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Hemin-Catalyzed, Cyclodextrin-Assisted Insertion of Carbenoids into N–H Bonds

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Abstract: An aqueous hemin-catalyzed, cyclodextrin-assisted N–H insertion reaction of α-diazo ester into aromatic amines is described here. This aqueous catalytic system showed good compatibility with various arylamines, with yields up to 96%. A size-controlled reaction phenomenon by different cyclodextrins (CDs) was also observed when ethyl diazoacetate (EDA) was used. The reaction mechanism was also preliminarily proposed on the basis of designed control experiments.

Keywords: cyclodextrins; diazo compounds; green chemistry; hemin; N–H insertion

Heme is not only one of the most abundant and widely used metalloporphyrins in catalysis, but also the crucial cofactor in a variety of metalloenzymes. In recent years, many heme-containing enzymes have received considerable attention in biosynthetic and bioanalytical chemistry,[1] such as cytochrome P450-involved carbenoid-relevant reactions,[2] and horseradish peroxidase (HRP)-catalyzed oxidation of resveratrol.[3] Possessing merits such as thermal stability and low cost, heme is considered as an ideal model compound for mechanistic study of ferriporphyrin-catalyzed reactions and broadening the application horizon of heme enzymes.

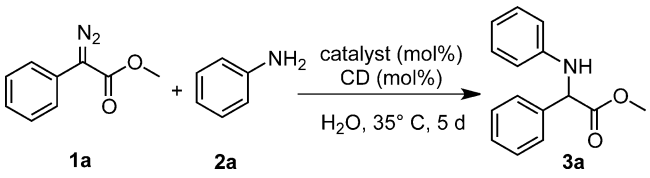
Metal-catalyzed N–H insertion of α-diazo esters with amines provides a facile way to prepare C–N bond-containing precursors of natural products and bioactive molecules,[4] such as α-amino acids,[5] peptides[6] and nitrogen-containing heterocycles.[7] In 1950s, Yates reported the first example of N–H insertion reaction by using copper catalysis,[8] and subsequently Paulissen and his co-workers employed the catalyst $Rh_2(OAc)_4$ to achieve this reaction.[9] Since then, a variety of copper-,[10] rhodium-,[11] ruthenium-,[12] iridium-,[13] and palladium-based[14] catalysts have been broadly applied to carbenoid insertion reactions. Recently, Zhou and his co-workers demonstrated the enantioselective N–H insertion of diazo compounds.[10a,11b] Iron corroles- and iron porphyrins-catalyzed insertions of EDA into N–H bonds have also been achieved by Gross[15] and Woo.[16] Nevertheless, most of these established reactions were conducted in organic solvents and required strict reaction conditions, such as rigorous operation and inert atmosphere. On the contrary, enzymatic carbenoid transformations in aqueous media remain rare,[2b,12,17] owing to the inclination of O–H insertion by water and the poor water-solubility of substrates.

Such issues also hindered the use of hemin in the catalysis of carbenoid insertions to amines. The catalytic ability of hemin often decreases in aqueous media owing to the hydrophobic nature of the porphyrin ring and the absence of the peptidic microenviroment that existed in native enzymes. Complementarily, cyclodextrins, with hydrophobic inner cavities and hydrophilic outer surfaces, can provide a favourable microenvironment for hemin and increase the solubility of organic substrates.[18]

The continuing interest in developing a sustainable reaction system to accomplish the target transformation under aqueous conditions by employing cheap, efficient and eco-friendly catalysts has inspired the present research. Herein, we report an efficient aqueous hemin-catalyzed, cyclodextrin-assisted protocol for the insertion of carbenoids into N–H bonds.

Our investigations commenced with the model substrate methyl phenyldiazoacetate (MPDA, **1a**) and aniline (**2a**) in the presence of 0.05 mol% heme-centered natural enzyme horseradish peroxidase (HRP) (entry 0 in Table 1). The reaction was carried out in aqueous solution at 35 °C for 5 days, affording the N–H insertion product (**3a**) in 9% yield determined by ^{1}H NMR, in which a new one-proton singlet peak appeared at 5.09 ppm for the new methane hydrogen.

Table 1. Optimization of the N–H insertion reaction conditions.[a,b]



1a 2a 3a

Entry	Cat. (mol%)	Cyclodextrin (mol%)	Yield[c] [%]
0	HRP (0.05)	–	9
1	hemin (10)	–	44
2	hemin (10)	α-CD (16)	71
3	hemin (10)	β-CD (16)	89
4	hemin (10)	γ-CD (16)	93
5	hemin (10)	β-CD (100)	63
6	hemin (10)	β-CD (50)	92
7	hemin (10)	β-CD (20)	89
8	hemin (10)	β-CD (10)	57
9	hemin (10)	β-CD (20)	91
10	hemin (5)	β-CD (20)	94
11	hemin (2.5)	β-CD (20)	69
12	hemin (1)	β-CD (20)	4
13	HRP (0.05)	β-CD (100)	6

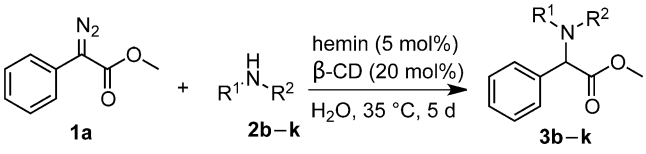
[a] A molar ratio of 1:1.2 for MPDA:aniline was employed, and reactions were carried out in a thermo shaker.
[b] The results of other PTAs are shown in supporting information.
[c] Yields were determined by ^{1}H NMR in $CDCl_3$.

When 10 mol% hemin was used instead of HRP, the reaction exhibited improved but still unsatisfactory reactivity by giving **3a** in 44% yield (entry 1 in Table 1). We assumed that the poor reactivity was due to the low solubility of the substrates, and then we turned to the addition of the frequently used phase-transfer agents (PTAs) to improve the reactivity. As shown in Table 1, cyclodextrins (entries 2–4) dramatically improved the yield of product **3a** (α-CD, 71%; β-CD, 89%; γ-CD, 91%), while the other eight PTAs (Table S1 in the Supporting Information) had no obvious effect on the transformation.

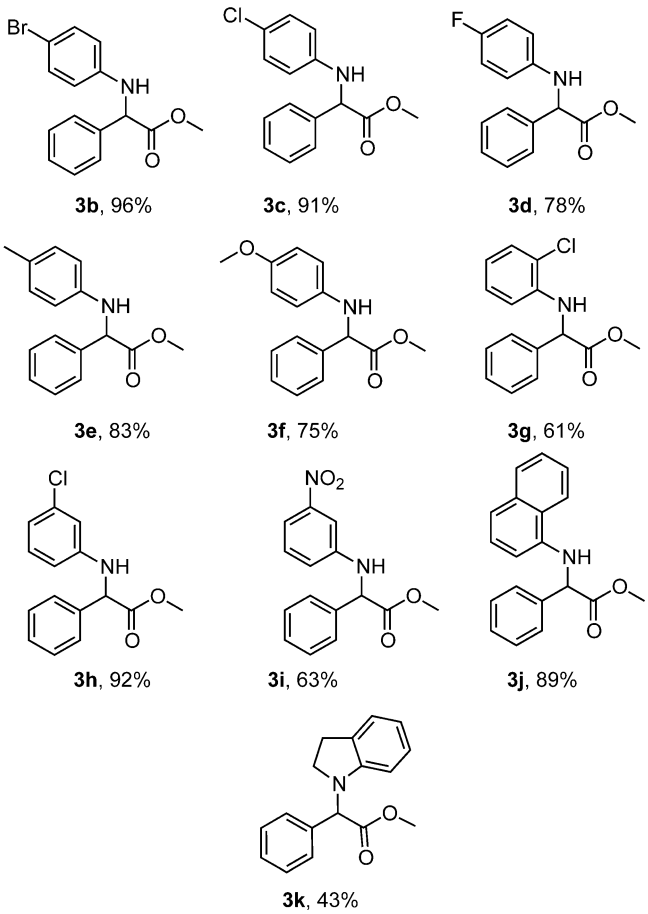
Considering the comparable results in the presence of β-CD and γ-CD and the relatively low cost of the former one, we selected β-CD as our ideal additive. After further screening of the catalytic amounts of hemin and CDs (entries 5–12 in Table 1), we were delighted to attain the optimal conditions with **3a** obtained in 94% yield: 5 mol% hemin and 20 mol% β-CD, 35 °C, 5 days in water (entry 10 in Table 1). However, a lower catalytic loading of hemin decreased the yield (entries 11 and 12 in Table 1). Given that the diazo compounds are potentially explosive, a higher reaction temperature was not considered. When we conducted this reaction in the catalysis of 0.05 mol% HRP with a stoichiometric amount of β-CD, still only a poor yield of the target product was achieved (entry 13 in Table 1).

With the optimized conditions in hand, we next examined the substrate scope of substituted arylamines by using MPDA as the diazocarbonyl reagent in this hemin-catalyzed system (Table 2). The corresponding N–H insertion products were obtained in moderate to excellent yields (43–96%). Almost all of the *para*-substituted anilines displayed high conversions without the side product formed through the dimerization of MPDA, and only a trace amount of the O–H insertion by-product formed by MPDA and water was detected. This reaction had excellent functional group tolerance, and both electron-withdrawing groups (**3b**, **3c** and **3d**) and electron-donating groups (**3e** and **3f**) remained intact in this reaction system. The comparable reactivity of 4-chloroaniline (**3c**) and 3-chloroani-

Table 2. N–H insertion reactions of diverse substituted amines.[a,b]



1a 2b–k 3b–k

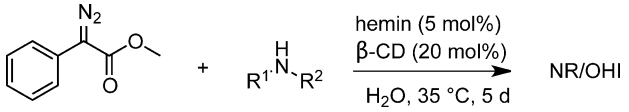


[a] A molar ratio of 1:1.2 for MPDA:amine was employed, and reactions were carried out in a thermo shaker.
[b] Yields were determined by ^{1}H NMR in $CDCl_3$.

line (**3h**) suggested that the *meta*- and *para*-substitutions showed no obvious position effects. However, the *ortho*-position of the substituents on the aryl group led to a slightly reduced yield of the corresponding product (**3c** and **3g**). This result might be due to the steric hindrance on the nucleophilic addition to the electron-deficient carbene intermediate. As an exception, a high yield (89%) of the desired product of 1-naphthylamine (**3j**) was formed in spite of the large steric hindrance, which indicated that the electron-donating naphthyl group could probably facilitate the reaction. Finally, the N-heterocyclic compound indoline could also undergo the N–H insertion under the standard reaction conditions to afford the corresponding product in moderate yield (**3k**).

However, some other amines or amides were tested and found to be incompatible with the reaction system, giving no N–H insertion products (Table 3).

Table 3. Investigation of unreactable amines.[a]



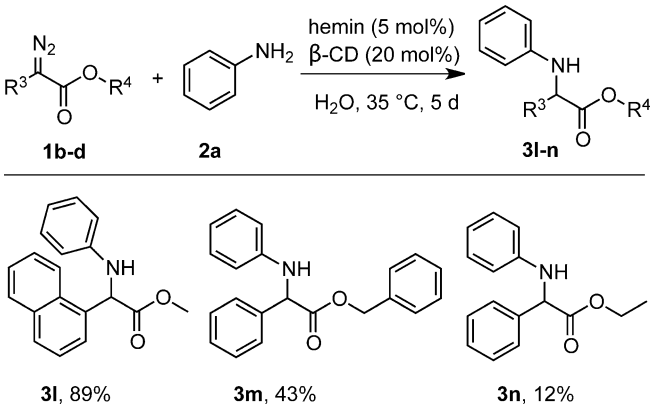
Results	Corresponding amines
OHI[b]	4-nitroaniline; 2-nitroaniline; diphenylamine; indole; pyrrole; 2-aminophenol; guanine; uracil; sulfanilic acid; benzamide; glucosamine; taurine; *o*-phthalimide
NR[c]	4-aminophenol; benzylamine; dibutylamine; *tert*-butylamine; *iso*-propylamine; piperidine

[a] A molar ratio of 1:1.2 for MPDA:amine was employed, and reactions were carried out in a thermo shaker.
[b] OHI signifies O–H insertion reaction between MPDA and water.
[c] NR signifies no reaction.

With the competitive hydroxy group at the *para*-position of aniline, no reaction happened, while the presence of *ortho*-hydroxy, *para*-nitro or *ortho*-nitro group led to the O–H insertion by-product formed by MPDA and water. In addition, most of the soluble amines were found to give no reactions, owing to the protonated amines acting as bystanders in water. As a consequence, we suppose that CD could act as a carrier enveloping the reactants within its hydrophobic environment, thus providing a protective sheath for the N–H insertion reactions.

The influence of the diazo ester type on this reaction was subsequently studied. Three phenyl diazoacetate substrates were synthesized and applied in the reaction under optimized conditions (Table 4). The desired N–H insertion product of methyl naphthyldiazoacetate was generated in high yield (**3l**, 89%). A relatively modest reactivity (**3m**, 43%) was observed

Table 4. N–H insertion reactions of different α-diazoacetate substrates.[a,b]

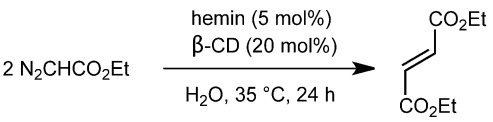


[a] A molar ratio of 1:1.2 for α-diazoacetate:aniline was employed, and reactions were carried out in a thermo shaker.
[b] Yields were determined by ^{1}H NMR in $CDCl_3$.

when benzyl phenyldiazoacetate was employed in the N–H insertion. Nevertheless, the reaction with ethyl phenyldiazoacetate resulted in a low yield of the corresponding product (**3n**, 12%), which suggests that different protecting groups of the esters could have an immense influence on this transformation. However, all the N–H insertion products **3a**–**3n** had almost no enantioselectivities with *ee* values under 5% (Table S3 in the Supporting Information).

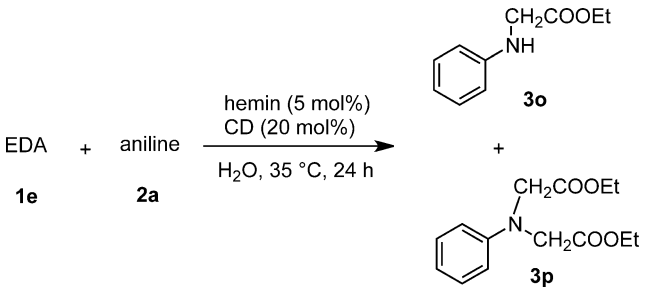
When this method was applied in the reaction between EDA and aniline with a ratio of 1:1, the double-insertion product **3p** was detected in 37% yield, along with the single-insertion product **3o** in 19% yield. And only trace amount of diethyl fumarate was formed. This reaction could be accomplished in 24 h, which is much more effecient than MPDA-involved reactions. After β-CD was replaced by equimolar α-CD or γ-CD, it was discovered that the single-insertion product **3o** was more favourably formed when the smaller α-CD was involved, whereas the double-insertion product **3p** was preferentially generated when the larger γ-CD was used (Table 5). It could be inferred that the product distribution can be controlled by the hydrophobic cavity size of CDs. This result also provides additional proof for the role of CD acting as a micro-reactor.

Furthermore, a mechanistic probe for carbene formation was designed in which EDA was treated with 5 mol% hemin and 20 mol% β-CD in water [Eq. (1)]. After 24 h, almost complete conversion to the car-



(1)

Table 5. CD size-controlled product distribution.[a]



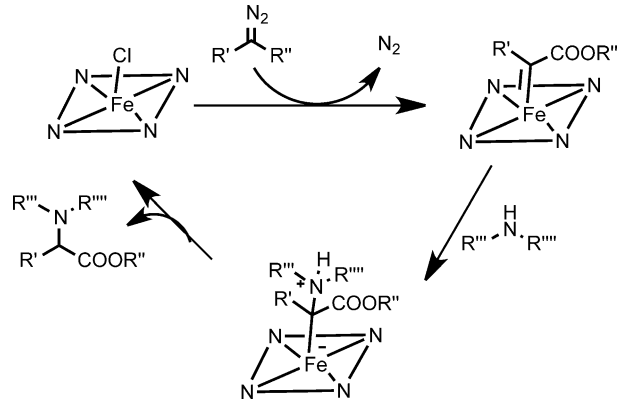
Entry	CD	Yield[b] [%] single insertion	double insertion
1	α-CD	61	12
2	β-CD	37	19
3	γ-CD	32	20

[a] A molar ratio of 1:1 for EDA:aniline was employed, and reactions were carried out in a thermo shaker.
[b] Yields were determined by ^{1}H NMR in $CDCl_3$.

bene dimerization product of EDA, namely, diethyl maleate, was observed, clearly indicating that the hemin-catalyzed N–H insertion reaction proceeds through a metal carbene pathway.

The proposed mechanism is depicted in Scheme 1. At the outset, the diazo compounds undergo an electrophilic addition to coordinate the unsaturated iron center of hemin to form a hemin carbene complex, by losing a molecule of nitrogen. Then, the N–H insertion products are generated through the nucleophilic attack by the amines. In spite of the difficulty to capture or trap the hemin carbene intermediates due to their rapid consumption, the disclosure of the fully characterized iron porphyrin carbene complex provides a rational evidence for the existence of a hemin carbene complex to a certain extent.[19]

In conclusion, the current investigation is focused on the N–H insertion reactions between aromatic amines and diazocarbonyl reagents under the catalysis of the commercially available and relatively inexpensive hemin in aqueous solution with the aid of β-CD. Moderate to excellent yields of N–H insertion products were obtained through a concise, green and efficient strategy. This aqueous catalytic system might be of great advantage in the transformation of carbenoids. The successful cooperation of hemin and cyclodextrin provides a preliminary possibility for applying heme enzymes in diazo ester-involved transformations.



Scheme 1. Plausible mechanism.

Experimental Section

General Procedure for Hemin-Catalyzed N–H Insertion Reactions

Amine (0.36 mmol) was added in 3 mL of an aqueous solution containing 0.015 mmol hemin/0.15 μmol HRP and 0.06 mmol CD, followed by addition of 0.3 mmol diazo reagent in one portion. The reaction vials were then placed in a constant temperature shaker and left to shake at 200 rpm under 35 °C. After 5 days, the mixture was extracted thrice with EtOAc and water. The organic layer was further washed with brine and then dried with Na_2SO_4. Finally, hemin was filtered by using a short silica gel column with EtOAc. The filtrate was concentrated under vacuum and subjected to silica gel and eluted with petroleum ether-EtOAc (50:1) to give the pure N–H insertion product. Yields were determined by ^{1}H NMR.

Acknowledgements

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