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Iron Catalyzed Efficient Synthesis of Poly-functional Primary Amines via Direct Use of Ammonia

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An iron catalyzed three-component reaction of alkyl diazoesters, isatins and ammonia is reported. This reaction provided convenient access to non-protected β-hydroxy-α-aminoesters with adjacent quaternary stereocenters. This transformation is achieved via trapping of ammonium ylide which is generated from a diazocompound and ammonia under mild reaction conditions. Poly-functional group unprotected amines are obtained exclusively with up to 77% yield and 62:38 dr.

As a cheap, abundant, and readily available feedstock, ammonia is mainly used for fertilizer.[1] The direct use of inexpensive ammonia to produce high value-added nitrogen-containing molecules has been an important goal pursued by chemists.[2] Primary amines are widely present in natural products and drugs.[3] Moreover, the ease in derivatisation, have enabled them to become useful building blocks in synthesizing complex nitrogen-containing molecules.[4] Primary amines are often prepared by protective group strategy[5] or via the reduction of nitro, azide or cyano groups[4a,6] in organic synthesis. The direct use of inexpensive ammonia to synthesize primary amines is a very attractive measure and is in great demand. However, such transformations are challenging for several reasons. Firstly, the selectivity required for producing single primary amines are frequently poor due to the higher reactivity of the resulting primary amines than ammonia.[7] Thus, most of the preparations of unprotected alkyl primary amines encounter problems associated with over-alkylation. Secondly, transition metals have been playing an important role in improving the selectivity and reactivity of ammonia transformations. However, the combination of transition metals and ammonia is challenging due to: the strong Lewis basicity of ammonia which induces Werner complex formation; and ligand exchange with transition metal complexes, that lead to low reactivity of metal catalysts. Thirdly, most of the reactions require harsh conditions comprising of high pressure and/or high temperature, and long reaction time,[2] making the construction of poly-functional molecules very difficult due to the decomposition of the products under reaction conditions. All of the aforementioned issues make the reaction types of the direct use of ammonia very limited. Previous studies have mainly focused on: hydroaminomethylation;[8a] reductive amination;[8b] amination of alcohols;[7a,8c] allylic substitution;[8d,8e] hydroamination[8f] and coupling with aryl halides[4d,8g] to make simple primary amines. New kinds of reactions that directly use ammonia as nitrogen source to synthesize poly-functional primary amines are highly desirable economically and environmentally. From research, there are very few practical examples of synthesizing poly-functional primary amines via direct use of ammonia.

Our group has been working on MCR (multi-component reaction) based on the trapping of reactive ylide[9] and zwitter ionic[10] intermediates for years, thereby providing efficient synthesis of poly-functional molecules. Given our previous success in the trapping of ammonium ylides generated from aliphatic amines and EDA (ethyl diazoacetate),[9c] we reasoned whether the trapping of ammonium ylides of ammonia could be realized. However, the catalytic transformation of ammonia with metal carbenes has long been an area to be discovered. In 2006, Gross group reported seminal work on Iron porphyrin catalyzed insertions of ammonia by EDA and EDP (ethyl diazopropanate) under mild conditions, though the mechanism of the catalytic N-H insertion is as yet unclear.[11] We wonder whether this reaction proceeds through a concerted N-H insertion (intermediate **I**) or ylide process (intermediate **II**) mechanism (Scheme 1).

3-Substituted 3-hydroxyoxindoles widely exist in natural products and pharmaceuticals.[12] Most of the reported methods for synthesizing 3-substituted 3-hydroxyoxindoles

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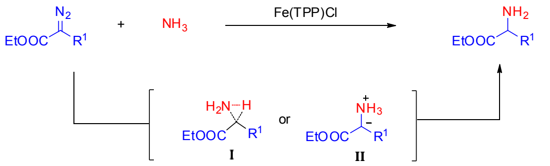
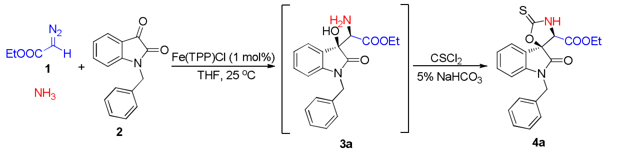
were accomplished via nucleophilic addition to isatins.[13] In 2007, our group reported a $Rh_2(OAc)_4$ catalyzed trapping of ammonium ylide by isatins to give poly-functional amines bearing 3-substituted 3-hydroxyoxindoles with two adjacent stereocenters.[9e] However, the amine substrates were limited to aromatic amines due to the poisoning of the rhodium catalysts by aliphatic amines and ammonia, and cooresponding free amines were extremely difficult to obtain due to stability issue under deprotection conditions, thus limiting the utility of this method. We reasoned that if the aforementioned N-H insertion of ammonia proceeds via the ylide process (**II**), the trapping of ammonia ylide by isatins could happen. A convenient method for synthesizing poly-functional primary amines bearing 3-substituted 3-hydroxyoxindoles moiety can therefore be developed.



Scheme 1 Concerted or ylide intermediate mechanism for N-H insertions of ammonia

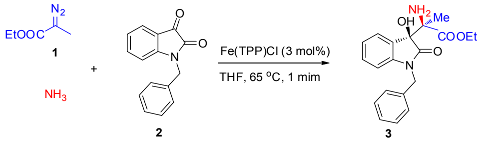
We initiated our study from the trapping of ammonia ylide by N-benzyl isatin. Under room temperature, after the addition of EDA to N-benzyl isatin dissolved in ammonia saturated THF in the presence of 1 mol% Fe(TPP)Cl (TPP = meso-tetrakisphenylporphyrinato dianion), immediately gas emission was detected, but the attempt to separate the unprotected β-hydroxy α-amino ester was unsuccessful. The derivation of the supposed product with $CSCl_2$ under basic conditions afforded spirooxindoles with 50:50 dr value in 52% yield (Scheme 2), indicating that the trapping process was successful.



Scheme 2 Derivatisation of supposed three-component reaction product

The substrate scope is not limited to EDA. Extension of the diazocompound to α-methyl diazoester (**1**) gave the unprotected α-amino ester in 60% yield with a 60:40 dr. More importantly, the chemoselectivity for producing the primary amines was excellent. No secondary or tertiary amine byproduct was detected, hence no evidence of over-alkylation. Optimization of the reaction conditions was operated carefully. Catalysts such as Co(TPP), $Rh_2(OAc)_4$ and $Cu(OTf)_2$ which are efficient metal catalysts for carbene transfer reactions failed to decompose the diazocompounds in the presence of ammonia. Elevated loading of iron catalyst led to increased yield with unchanged selectivity. THF turned out to be the best solvent after the screening of different solvents (Table 1, Entry 5).

Table 1 Optimization of the reaction conditions[a]

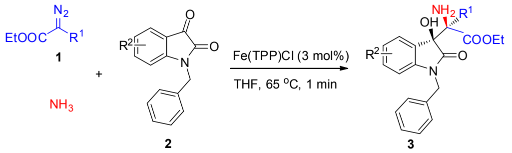


Entry	Solvent	Catalyst	Loading (x mol)	Yield[b] (%)	Dr[c] (*syn*-3:*anti*-3)
1	THF	$Rh_2(OAc)_4$	1	NR*	ND*
2	THF	Co(TPP)	1	NR	ND
3	THF	$Cu(OTf)_2$	1	NR	ND
4	THF	Fe(TPP)Cl	1	60	60:40
5	**THF**	**Fe(TPP)Cl**	**3**	**72**	**60:40**
6	Toluene	Fe(TPP)Cl	3	56	58:42
7	DMF	Fe(TPP)Cl	3	42	55:45
8	Acetone	Fe(TPP)Cl	3	trace	ND
9	dioxane	Fe(TPP)Cl	3	55	60:40
10	EA	Fe(TPP)Cl	3	17	62:38
11	$CHCl_3$	Fe(TPP)Cl	3	53	59:41
12	CH_2Cl_2	Fe(TPP)Cl	3	NR	ND

[a]reaction conditions: all reactions were conducted in 0.2 mmol scale of **2**, **1**:**2** = 1.5:1. See ESI† for experimental details. [b]Isolated yield after column chromatography. [c]Determined by crude ^1H NMR. *NR- No reaction. * ND- Not determined

We then examined the scope of other alkyl diazocompounds (Table 2). With the optimized conditions in hand, we found that ethyl, propargyl, and allyl substituted diazo compounds afforded the desired three component products (**3c**-**3e**) in good yields and similar diastereoselectivities. Allyl and propargyl groups often suffer from cyclopropanation or cyclopropenation in metal catalyzed carbene transfer reactions, but it is not the case under iron porphyrin catalysis. Benzyl diazoacetates and aryl diazoacetates did not decompose under reaction conditions probably due to steric effect. We further evaluated a wide range of substituted isatins. The scope with respect to R^2 was good, including substitutions at 4,5,6,7-positions of isatin substrates (**3f**-**3k**). Isatin derivatives bearing both electron-donating and –withdrawing groups afforded the corresponding products in good yields.

Table 2 Scope of the three-component reaction[a]



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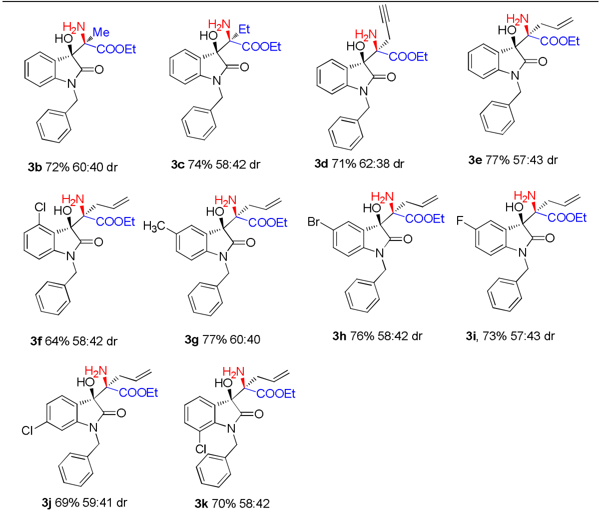
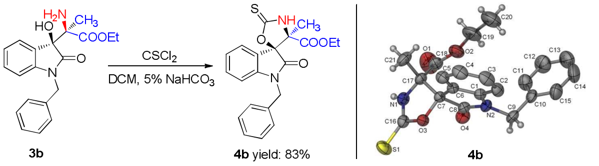


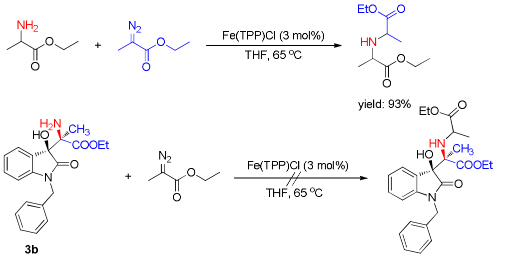
[a] All reactions were conducted in 0.2 mmol scale of **2**, **1**:**2** = 1.5:1. See ESI† for experimental details. Yields were detected after column chromatography. Dr values were determined by crude ^{1}H NMR after a short pad of flash chromatography.

Cyclization of **3b** with thiophosgen proceeded smoothly, providing a convenient method for synthesizing 3-spirooxindoles14 (Scheme 3). The relative stereochemistry of the products was assigned as *syn* according to the single-crystal X-ray diffraction of **4b**.



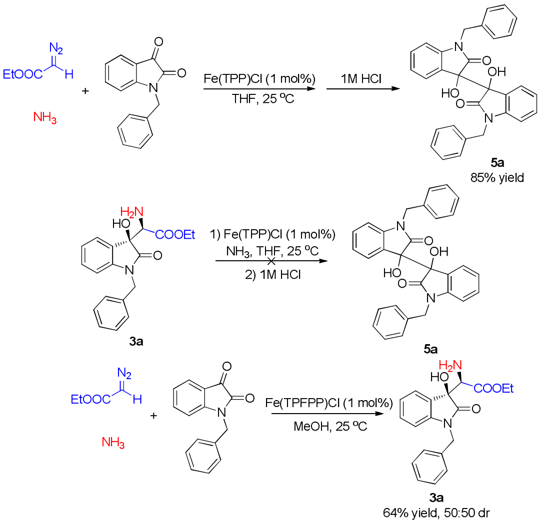
Scheme 3 Derivatisation of **3b** and relative stereochemistry assignment

We were more interested in the chemoselectivity for producing primary amines over the over-alkylation byproducts. To gain insight into this unique chemoselectivity of the reaction, control experiments were undertaken (Scheme 4). Ethyl 2-aminopropanoate reacted with EDP under reaction conditions in 93% yield. However, no insertion product of **3b** with EDP was detected under the same reaction conditions. We reasoned that, the steric effects of the products controlled the chemoselectivity of the reaction (steric hindered amines showcased more difficulty in forming ylide intermediates).



Scheme 4 Control experiments

We were curious about why compound **3a** (derived from EDA) failed to be isolated? The reaction of EDA, ammonia and N-benzylisatin was further studied. Interestingly, after the completion of the trapping reaction, acidification of the mixture afforded isatide (**5a**) immediately (see the ESI†). To verify the stability of **3a** under reaction conditions, we made **3a** according to an alternative method reported in literature.[15] It was found that **3a** is very stable under the three-component reaction conditions, indicating that the cyclization product **4a** was not derived from **3a**. To our delight, when protic solvent such as methanol was used as the solvent, **3a** was isolated in 64% yield and 50:50 dr under catalysis of Fe(TPFPP)Cl[16] (TPFPP = meso-tetrakis pentafluorophenylporphyrinato dianion).



Scheme 5 Mechanistic investigation into the reaction of EDA, ammonia and N-benzylisatin

As a result of these studies, we propose **III** as the reaction intermediate of the reaction among EDA, ammonia and N-benzylisatin in THF. The formation of **4a** suggested the successful trapping process in THF, and the three-component product scaffold was formed. Considering the fact that the basicity of ammonia disfavors proton transfer, resultantly, proton transfer might be inhibited by ammonia. A DFT calculation was undertaken to determine if the proton in **III** was transferred to ammonia. The ΔG of the process was found to be 12.4 kcal/mol, suggesting that intermediate **III** is favored in the proton transfer reaction. Alkyl substituted diazocompounds disfavor the formation of **III** in THF. This might be attributed to a destabilizing steric interaction between steric hindered alkyl groups and the adjacent ammonium cation groups.

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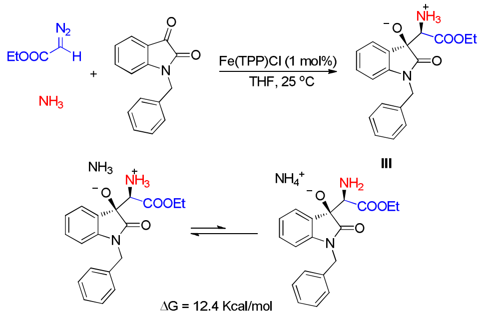
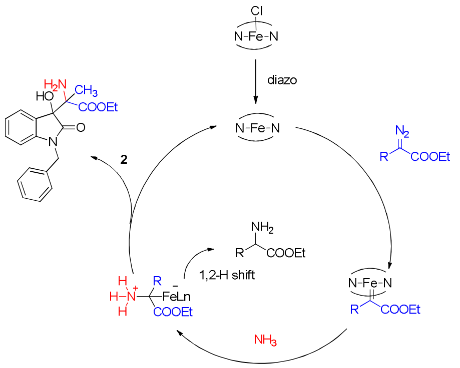


Scheme 6 Proposed intermediate of the reaction of EDA, ammonia and N-benzylisatin in THF

A plausible mechanism was proposed (Scheme 7). At the beginning, Fe(TPP)Cl was reduced to Fe(TPP) by diazo compound,[17] followed by the treatment of diazocompound to produce iron carbene. The carbene complex then suffered from a nucleophilic attack of ammonia to produce ylide intermediate. Trapping of this reactive species afforded the target multi-functional unprotected primary amine.



Scheme 7 Proposed mechanism

In summary, we have developed an efficient process of construction of poly-functional primary amines, which proceeds via trapping of ammonium ylides generated from diazocompounds and ammonia. The reaction works efficiently with excellent chemoselectivity for producing unprotected amines under mild reaction conditions. We expect this transformation will be of use to synthesize poly-functional primary amines.

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