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Iron(III) Corroles and Porphyrins as Superior Catalysts for the Reactions of Diazoacetates with Nitrogen- or Sulfur-Containing Nucleophilic Substrates: Synthetic Uses and Mechanistic Insights

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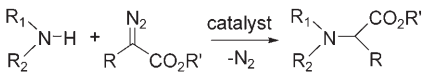
Abstract: A thorough mechanistic investigation has been performed on the reactions of primary and secondary amines with diazoacetates, which proceed uniquely quickly and efficiently when catalyzed by iron(III) corroles and porphyrins. Two major differences in relation to other metal-based catalysts are that the iron complexes are not poisoned by excess amine and that metal–carbene intermediates are apparently not involved in the reaction pathway. The results instead point towards nitrogen ylide intermediates formed by nucleophilic attack of the amines on diazoacetate-coordinated iron complexes. Nitrogen ylides are also formed when allyl- and propargyl-substituted tertiary amines react with diazoacetates, a scenario that smoothly leads to 2,3-rearrangement reaction products with catalytic amounts of the iron(III) complexes. Similar findings regarding the superiority of the iron(III) complexes (in terms of catalyst loading, chemical yields, and reaction conditions) were obtained with thiols (S–H insertion) and sulfides (2,3-rearrangement reactions), which suggest similar mechanisms operate in these cases.

Keywords: catalysis · corroles · iron · porphyrinoids · reaction mechanisms

Introduction

The catalytic transfer of a carbene moiety from diazo compounds to organic substrates is a very powerful tool in organic synthesis used for the production of numerous compounds.[1] One example is the use of quite stable α-diazo esters (ethyl diazoacetate (EDA) is commercially available) for the insertion of $CRCO_2R'$ into X–H bonds, in which X = R_3C, R_2N, RO, or RS.[2] The N–H insertion reaction is particularly versatile and leads to the synthesis of α-amino esters, dipeptides, nitrogen-containing heterocycles, and other protected α-amino acid derivatives that can be used as precursors to natural products (Scheme 1).[3]

The first reported catalysts for N–H insertion reactions were copper bronze[4] and CuCN.[5] These catalysts were overshadowed by $[Rh_2(OAc)_4]$, developed as a catalyst in the 1970s by Paulissen et al.[6] However, both the earlier and the more recently developed copper-, silver-, gold-, and ruthenium-based catalysts are usually required in amounts of 1 to 10 mol% and suffer from one or more of the following limitations: gradual addition of the diazo compound to avoid dimerization byproducts, gradual addition of the amine to avoid catalyst poisoning, long reaction times, and low-to-moderate chemical yields.[2,7–9]



Scheme 1. Insertion of carbene moieties derived from α-diazoacetates into amine N–H bonds.

Decade-long efforts were devoted to the development of catalysts for enantioselective metal–carbene insertion into N–H bonds. Chiral auxiliaries served quite well for inducing rhodium-catalyzed asymmetric intramolecular N–H insertion (optically active proline derivatives were obtained),[10] but their extension to intermolecular reactions met with very limited success. Twenty one different chiral Rh^{II} catalysts were examined for that purpose in one reaction, but the highest enantiomeric excess (*ee*) obtained was 9%. Even the diastereoselectivity appeared to be low because the use of chiral amino acid derivatives as substrates resulted in diastereomeric excesses (*de*) of only up to 37%.[11]

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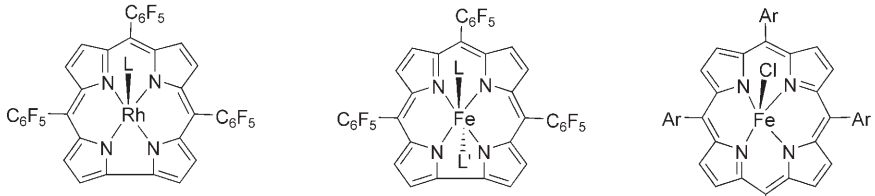
Better results (up to 45% *ee*) were reported by Garcia et al. who developed an asymmetric intramolecular N–H insertion based on chiral Rh^{II} catalysts.[12] In a more recent effort, Jørgensen and co-workers obtained 27% *ee* with Cu^{I} and 48% *ee* with an Ag^{I}-based catalyst in the intermolecular N–H insertion of diazoacetates into substituted anilines.[7b] The only really successful example was reported last year by Zhou and co-workers: copper complexes of chiral spiro bisoxazolines catalyzed the highly enantioselective intermolecular insertion of ethyl diazopropionate (EDP) into anilines.[13]



Scheme 2. Corrole- and porphyrin-based catalysts used in the investigations.

The mechanism of metal–carbene insertion reactions into C–H bonds has been extensively explored with rhodium acetate as a catalyst and is generally accepted to be a concerted process that proceeds through either one of the transition states proposed by Doyle, Taber, and Nakamura and their co-workers.[2,14] A concerted mechanism for silver- and copper-based catalysts postulated from computational models was also suggested by Pérez and co-workers.[15] There have also been several mechanistic investigations into O–H insertion reactions in which both concerted and stepwise pathways were considered.[2,16] A Hammett plot analysis led Wang and co-workers to conclude the reaction proceeded through a concerted transition state,[17] whereas Hu and co-workers found very strong evidence in favor of a stepwise reaction pathway.[18] Aldehydes and imines were used as electrophilic trapping agents of the proposed reaction intermediate, an oxonium ylide formed by the nucleophilic addition of the alcohol to the metal–carbene. This scenario is of synthetic utility for three-component reactions of aryl diazoacetates, alcohols, aldehydes, and imines.

One shortcoming, which apparently hampers the development of catalysts for enantioselective insertion of diazoacetates into N–H bonds, is that surprisingly little is known about the mechanistic aspects of this reaction. Stepwise reaction sequences involving ylides and concerted three- or four-centered transition states have been proposed in the literature.[1a,2] Investigations focusing on the stereochemical outcome of the N–H insertion process led Davis et al. to propose a concerted mechanism,[10] whereas evidence for a stepwise mechanism involving a nitrogen ylide came from investigations of three-component experiments with imines or azodicarboxylates as electrophiles to trap this intermediate.[1b,19] Importantly, practically all discussions about metal-catalyzed reactions of diazoalkanes with compounds that contain CH, OH, or NH bonds assumed that a metal–carbene (M=CRR′, in which M = transition metal, R = H, and R′ = CO_2Et in the case of EDA) is formed (usually in the rate-limiting step) prior to interaction with the substrate.

As part of the large developments in corrole-based applications,[20] we recently reported that the iron(III) complexes of triarylcorroles and tetraarylporphyrins (Scheme 2) display unique features with regards to the insertion of diazoacetates into the NH bonds of anilines (Scheme 1). Full and very fast conversion was obtained by simultaneous addition of equimolar amounts of the substrates to the catalyst (0.1 mol%) and the selectivity towards activation of the N–H bond (vs. C=C, CH, and OH bonds) was absolute.[21] We also reported the success of the same catalysts in a much more challenging reaction, the activation of the N–H bond of ammonia (Scheme 1, $R_1 = R_2 = H$, R = H or CH^3). In fact, the iron complexes appeared to be the first catalysts capable of inducing the formation of nitrogen-free glycine and alanine esters from ammonia and diazo esters.[22] We now report a full study of these intriguingly facile transformations that focused on the following aspects: Identification of the key reaction intermediate involved in the reactions, and more importantly, the mechanism of its formation; catalysis in aqueous solutions with the aid of both biological and biomimetic catalysts; extension of the synthetic utility of the reaction to nonaromatic amines, carbon-substituted diazoacetates, and thiols; and the design of very efficient reaction conditions for obtaining the 2,3-sigmatropic rearrangement products from diazoacetates and tertiary amines or sulfides. All of these reactions were found to proceed faster and with lower catalyst loadings than in previously reported systems. We also show that, in contrast with the proposals for other catalysts, the iron-catalyzed reactions apparently do not proceed through metal–carbene intermediates.

Results and Discussion

Insertion of the carbene moiety from EDA into amine N–H bonds: The data presented in Table 1 compares the potency of iron corroles/porphyrins with other metal complexes in the catalysis of the reaction of aniline with EDA. The iron(III) complexes are clearly unmatched by any other catalyst in terms of the following parameters: catalyst loading (0.1 mol%), reaction time (min vs. h), reaction conditions (aerobic and reagents added as a single portion), and chemical yields of isolated products.

More detailed information is provided in Table 2, which summarizes the results obtained for the reactions of many aniline derivatives with EDA (Scheme 3) utilizing specific iron(III) corroles and porphyrins as catalysts.

Table 1. Metal-catalyzed reactions of aniline with EDA (at room temperature unless specified differently).

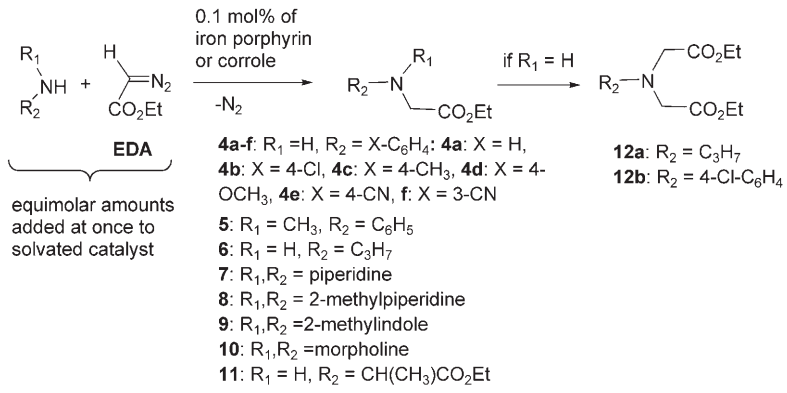
Metal catalyst	Aniline/EDA/catalyst	Reaction conditions	Yield [%]	Time	Ref.
Fe^{III} corrole or porphyrin	1000:1000:1	aerobic, added in one portion	>92[a]	<3 min	[b]
$[Rh_2(OAc)_4]$	1000:1000:1	aerobic, added in one portion	<5[c]	1 h	[b]
[Fe(salen)]	1000:1000:1	aerobic, added in one portion	0	24 h	[b]
Ru corrole	1000:1000:1	aerobic, added in one portion	0	24 h	[b]
$[Rh_2(OAc)_4]$	no data	80 °C	no data		[6]
Cu^{I}	50:50:1	aerobic, syringe pump	8[a]	20 h	[7a]
$[Cu(acac)_2]$	20:20:1	anaerobic, ionic liquids, slow addition of EDA	8[a]	20 h	[23b]
Ag^{I}	10:10:1 (with EDP)	anaerobic, dropwise addition	8[a]	20 h	[7b]
Au^{I}	5500:25:1	50% aniline in CH_2Cl_2	>99[d]	24 h	[6b]
Ru^{II} porphyrin	100:150:1 (with 4-Me-aniline)	anaerobic, slow addition of both reagents	64[c]	>5.5 h	[8a]
Re^{VII} (MTO)	270:250:1	anaerobic, aniline as solvent, slow addition of EDA	89	1 h	[23b]

[a] Isolated yield. [b] This work. [c] Yield determined by in situ NMR spectroscopy. [d] Yield determined by in situ GC.

Table 2. Metal-catalyzed reactions of ring-substituted anilines with EDA.[a]

Entry	Catalyst	Substrate	Time	Yield [%]	Product
1	**2a**	4-Cl-$C_6H_4NH_2$	3 min	92	**4b**
2	**2a**	3-CN-$C_6H_4NH_2$	5 min	94	**4f**
3	**2b**	4-Cl-$C_6H_4NH_2$	3 min	92	**4b**
4	**2b**	$C_6H_4NH_2$	3 min	93	**4a**
5	**2b**	4-MeO-$C_6H_4NH_2$	2 min	95	**4d**
6	**2b**	4-Me-$C_6H_4NH_2$	2 min	90	**4c**
7	**2b**	*N*-methylaniline	2 min	91	**5**
8	**2b**[b]	$C_6H_4NH_2$	6 min	93	**4a**
9	**2c**	4-Cl-$C_6H_4NH_2$	3 min	90	**4b**
10	**3a**	4-Cl-$C_6H_4NH_2$	3 min	94	**4b**
11	**3a**	4-CN-$C_6H_4NH_2$	2 min	97	**4e**
12	**3a**	*N*-methylaniline	2 min	96	**5**
13	**3b**	4-Cl-$C_6H_4NH_2$	3 min	95	**4b**
14	**2a**[c]	**4b**	15 min	91	**12b**
15	**3a**[c]	**4b**	3 min	92	**12b**
16	$[Rh_2(OAc)_4]$	4-Cl-$C_6H_4NH_2$	1 h (24 h)	<5 (25)	**4b**
17	**1a**[d]	4-Cl-$C_6H_4NH_2$	1 h	92	**4b**
18	[Fe(salen)Cl][d]	4-Cl-$C_6H_4NH_2$	24 h	no reaction[e]	–
19	[Ru(tpfc)NO][d]	4-Cl-$C_6H_4NH_2$	24 h	no reaction	–

[a] Catalyst/EDA/substrate 1:1000:1000 with 0.3–0.75 mM catalyst at room temperature in diethyl ether. EDA and the substrate were added together in one portion and the reported yields are of isolated products. [b] Catalyst/EDA/substrate 1:1000:500. [c] Catalyst/EDA/substrate 1:100:100. [d] Catalyst/EDA/substrate 1:50:100. [e] There was also no reaction when this reaction was performed in methanol in the presence of iron powder.



Scheme 3. Catalytic insertion of the carbene moiety derived from EDA into amine N–H bonds.

Despite the very simple reaction conditions (both reagents added as a single portion to an open-to-air solution of catalyst in nonpurified solvent) and the use of only 0.1 mol% of catalyst, *N*-arylglycine esters **4a–f** were isolated in very high yields in all cases. The reactions were also not limited to primary amines. The *N*-(4-chlorophenyl)glycine ester (**4b**, obtained from 4-chloroaniline and EDA) was efficiently converted into bis-substituted *N*,*N*-bis(4-chlorophenyl)glycine ester **12b** (entries 14 and 15) and *N*-methylaniline also provided the expected product **5** (entries 7 and 12). None of the other complexes, which includes the most commonly used $[Rh_2(OAc)_4]$ (entry 16), catalyzed the reactions to any significant extent when applied under the reaction conditions used with the iron(III) corroles and porphyrins. With one order of magnitude lower amounts of aniline and 2 mol% rather than 0.1 mol% of catalyst, rhodium corrole **1a** was capable of catalyzing the N–H insertion reaction. The expected product was obtained within one hour with high selectivity (only traces of diethyl maleate and diethyl fumarate were obtained, entry 17). This demonstrates that the rhodium corrole is capable of catalyzing the reaction, but that only quite small amounts of (the not very basic) aniline can be used; therefore, catalyst **1a** is not suitable for synthetic use. Iron salen and ruthenium corrole did not catalyze the reaction even under these less demanding reaction conditions (entries 18 and 19). The superiority of the iron complexes as catalysts for NH insertion reactions is very different from the results obtained for reactions between EDA and ole-

fins or alcohols.[21,23] In these reactions the iron complexes are actually much poorer catalysts than $[Rh_2(OAc)_4]$, rhodium corroles, and ruthenium porphyrins.

The poor performance of $[Rh_2(OAc)_4]$ in the reaction with amines reflects catalyst poisoning by the substrate,[2] and a similar effect apparently explains the inefficiency of **1a**, [Ru(tpfc)(NO)] (tpfc = the 5,10,15-trispentafluorophenylcorrole trianion), and ruthenium porphyrins. Evidence to prove that coordination of aniline to rhodium (and subsequent catalyst poisoning) occurs is given in Figure 1. Addition of 4-chloroaniline to a solution of the red-colored complex **1a** induced a color change to green and the electronic spectrum changed to one characteristic of bis-amine-coordinated corroles.[24] Similarly, the color of the reaction mixture immediately changed from brown to green when the substrates were added to the solvated catalyst in reactions in which the ruthenium corrole was used as the catalyst (entry 17). In contrast, the electronic spectra of the iron(III) complexes were not affected by aniline and the same conclusion regarding noncoordination of the two was reached from NMR spectroscopy investigations. The characteristic β-pyrrole resonance at $\delta = +80$ ppm for the five-coordinated d^5 high-spin complex **2b** (6 mM in $CDCl_3$) was not affected by a 50 molar excess of aniline, which is in contradiction with the formation of a complex with a different coordination environment or oxidation state.[25]

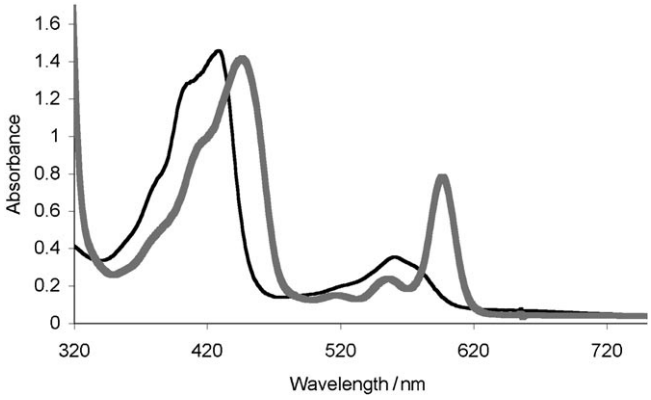


Figure 1. Electronic spectrum of [Rh(tpfc)(PPh_3)] (**1a**) in CH_2Cl_2 (black) and in the presence of 4-chloroaniline (gray).

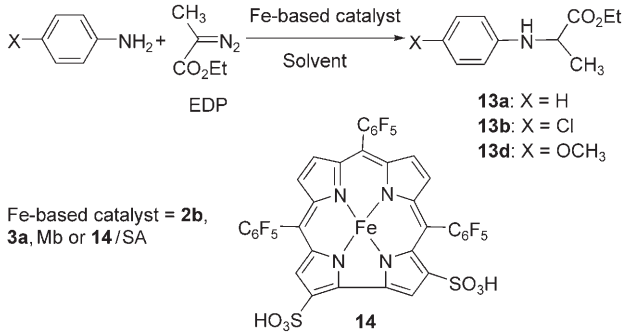
The apparent nonpoisoning of the iron corroles and porphyrins by aniline derivatives suggests that much more coordinating amines may also be used in this system (Scheme 3, Table 3). Piperidine, 2-methylpiperidine, and 2-methylindoline were indeed functionalized under the same reaction conditions as those used for anilines to give the corresponding products in isolated yields of 97, 94, and 93%. The reactions were very fast and were completed within a few minutes (entries 1–3) with 0.1 mol% of **3a** as the catalyst. The use of 1 mol% of the catalyst with morpholine resulted in the formation of the desired product and the reaction proceeded much faster with the porphyrins than with the corrole (entries 4–6). The use of porphyrin-based catalysts **3a** and **3b** to activate the primary amines alanine ethyl ester and propylamine was also fruitful and the expected products were obtained in high overall yields (entries 7–9). The bis-activated product **12a** (a tertiary amine) was the main product obtained with propylamine as the substrate even when the amine/EDA ratio was 1:1. This indicates that, in this case, monosubstituted product **6** (a secondary amine) undergoes insertion faster than the original substrate, the primary propylamine.

Table 3. Metal-catalyzed reactions of nonaromatic amines with EDA.[a]

Entry	Catalyst	Substrate	Time	Yield [%]	product
1	**3a**[b]	piperidine	7 min	97	**7**
2	**3a**[b]	2-methylpiperidine	5 min	94[c]	**8**
3	**3a**[b]	2-methylindoline	5 min	93	**9**
4	**2b**[d]	morpholine	4 h	89[c]	**10**
5	**3a**[d]	morpholine	5 min	96	**10**
6	**3b**[d]	morpholine	5 min	95	**10**
7	**3b**[d]	propylamine	15 min	70	**12a**
				30	**6**
8	**3a**[e]	propylamine	15 min	95	**12a**
9	**3a**[f]	alanine ethyl ester	5 min	89	**11**

[a] EDA and the substrate were added together in one portion into 0.5 mL of catalyst dissolved in diethyl ether and the reported yields are of isolated products. [c] In CH_2Cl_2. [b] Catalyst/EDA/substrate 1:1000:1000. [d] Catalyst/EDA/substrate 1:50:50. [e] Catalyst/EDA/substrate 1:1000:500. [f] Catalyst/EDA/substrate 1:100:100.

Use of ethyl diazopropionate and aqueous solutions for possible enantioselective N–H activation: One extension of the above results was the use of EDP instead of EDA, the goal being to develop routes to nonracemic alanine derivatives (Scheme 4).[13] The results presented in Table 4 show that the iron complexes are good catalysts for the transformation of anilines into expected products **13a–d** in high yields. Reactions in organic solvents were completed within minutes with the iron porphyrins and corroles (entries 1–6) compared with hours with the rhodium corroles (entries 7 and 8).



Scheme 4. Alanine derivatives from the catalytic insertion of the carbene moiety derived from EDP into anilines. Mb = myoglobin, SA = serum albumin.

The goal of obtaining enantiomerically enriched products could have been addressed by either preparing iron com-

Table 4. Metal-catalyzed reactions of anilines with EDP.[a]

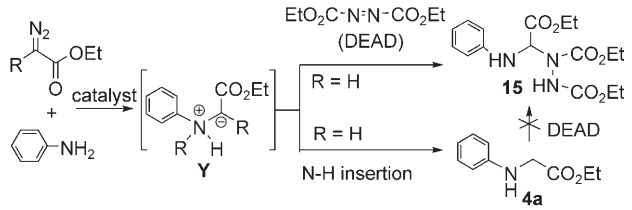
Entry	Catalyst	Substrate	Time	T [°C]	Yield [%]	Solvent
1[a]	**3a**	4-Cl-$C_6H_4NH_2$	3 min	25	91	Et_2O
2[a]	**3a**	$C_6H_4NH_2$	4 min	25	93	Et_2O
3[a]	**3a**	$C_6H_4NH_2$	2 min	25	93	CH_2Cl_2
4[a]	**3b**	$C_6H_4NH_2$	3 min	25	89	CH_2Cl_2
5[a]	**2b**	4-Cl-$C_6H_4NH_2$	30 min	25	92	Et_2O
6[a]	**2b**	$C_6H_4NH_2$	30 min	25	94	Et_2O
7[a]	**1a**	4-Cl-$C_6H_4NH_2$	10 h	25	86	CH_2Cl_2
8[a]	**1b**	4-Cl-$C_6H_4NH_2$	10 h	25	89	CH_2Cl_2
9[b]	Mb	$C_6H_4NH_2$	15 min	65	87	THF/ H_2O
10[b]	Mb	4-CH_3O-$C_6H_4NH_2$	15 min	65	85	THF/ H_2O
11[c]	**14**/BSA	$C_6H_4NH_2$	5 h	25	85	H_2O[d]
12[c]	**14**/HSA	$C_6H_4NH_2$	5 h	25	85	H_2O[d]
13[c]	**14**/RSA	$C_6H_4NH_2$	5 h	25	n.d.	H_2O[d]
14[c]	**14**/PSA	$C_6H_4NH_2$	5 h	25	n.d.	H_2O[d]
15[c]	**14**/SSA	$C_6H_4NH_2$	5 h	25	n.d.	H_2O[d]
16[c]	**14**/BSA	$C_6H_4NH_2$	24 h	4	n.d.	H_2O[d]
17[c]	**14**/BSA	$C_6H_4NH_2$	5 h	25	n.d.	H_2O[e]
18[f]	**14**/BSA	$C_6H_4NH_2$	5 h	25	n.d.	H_2O[g]
19[h]	**14**/BSA	$C_6H_4NH_2$	1 h	25	n.d.	H_2O[i]

[a] Catalyst/EDP/substrate 1:100:100 with 0.4–0.5 mM catalyst in 2 mL of solvent at RT. [b] Mb (5 mg), EDP (0.156 mmol), and amine (0.156 mmol) in solutions of phosphate buffer (pH 7)/10% THF (1.5 mL). [c] **14** (0.2 mM)/albumin/aniline/EDP 1:1.5:120:120 in phosphate buffer, n.d. = not precisely determined (>70 yield), BSA, HSA, RSA, PSA, and SSA = bovine, human, rat, pig, and sheep serum albumin, respectively. [d] pH 7. [e] pH 5.8. [f] Trizma buffer. [g] pH 9. [h] Acetate buffer. [i] pH 4.

plexes of chiral porphyrins/corroles or by using proteins that contain natural (heme) or synthetic iron complexes. The latter approach was adopted despite the fact that it requires work in aqueous solution, which is challenging for many reasons. The limitation unique to working with diazoacetates is that they might react with water, especially in the presence of metal complexes that might catalyze OH insertion reactions. Nevertheless, and in accordance with previous research that showed that the iron-based catalysts display a very high selectivity towards the activation of NH compared with OH bonds,[21] aniline did react with EDA at room temperature to form expected product **4a** when combined with 0.2 mM of the iron porphyrin containing protein myoglobin (Mb) in a solution of 10% THF/90% aqueous buffer. The same reaction, but with EDP instead of EDA (Scheme 4), worked well when performed at 65°C. Alanine-related products **13a** and **13d** were formed in very high yields and in very short reaction times (Table 4, entries 9 and 10), but as racemic mixtures (confirmed by HPLC on a chiral stationary phase). One obvious reason for the apparent failure of the protein with regard to chiral induction could be that it was denatured under the reactions conditions. This hypothesis was disproved by examination of the CD spectrum of Mb before and after reaction. As there was no change in the spectrum, the non-enantioselectivity of the process apparently does not reflect damage to the chirality-inducing host of the prosthetic iron porphyrin. Another attempt to obtain enantioselective reactions between aniline and EDP took advantage of the noncovalent conjugates formed between iron corrole **14** (Scheme 4) and serum albumins, a combination that has been successfully used for chiral induction in the sulfoxidation of thioanisoles by H_2O_2.[26] This approach led to high yields when performed at 25°C in aqueous solutions with 0.1 mol% of **14** (Table 4, entries 11–19). However, despite the milder reaction conditions, the use of five different albumins, and the various pH conditions applied, the alanine derivative was always obtained as a racemic mixture.

To conclude, we found that Mb and iron corrole conjugated albumins were capable of catalyzing the reactions of amines and diazo compounds in aqueous solutions. However, the reactions did not lead to enantiomerically enriched products. As previous success in similar approaches to a different reaction indicates that poor chiral induction by the protein is unlikely to be the reason for the failure in this case,[26] a mechanistic reason seemed more likely,[1b,19] and this aspect has been explored.

Mechanistic investigations addressing the formation of an ylide intermediate on the pathway to the final product: The most straightforward indication of the formation of ylide intermediates is the trapping of their nucleophilic moiety by electrophiles, of which diethyl azodicarboxylate (DEAD) is most commonly used (Scheme 5).[1b]

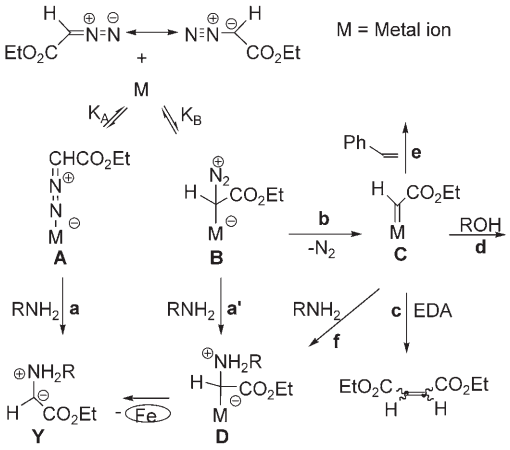


Scheme 5. Efficient trapping of ylide intermediate **Y** by DEAD.

To check for a possible ylide intermediate (**Y** in Scheme 5) in the current case, the reaction between aniline, EDA, and DEAD was tested with iron catalysts **2b**, **3a**, and **3b**. Equimolar amounts of the three reagents were mixed and added in a single portion to solutions of the catalyst at room temperature. The sole product in all cases was **15**, which was fully formed within minutes with iron porphyrins **3a** and **3b** and within hours with iron corrole **2b**. This is reminiscent of an investigation reported by Hu and co-workers who used rhodium acetate as the catalyst in CH_2Cl_2 at reflux under argon with dropwise addition of a dilute EDA solution over one hour.[1b] To verify the result, the isolated aniline glycine ester **4a** was allowed to interact with DEAD in the presence of **2b** (or **3a**). In this case, no reaction occurred even after 18 h. The most important outcome of this short investigation is that it readily explains the lack of chiral induction for the reaction of EDP when performed in the chiral environment provided by proteins (Scheme 4). Apparently, the lifetime of reaction intermediate **Y** (R = CH_3 in Scheme 5) is long enough (i.e., internal nitrogen-to-

carbon proton transfer is relatively slow) to allow full racemization of its negatively charged carbon atom.

Mechanistic investigations into the events leading to the formation of the ylide intermediate: In spite of many other investigations (mainly on rhodium-based catalysts), it may not be too surprising that either free (**Y**) or metal-bound (**D**) nitrogen ylide intermediates are also formed in the current system (Scheme 6). Many groups have in fact demonstrated

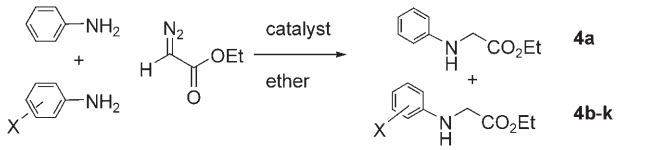


Scheme 6. Plausible steps leading to metal–carbene and nitrogen ylide intermediates in the metal-catalyzed reactions of amines with EDA.

the synthetic utility of three-component reactions that proceed via oxygen or nitrogen ylides of late transition metals formed in situ.[1b,18,19,27] There is also one report of a related case that involves iron porphyrin **3b** as the catalyst in a three-component reaction between aldehyde, phenyldiazomethane, and trimethyl phosphite.[28] In all of these investigations, the precursor of the ylide was proposed to be a metal–carbene formed by the interaction of the diazoalkane with the metal (**B**→**C** in Scheme 6). In fact, a metal–carbene complex was also the starting point in research that concluded that ylides are not formed on the pathway that leads to the final products.[10]

The fact that a metal–carbene intermediate is unlikely in the current case is illustrated by Scheme 6, which outlines the plausible elementary steps that lead from the reactants to the products. Computational data (mainly for M=Rh) suggests that the rate-limiting step is the formation of a carbene intermediate **C** from **B** with an activation energy of about 17 kcal mol^{-1} followed by its fast reaction with a substrate (EDA, alcohol, olefin, or amine by routes **c**–**f**, respectively, in Scheme 6).[14] The activation energy for forming the iron–carbene intermediate (M=Fe in Scheme 6) is most likely to be even larger than that for rhodium because the $[Rh_2(OAc)_4]$-catalyzed reaction between EDA and olefins is much faster than that catalyzed by iron(III) corroles and porphyrins.[21] On the other hand, the synthetic results obtained for the iron-catalyzed reactions between EDA and amines seem inconsistent with any proposal that involves the rate-limiting formation of a metal–carbene intermediate on the pathway to the ylide and the final products. In particular, it cannot explain why the reactions of amines are so much faster than those of other substrates. The most extreme example relates to iron(III) porphyrin **3b** in which there was no reaction when **3b** and EDA were present in solution for hours, but addition of amine caused the full release (about 900 catalytic turnovers) of nitrogen gas within seconds.[22] One could have considered the amines as potential reducing agents of **3b** to the more reactive [Fe^{II}(tpp)] (tpp=tetraphenylporphyrin), but it is known that most amines used in this work are not capable of doing so (as we have confirmed for aniline, see above).[29]

To shine some light on the mechanism of N-ylide formation, the electronic effect on the product-forming step in the iron corrole/porphyrin catalyzed N–H insertion reactions was deduced from intermolecular competition experiments between a series of ring-substituted aniline derivatives and limiting quantities of EDA (5 mol% relative to the amines; Scheme 7). N-Substituted glycine ethyl esters **4a**–**k** were the



Scheme 7. Competitive N–H insertion of EDA into phenyl-substituted anilines.

sole products, which allowed straightforward determination of the relative reactivities of the substituted anilines from the observed product ratios. The corresponding Hammett plot obtained with **2b** as the catalyst correlated much better with σ ($r^2=0.9449$ for all data and $r^2=0.9928$ without 4-CN-aniline) than with σ^+ ($r^2=0.8416$ for all data and $r^2=0.8879$ without 4-CN-aniline).[30] The same trend held for porphyrin complex **3a**, but both 3-CN- and 4-CN-substituted anilines did not fit well with the correlation. For a fair comparison between the results obtained for the corrole and the porphyrin iron complexes, the data for both 3-CN- and 4-CN-substituted anilines were ignored, which led to $\rho=-1.82$ ($r^2=0.9912$) for the former and $\rho=-1.53$ ($r^2=0.9741$) for the latter (Figure 2). The smaller value of ρ obtained with **3a** than with **2b** is consistent with the experimental observations that show the porphyrin complex reacts faster than the corrole. According to the Hammond principle, this should be reflected in an earlier transition state and a smaller ρ value. The more important information is that the ρ values of -1.82 and -1.53 are much smaller than those obtained for the protonation or acylation of anilines for which the reported ρ values are -2.89 and -3.21, respectively.[31] This implies that although the nucleophilicity of amines is important, it is apparently not the only factor contributing to their reactivity in the current system.

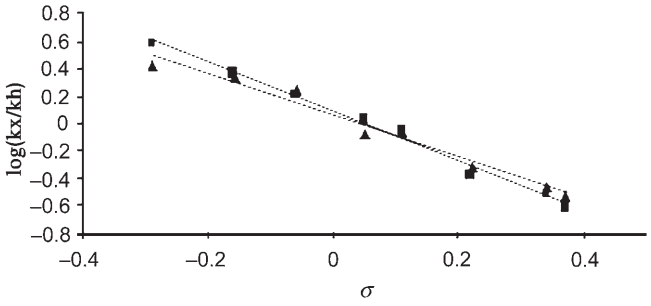
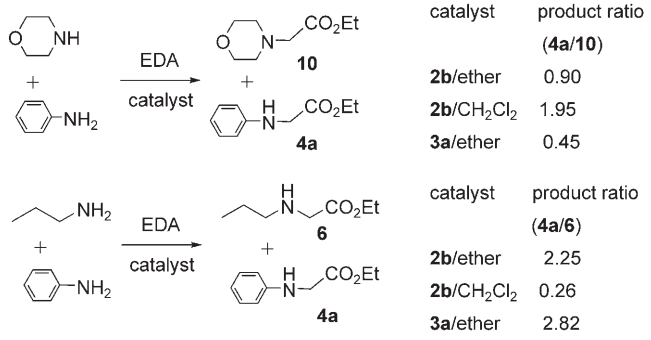


Figure 2. Hammett plots for the N–H insertion of EDA into *para*- and *meta*-substituted anilines, catalyzed by the iron corrole **2b** (squares) and the iron porphyrin **3a** (triangles).

As an additional probe for evaluating the importance of nucleophilicity, competition reactions between aniline/morpholine and aniline/propylamine were carried out with **2b** and **3a** as the catalysts (Scheme 8). Although the difference



catalyst	product ratio (**4a**/**10**)
2b/ether	0.90
2b/CH_2Cl_2	1.95
3a/ether	0.45

catalyst	product ratio (**4a**/**6**)
2b/ether	2.25
2b/CH_2Cl_2	0.26
3a/ether	2.82

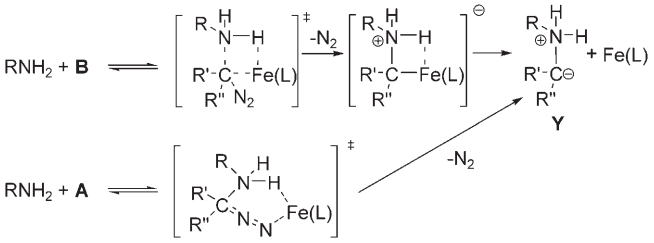
Scheme 8. Competition between aniline and morpholine (top) and propylamine (bottom).

in purely nucleophilic reactions is several orders of magnitude in favor of the nonaromatic amines,[32] the results from this work clearly show that there is no pronounced preference for the formation of products resulting from the reactions of morpholine or propylamine. In all cases the aniline-related products were also formed and sometimes even in preference. The approximately equal reactivity that aniline and nonaromatic amines displayed in the N–H insertion reaction adds confidence to the conclusions obtained from the Hammett plots, that is, that nucleophilicity is not the sole factor that affects the reactivity of amines towards diazo compounds under catalysis by iron corrole/porphyrins.

The main clues obtained from the current investigation with regards to the mechanism of the N–H insertion reactions are the unlikelihood of a metal–carbene intermediate and the limited importance of the nucleophilicity of the amine. In fact it is clear that the results cannot be explained by assuming that an intermediate is formed in an irreversible reaction (even if not rate limiting) between the metal and the diazo compound prior to the interaction with the amines. Accordingly, we have proposed alternative pathways for the formation of the ylide intermediates from the iron-catalyzed reaction of amines with EDA.

Proposed mechanism for the formation of nitrogen ylides: Analysis of the data accumulated so far is shown in Scheme 6 in which all steps except K_A and K_B may safely be assumed to be irreversible reactions. The initial step consists of the coordination of EDA to the metal center to form either **A** or **B**. Literature data may safely be used to suggest that the equilibrium leading to **A** is faster than that leading to **B**,[33] and that **B** is the precursor of metal–carbene intermediate **C**. In most cases, and in practically all mechanistic discussions in the literature, the formation of **C** en route to the final product is taken for granted. The various mechanistic proposals focus on the step that follows step **b**, that is, whether the attack on **C** is concerted (three- or four-centered, synchronous or not, etc.) or stepwise via ylide intermediates, such as **D** (and **Y**), with amines. However, the evidence against the formation of **C** in the reaction of EDA with amines is quite strong for the iron-based catalysts employed in the current investigations. There is no simple way to explain why the reaction of amines liberates nitrogen within seconds, whereas in the absence of amines there is either no reaction (with iron porphyrin catalyst **3b**) or a very slow one with EDA, alcohols, or olefins (routes **c**–**e**). Although one could argue that the metal coordination of amines possibly accelerates the formation of **C**, this option is particularly unlikely for the iron(III) porphyrins (and was ruled out for **3b**, see above), which are actually coordinatively saturated in intermediate **B** owing to the chloride ligand that is *trans* to the coordinated EDA. The absolute selectivity for amine-derived products found in the iron-catalyzed competition reactions of amines and olefins with EDA,[21] a feature not shared by rhodium-based catalysts, is a further indication that the two systems proceed through substantially different reaction intermediates.

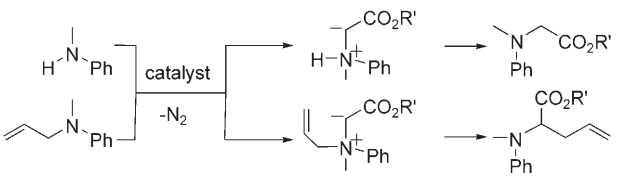
Based on all of the above, we propose that intermediate **C** is not formed in the reaction with amines, although this pathway is reasonable for other substrates. We note that even in reactions with somewhat nucleophilic alcohols (route **d** of Scheme 6), the overall reaction was very slow and route **c** was highly competitive (30% alcohol-derived product and 70% from EDA coupling).[21] The amines, however, apparently adopt a lower-energy pathway that is only available as a result of their greater nucleophilicity relative to other substrates. One alternative that is consistent with the very fast emission of nitrogen is the reaction of amines with EDA activated by either N- or C-coordination to the iron(III) corrole/porphyrin (Scheme 6; routes **a** and **a′** to intermediates **A** and **B**, respectively). Transition-state structures proposed for the processes that lead to the ylide intermediates obtained from either **A** or **B** are shown in Scheme 9. They are formed by nucleophilic attack of the amine on the N_2-carrying carbon atom of EDA with a partial hydride-like donation to the iron atom in either a four- or six-centered fashion. This explains the main findings obtained in the current investigation: the quite non-nucleophilic anilines react very quickly because they are relatively strong hydride donors, whereas the much more nucleophilic amines do not react faster than anilines because they are



Scheme 9. Possible transition states for the iron corrole/porphyrin catalyzed formation of ylide **Y** from the reactions of amines with EDA coordinated to the metal through its carbon (**B**) or nitrogen (**A**) atom (R′= H, R″= CO_2Et, L= corrole^{3-} or (chloro)porphyrin^{3-}).

weak hydride donors. The relatively low ρ value obtained for ring-substituted anilines is also consistent with the proposed transition states as the large negative value expected for nucleophilic attack is reduced by the contribution of a positive value expected for hydride transfer. In fact, this proposal might even explain the superiority of porphyrin relative to iron(III) corrole complexes. The reduction potential of the former is much less negative than that of the latter,[34] and accordingly, partial hydride transfer is more significant for the former.

A final test for probing the proposed mechanism was performed by comparing the reactivity of a secondary and a tertiary amine with practically identical nucleophilicity (Scheme 10). If partial hydride transfer was not important, the rate of formation of the corresponding ylides should be very similar. Separate experiments carried out with *N*-methylaniline and *N*-allyl-*N*-methylaniline showed that the reaction of the former was complete within seconds and with absolute selectivity for the N–H insertion product, whereas the reaction of the latter was much slower (about 30 min) and provided a mixture of ylide-derived and EDA-coupled products. Moreover, when a 1:1 solution of the two amines



Scheme 10. Reaction products obtained from ylides derived from secondary and tertiary amines.

was mixed with a limited amount of EDA (30 mol% relative to the amines), only the product derived from *N*-methylaniline was obtained. The advantage of this last result is that it rules out other possibilities regarding the effect of aniline, such as changing the reactivity of the metal because of coordination or reduction. All together, the competition between the two substrates is indicative of the importance of NH bonds for facilitating the formation of the ylide intermediates.

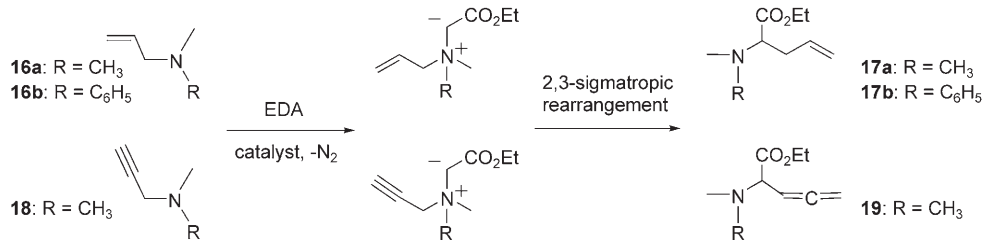
Synthetic use of ylides formed in the reactions of allyl- and propargyl-substituted tertiary amines with EDA: Both isolated and ylides formed in situ are of great synthetic value in many cases.[2,35] One use relevant to the current case is the in situ generation of ammonium ylides by metal-catalyzed reactions of diazo compounds with allylic or propargylic amines followed by 2,3-sigmatropic rearrangement to produce a new C–C bond (Scheme 11). Such reactions with cobalt-, copper-, rhodium-, and ruthenium-based catalysts have been previously reported,[2,36] but none with iron complexes. The strong indications for the highly facile formation of ammonium ylides in the reactions of NH-containing amines with EDA under catalysis by iron(III) complexes of porphyrins and corroles suggest that these complexes could have significant added value when used with tertiary amines.

The above hypothesis was indeed found to be valid (Scheme 11 and Table 5). The reaction between **16a** and EDA (1:1) in the presence of **2b** (0.5 mol%) proceeded very well. Full and very fast conversion into the 2,3-sigmatropic rearrangement product **17a** (entry 1, ≈500 catalytic turnovers, 96% isolated yield) was obtained within one minute during which time bubbles of nitrogen gas were

Table 5. Metal-catalyzed reactions of EDA with tertiary amines that are suitable for the formation of 2,3-sigmatropic rearrangement products.[a]

Entry	Catalyst	Substrate	Time	Yield [%]	Product
1	**3a**	**16a**	1 min	96	**17a**
2	**3b**	**16a**	24 h	92	**17a**
3	**2b**	**16a**[b]	24 h	91	**17a**
4	$[Rh_2(OAc)_4]$	**16a**	3 d	0	–
5	**3a**	**16b**[b]	30 min	52	**17b**
6	**3a**	**18**	1 min	96	**19**

[a] Catalyst/EDA/substrate 1:500:500 in CH_2Cl_2 (2 mL) at RT. EDA and the substrate were added together in one portion. Yields are of isolated products. [b] 1 mol% of catalyst.



Scheme 11. Products obtained from ammonium ylides formed in situ.

clearly observed. The same reaction with the more electron-rich porphyrin and corrole iron complexes also led to **17a** in high yield and selectivity, but in a longer time (entries 2 and 3). On the other hand, the reaction completely failed when $[Rh_2(OAc)_4]$ was used under otherwise identical reaction conditions (entry 4). This finding emphasizes the superiority of the iron-based catalysts because success with $[Rh_2(OAc)_4]$ and other previously reported catalysts required the slow addition of reagents, higher temperatures, or other limiting reaction conditions.[36] Even the much less nucleophilic *N*-allyl-*N*-methylaniline (**16b**) was converted into the expected product when catalyzed by **3a**, although the yield was lower and EDA coupling products were also obtained in this case (entry 5). The **3a**-catalyzed reaction of EDA with *N*,*N*-dimethylpropargylamine (**18**, entry 6) was as efficient in terms of reaction time as that of allylamine to give allenyl-substituted α-amino ester **19** in an isolated yield of 96%. A comparison with literature data for the same reaction with other catalysts revealed that the iron porphyrin is superior in all aspects of synthetic efficiency. These results are also fully consistent with the mechanistic aspects discussed earlier with regards to the very fast formation of ylide intermediates when catalyzed by the iron(III) corroles and porphyrins.

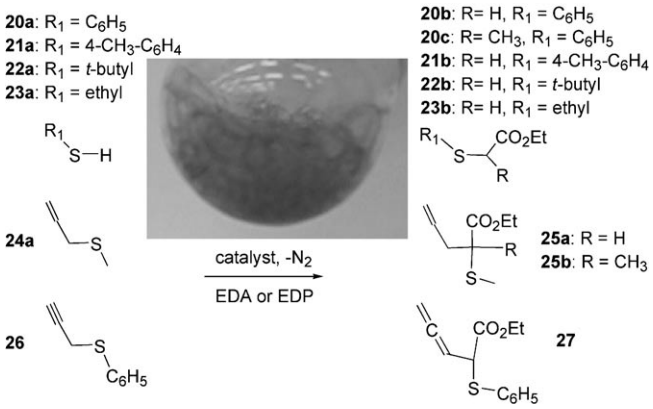
S–H insertion reactions and 2,3-sigmatropic rearrangements in ylides formed by the reactions of sulfides with diazoacetates: The above results suggested that the same iron-based catalysts could be highly useful for the formation of sulfur ylides in situ, which are of highly significant synthetic value.[37] The iron(III) corrole and porphyrin complexes were indeed excellent catalysts for the reactions of EDA/EDP with both thiols and sulfides. The results summarized in Table 6 (0.1 mol% catalyst) show that both thiophenols (entries 1–5) and nonaromatic thiols (entries 6 and 7) are converted very quickly and in very high yields into the expected S–H insertion products, α-thio ethyl ester derivatives (Scheme 12).[8,38] The reactions were very fast (see picture in Scheme 12), and even the less reactive EDP reacted quickly with thiophenol (entries 8 and 9) to provide **20c**.

Although a full mechanistic study was not performed for this reaction, it apparently proceeds in a similar manner to the reaction of amines. The reactivity of thiols and amines is also not very different because the reaction of EDA with equimolar amounts of thiophenol and aniline provided a mixture that contained products derived from both reagents. More important, the iron-catalyzed reactions of EDA with allyl- and propargyl-substituted sulfides were also very facile, leading to the expected products in very high yields within very short reaction times (entries 10–12). In a similar manner to the observations with amines, the iron(III) salen complex was not able to catalyze the reaction (entry 13). The other end of the reactivity scale is allyl methyl sulfide (**24a**; entry 14), which did undergo the corresponding reaction (to give **25b**) even with the much less reactive diazo compound EDP, a reaction that did not succeed with the analogous amine **16a**.

Table 6. Metal-catalyzed reactions of EDA/EDP with thiols and sulfides that are suitable for the formation of 2,3-sigmatropic rearrangement products.[a]

Entry	Catalyst	Substrates	Time	Yield [%]	Product
1	**3a**[b]	**20a**/EDA	<1 min	98	**20b**
2	**3b**[b]	**20a**/EDA	1 min	97	**20b**
3	**2a**[b]	**20a**/EDA	2 min	95	**20b**
4	**2b**[b]	**20a**/EDA	1 min	95	**20b**
5	**3a**[b]	**21a**/EDA	<1 min	96	**21b**
6	**3a**[b]	**22a**/EDA	<1 min	92	**22b**
7	**3a**[b]	**23a**/EDA	<1 min	93	**23b**
8	**3a**[c]	**20a**/EDP	2 min	89	**20c**
9	**2b**[c]	**20a**/EDP	2 min	90	**20c**
10	**3a**[d]	**24a**/EDA	1 min	95	**25a**
11	**3a**[d]	**26**/EDA	1 min	94	**27**
12	**2b**[d]	**24a**/EDA	20 min	93	**25a**
13	[Fe(salen)Cl][d]	**24a**/EDA	24 h	0	–
14	**3a**[c]	**24a**/EDP	1 h	91	**25b**

[a] All reactions were performed in CH_2Cl_2 (2 mL) at room temperature and EDA/EDP and the substrate were added together in one portion. Yields are of isolated products. [b] Catalyst/EDA/substrate 1:1000:1000. [c] Catalyst/EDP/substrate 1:100:100. [d] Catalyst/EDP/substrate 1:500:500.



Scheme 12. Reactions of diazoacetates with thiols and sulfides. The picture (demonstrating the intense nitrogen release) was taken 5 s after the addition of thiophenol and EDA to a solution of catalyst **3a**.

Conclusion

A detailed mechanistic investigation of the outstandingly high activity of corrole and porphyrin iron(III) complexes in the catalysis of NH-containing amines to amino acid esters by their reaction with diazoacetates has led to the following conclusions: Nitrogen ylides are key reaction intermediates, they are not produced by a reaction pathway that involves metal–carbenes, and both the nucleophilicity and hydride-transfer capability of primary and secondary amines are important aspects involved in the transition states leading to the ylides. The very fast formation of N-ylides was then applied to the reactions of tertiary amines that contain either allyl or propargyl substituents; 2,3-sigmatropic rearrangement products were formed more efficiently when catalyzed by the iron(III) complexes than with previously reported catalysts. Similar findings regarding the superiority of the iron complexes were obtained with thiols and sulfides, which

suggests the operation of similar mechanisms in these cases. Work on using the knowledge acquired in this study to solve the challenge of turning these reactions into enantioselective processes is under investigation.

Experimental Section

Chemicals: Standard reagents and solvents (including $[Rh_2(OAc)_4]$ and the iron porphyrins) were used as received from commercial sources without any further purification. EDP and *N*-allyl-*N*-methylaniline were synthesized according to published procedures.[39] The iron and rhodium corroles were prepared as described in previous publications.[40]

Quantitative reactions of amines with EDA: A solution of EDA and the substrate (1–1.5 mmol in 0.5 mL diethyl ether) was added in a single portion to a solution of the catalyst (1 mg, 1–1.5 μmol in 1.5 mL diethyl ether). The 4-Cl, 4-CN, and 3-CN-substituted aniline-derived products precipitated from the reaction mixture, whereas the products of the other amines were obtained by evaporating the solvent and by treatment of the solid material with cold diethyl ether. Reported yields are for isolated products (0.2–0.3 g); their purities were checked by GC analysis (>99% for all the products) and identities were confirmed by NMR spectroscopy analysis (see the Supporting Information) and comparison with previous reports of the same compounds.

Reaction between EDA and aniline, catalyzed by Mb: Mb (5 mg, 0.2 μmol), EDA (16.4 μL, 0.156 mmol), and aniline (14.2 μL, 0.156 mmol) were stirred in a solution of THF (10%)/aqueous phosphate buffer (pH 7, 1.5 mL) at room temperature until all of the EDA was consumed (5 min). Extraction with diethyl ether provided pure **4a** as a white solid (25 mg, 90% isolated yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.17 (t, 2H), 6.72 (t, 1H), 6.57 (d, 2H), 4.20 (q, J=7.2 Hz, 2H), 3.86 (s, 2H), 1.26 ppm (t, J=7.2 Hz, 3H).

Reaction between EDP and aniline, catalyzed by Mb: Mb (5 mg, 0.2 μmol), EDP (20 mg, 0.156 mmol), and aniline (14.2 μL, 0.156 mmol) were stirred in a solution of THF (10%)/aqueous phosphate buffer (pH 7, 1.5 mL) and placed in a heating bath at 65°C until all of the EDP was consumed (15 min). Extraction with diethyl ether provided pure **13a** as a colorless oil (25.6 mg, 87% isolated yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.16 (t, 2H), 6.73 (t, 1H), 6.59 (d, 2H), 4.17 (q, J=7.2 Hz, 2H), 4.09 (q, J=6.9 Hz, 1H), 1.45 (d, J=6.9 Hz, 3H), 1.23 ppm (t, J=7.2 Hz, 3H).

Reaction between EDP and aniline, catalyzed by 14/BSA: EDP (3 mg, 23.4 μmol) and aniline (2.1 μL, 23.4 μmol) were added to a small vessel. A solution of aqueous phosphate buffer (pH 7, 1 mL) containing iron corrole **14** (0.2 mg) and BSA (20 mg) was then added. The reaction mixture was stirred at room temperature until complete consumption of EDP was evident by TLC. The solution was extracted with diethyl ether to provide **13a** (3.84 mg, 85% yield). The extracts were concentrated under a stream of argon and the residue was diluted with HPLC-grade solvents (hexane/isopropanol 9:1) and analyzed by HPLC for possible enantiomeric enrichment. Similar results were obtained when this reaction was carried out with HSA, PSA, SSA, and RSA as the albumin source instead of BSA. No enantiomeric excess was observed in any of the reactions.

Procedure for reactions of tertiary amines/sulfides with EDA: A solution of EDA and the substrate in CH_2Cl_2 (0.5 mL, 500-fold excess, 0.5–0.7 mmol, of each relative to the catalyst) was added in a single portion to a solution of the catalyst (1 mg, 1–1.5 μmol in 1.5 mL CH_2Cl_2). Reported yields are for isolated products; their purities were checked by GC analysis (>99% for all the products) and identities were confirmed by NMR spectroscopy analysis and compared with previous reports of the same compounds. The colorless oil obtained from the reaction of *N*,*N*-dimethylallylamine with EDA was **17a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ= 5.72 (m, 1H), 5.04 (m, 2H), 4.14 (q, J=7.2 Hz, 2H), 3.14 (dd, J=8.3, 6.6 Hz, 1H), 2.41 (m, 2H), 2.35 (s, 6H), 1.24 ppm (t, J=7.2 Hz, 3H).

Procedure for the quantitative reaction of thiols with EDA (or EDP): A solution of EDA and the substrate in CH_2Cl_2 (0.5 mL, 1000-fold excess, 1–1.5 mmol, of each relative to the catalyst) was added in a single portion to a solution of the catalyst (1 mg, 1–1.5 μmol, in 1.5 mL CH_2Cl_2). Reported yields are for isolated products; their purities were checked by GC analysis (>99% for all the products) and identities were confirmed by NMR spectroscopy analysis and compared with previous reports of the same compounds. The colorless oil obtained from the reaction of thiophenol with EDA was **20b**. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.39 (m, 2H), 7.26 (m, 3H), 4.15 (q, J=7.2 Hz, 2H), 3.61 (s, 2H), 1.20 ppm (t, J= 7.2 Hz, 3H).

Acknowledgement

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