sources, the **A/A** carbene sources display interesting reactivity patterns owing to their good

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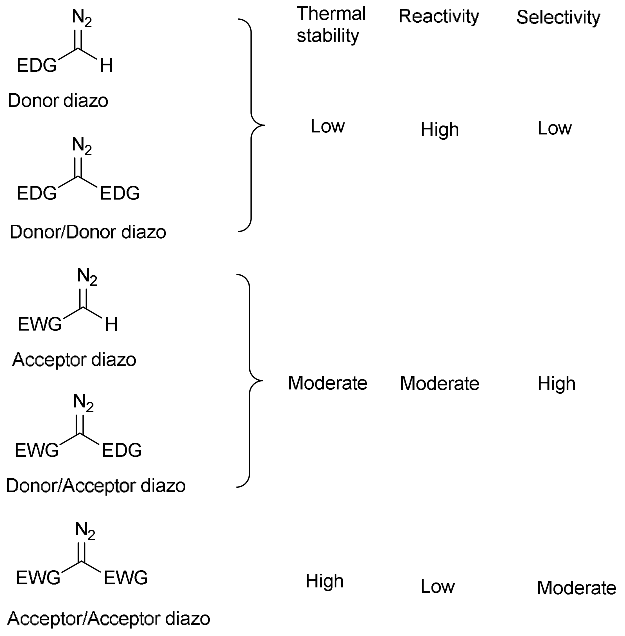
thermal stability and scope for wide functional groups. Owing to the high thermal stability of **A/A** carbene source, one has to use catalysts such as Rh, Ir, Co or Ru under harsh reaction conditions especially for C-H activation and heterocycles construction.[25–29]



Scheme 1. Overview of classification of different diazo compounds

The **A/A** carbenes have also been used for cyclization of alkenes and alkynes,[30–35] and carbene insertion into N−H and O−H bonds of amides and acids respectively are known only in organic solvents.[12,36–38] So far only Rh based catalysts and harsh reaction conditions have been used for **A/A** carbenes insertion into N−H bond and produced poor to moderate yields,[36–39] these harsh reaction conditions resulted in low selectivity and produced several unwanted side products.[10] In this line, so far no reports are available in the literature for the utilization of **A/A** carbenes insertion in an environmentally benign reaction conditions.

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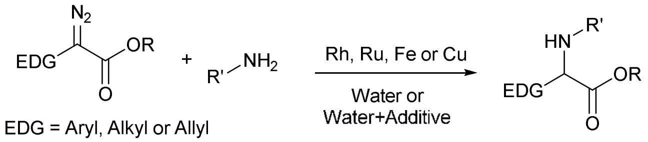


Scheme 2. Known carbene insertion into N−H bond in aqueous medium

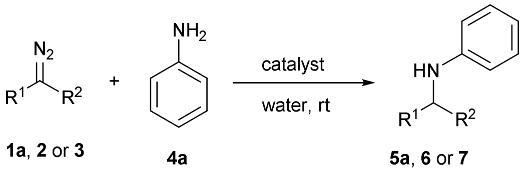
Francis *et al*. successfully utilized Rh catalyzed **D/A** carbene insertion into N−H bond as a tool to modify the protein,[40] and this strategy has become one of the important methodologies for protein modification and labelling.[41–43] Thereafter significant advancements have been made with respect to finding new catalysts for the reaction of **D/A** carbenes insertion into N−H bond in aqueous medium especially for protein modification (Scheme 2).[44–47] In this line, recently our group also reported an efficient method for synthesis of amino phosphonates in aqueous medium from diazo phosphonates and anilines catalyzed by Cu(I) catalyst.[48] Although the **D/A** carbenes used in the protein chemistry, **A/A** carbenes have not been used therefore in order to extend the scope of **A/A** carbene reactions for protein labeling, protein modification and in total synthesis, some effective catalysts which works under mild reaction conditions with high selectivity in aqueous medium are to be discovered. By considering the importance of **A/A** carbene insertion reactions and continuation of our research on carbene related reactions[13,15,48,49] herein we report a feasible method for **A/A** carbene insertion into N−H bond in water medium under mild reaction conditions using Ir(I) complex as a catalyst. The already known Ir complexes are capable of inserting only **D/A** class of carbenes into N−H bond in organic solvents therefore our methodology would be more useful in the synthetic organic chemistry.[50,51]

DOI: 10.1039/C7OB00177K

Results and discussion:

We have chosen diethyl 2-diazomalonate (**1a**) as a **A/A** carbene source, which is highly stable among all commonly used carbene sources and relatively less explored.[11] For the sake of reactivity comparison, methyl 2-diazo-2-(4-methoxyphenyl)acetate (**2**) and 4,4'-(diazomethylene)bis(methoxybenzene) (**3**) precursors have also been used in the present study as the representative examples for **D/A** and **D/D** carbene sources respectively (Table 1). We have also chosen different transition metal complexes and salts as catalysts for carbene insertion reaction in water medium.

Table 1. Screening of the various catalysts for carbene insertion into N−H bond in water medium



A/A: $R^1 = R^2$ = -COOEt D/D: $R^1 = R^2$ = -*p*-OMePh D/A: R^1 = -*p*-OMePh, R^2 = -COOMe

entry[a]	catalyst	catalyst load (mol %)	A/A		D/A		D/D	
			time	yield(%)	time	yield(%)	time	yield(%)
1	$[(CH_3CN)_4Cu]ClO_4$	2	12 h	51	1 min	37	1 min	<10
2	$Cu(OTf)_2$	2	12 h	47	1 min	28	1 min	<10
3	$Rh_2(OAc)_4$	1	24 h	ND	1 min	34	24 h	<10
4	$[(COD)RhCl]_2$	1	24 h	trace	4 h	83	24 h	trace
5	$[(COD)IrCl]_2$	1	12 h	81	6 h	87	24 h	<10
6	[(*p*-cymene)$RuCl_2]_2$	1	24 h	trace	24 h	61	24 H	<10
7	AgOTf	2	24 h	trace	24 h	54	5 min	56
8	AuCl	2	24 h	ND	24 h	trace	1 h	37
9	$Pd_2(dba)_3$	1	24 h	ND	30 min	90	24 h	17
10	$PdCl_2$	2	24 h	ND	6 h	89	8 h	26

[a] All the reactions are carried out with 1 mmol of aniline and 1.1 mmol of diazo compound. Yield: Pure compound after column chromatography.

In case of **A/A** diazo compounds, the $[(COD)IrCl]_2$ produced 81% (Table 1, entry 5) of expected N−H inserted product over 12h while other catalysts produced less yields and taken more time (Table 1). In case of **D/A** diazo compounds, the reaction was completed over 30 min and offered

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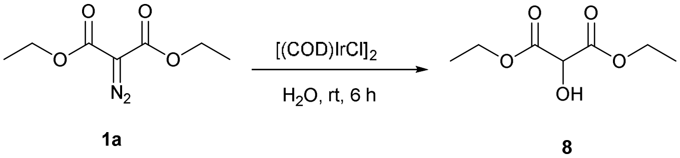
90% of N−H inserted product while $Pd_2(dba)_3$ was used as a catalyst (Table 1, entry 9) whereas other catalysts produced either comparable amount of yields or lesser than the yield observed for $Pd_2(dba)_3$. In case of **D/D** diazo compounds, the AgOTf offered 56% of N−H inserted product (Table 1, entry 7) while other catalysts produced relatively less yields.



1a **8**

Scheme 3. Reaction of **A/A** diazo compound in water catalyzed by $[(COD)IrCl]_2$ (O−H insertion)

When we conducted the reaction using $[(COD)IrCl]_2$ as a catalyst in the absence of amine source, the **A/A** diazo compounds offered exclusively 77% of water O−H inserted product (**8**) over 6 h (Scheme 3). However when we conducted the reaction in the presence of aniline, we have not observed any water O−H inserted product. From the above study it can be noted that the carbene insertion into N−H bond seems to be faster than the carbene insertion into O−H bond of water.

Subsequently we attempted to explore the scope of anilines for **A/A** diazo compounds in water medium. In order to demonstrate the substrate scope for different anilines, we screened a large number of anilines with electron donating and electron withdrawing groups (Scheme 4). All the anilines (**5b**−**5f**) having electron donating groups offered N−H inserted products in excellent yields. We observed highest yield (98%) in case of 2,4,6-trimethyl aniline (**5e**) and lowest yield (88%) with para toluidine (**5b**). To our surprise, steric factor does not affect the product yields, for an example 2,6-diisopropyl aniline (**5d**) offered excellent yield (96%).

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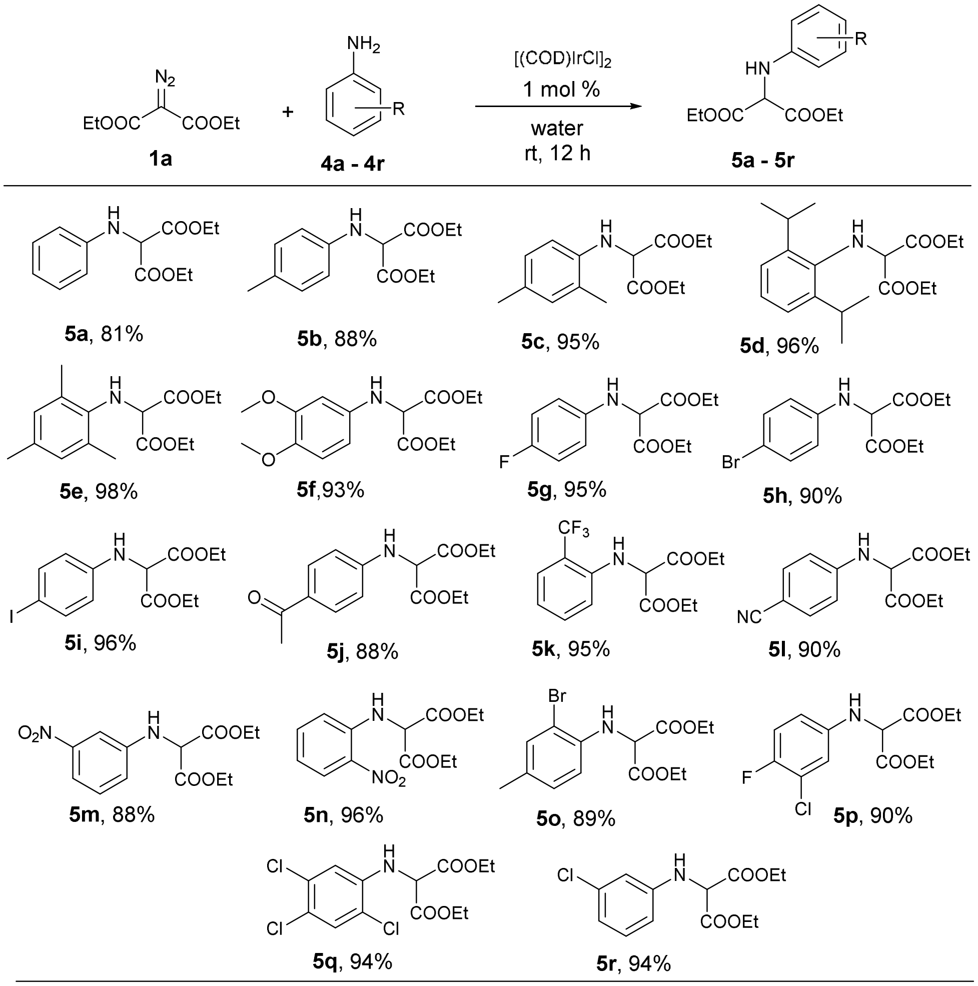

Scheme 4. Scope of anilines for **A/A** carbene insertion into N−H bond in water medium catalyzed by $[(COD)IrCl]_2$

In case of electron withdrawing groups (**5g**−**5s**), among all the screened anilines having electron withdrawing groups, 2-nitro and 4-iodo aniline offered 96% yield (**5i** and **5o**). All the halogen substituted anilines offered good yields (**5g**−**5i** and **5o**−**5r**). Other functional groups such as nitro and acetyl does drastically affect the yields (**5j**−**5n**). Among all the nitro anilines, 2-nitro aniline offered excellent yield (96%). In case of amino benzo nitrile, we observed 90% yield, similarly trifluromethyl aniline offered very good yield 95% (**5k**). Although aniline derivatives offered

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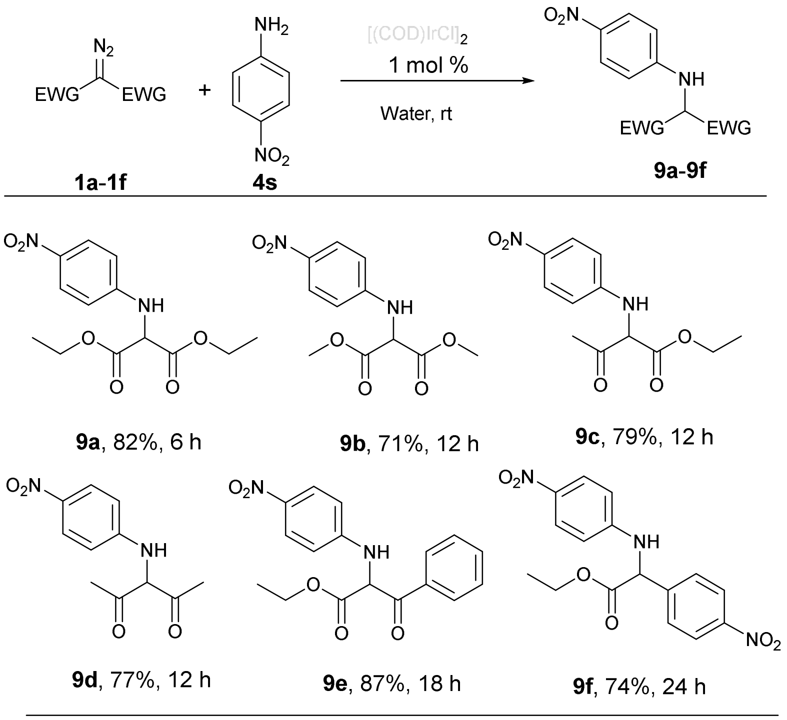
good to excellent yields, aliphatic amines such as benzyl amine and hetero aromatic amines (2-aminopyridine) offered trace amount of N−H inserted product.

After screening different anilines, we focused our studies on the scope of different **A/A** diazo compounds. We have chosen 4-nitro aniline to react with various **A/A** diazo compounds (Scheme 5) owing to the compatibility in handling. When we used dimethyl 2-diazomalonate, the reaction offered N−H inserted product in 71% yield over 12 h (**9b**) (Figure S1). Whereas ethyl 2-diazo-3-oxobutanoate offered good yield (79%) over 12 h (**9c**), 3-diazopentane-2,4-dione diazo offered N−H inserted product in 77% yield over 12 h (**9d**) and ethyl 2-diazo-3-oxo-3-phenylpropanoate offered 87% yield over 18 h (**9e**). We have also used other diazo compounds such as ethyl 2-diazo-2-(4-nitrophenyl)acetate and the reaction proceeded slowly to offered 74% yield over 24 h (**9f**).



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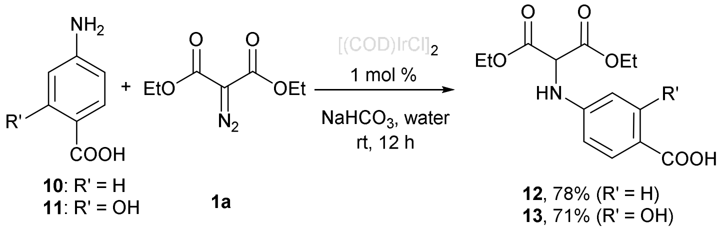
Scheme 5. Scope of anilines for **A/A** carbene insertion into N−H bond in water medium catalyzed by [(COD)IrCl]$_2$



Scheme 6. Derivatization of amino benzoic acids using **A/A** carbene insertion into N−H bond in water medium catalyzed by [(COD)IrCl]$_2$

After examining the substrate scope for Ir(I) catalyzed **A/A** carbene insertion into N−H bond in water medium, our interest turned towards derivatization of some biologically important molecules. In this line as representative substrates, we have chosen 4-aminobenzoic acid and 4-amino-2-hydroxybenzoic acids (anti tuberculosis agent), which are biologically and synthetically important molecules[52,53] and produced expected N−H inserted product (78% (**12**) and 71% (**13**) respectively) with **A/A** type carbenes over the period of 12 h (Scheme 6). Apart from these molecules, we have also attempted to derivatize some aliphatic amino acids, nevertheless owing to the limitation of this method on aliphatic amines we ended up with water inserted product (**8**).

In conclusion, we have developed an efficient green method for **A/A** type carbene insertion into N−H bond of various anilines in water medium. In order to achieve this, we screened many catalysts for **A/A**, **D/A** and **D/D** carbene insertion into N−H bond of aniline in water medium and we found that [(COD)IrCl]$_2$, Pd$_2$dba$_3$ and AgOTf are efficient catalysts for **A/A**, **D/A** and **D/D**

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carbenes respectively. Using our developed methodology, we have synthesized a large number of α-amino diesters and fully characterized. On the way to extend the scope of present methodology, we screened variety of **A/A** diazo compounds and characterized the corresponding products using standard analytical and spectroscopic techniques. In the near future, this novel methodology may provide some useful applications for the synthesis of heterocycles and protein labelling, and modification in water medium.

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Electronic supplementary information (ESI) available

Analytical data, ^{1}H, ^{13}C NMR Spectra and X-ray crystallographic data.

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TOC

Highly stable acceptor/acceptor type of carbenes can be inserted into N−H bond of aromatic amines using Ir(I) catalyst in water medium.