Iron Corroles and Porphyrins as Very Efficient and Highly Selective Catalysts for the Reactions of α-Diazo Esters with Amines

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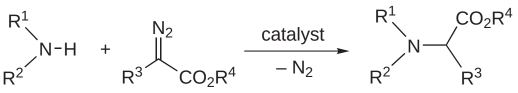
Abstract: Iron corroles and porphyrins catalyze the reactions of amines with ethyl diazoacetate extremely efficiently, leading to complete and rapid conversion into N-substituted glycine ethyl esters by simultaneous addition of the substrates to the catalysts. The selectivity toward activation of the NH bonds is remarkable and quite different from other catalysts.

Key words: diazo compounds, iron, corroles, porphyrins, catalysis

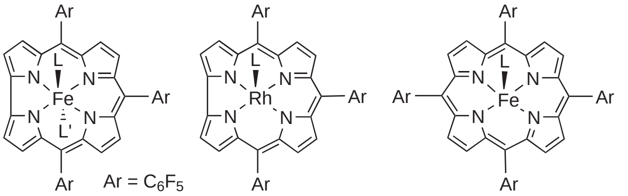
Metal-catalyzed transfer of carbene moieties from diazo compounds to organic substrates, generally considered to proceed via rate-limiting formation of metallocarbenoid intermediates, is most frequently applied to additions to double bonds.[1] The same synthetic methodology is also useful for the related insertion reactions into non-polar C–H and polar X–H bonds (X = R_2N, RO, RS) and this subject is of significant current interest.[1,2] One particularly important application is the synthesis of protected α-amino acid derivatives from α-diazo esters and amines (Scheme 1).



Scheme 1

The first reported catalysts for such NH insertion reactions were copper bronze and CuCN,[3,4] which were overshadowed by the 1970s work of Paulissen et al. with $Rh_2(OAc)_4$ as catalyst.[5] All of the recently introduced copper-, silver-, and ruthenium-based catalysts suffer from one or more of the following limitations: restricted reaction conditions (dropwise addition of the diazo compound), long reaction times, and low to moderate chemical yields.[2,6,7]

Recent research regarding the potential of metallocorroles in catalysis revealed that rhodium(III) complexes are particularly effective for cyclopropanation while iron complexes are versatile catalysts for epoxidation, cyclopropanation, and aziridination of C=C bonds, as well as C–H hydroxylation.[8,9] We found that the easily prepared iron corroles **1a** and **1b** (Figure 1)[10] catalyze the NH insertion of ethyl diazoacetate (EDA) into amines with high efficiency. Complete and rapid conversion into N-substituted glycine ethyl esters was obtained by adding EDA and the substrate to the catalyst simultaneously. The selectivity of the iron corroles toward NH insertion is remarkable and shared only with iron porphyrins.



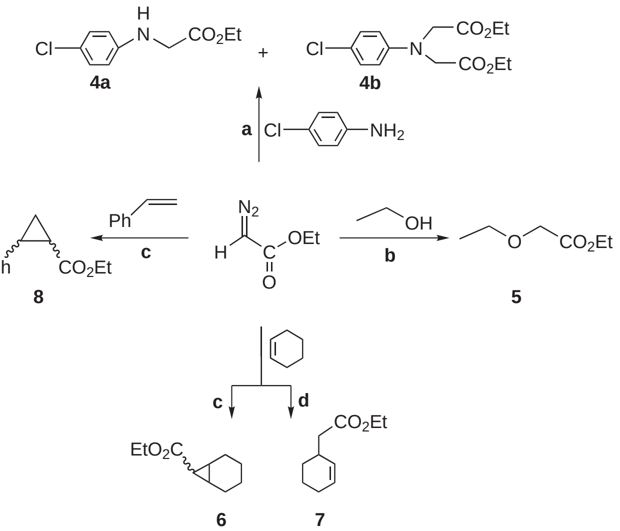
1a: L = Cl
1b: L = L' = OEt_2

2: L = PPh_3

3a: L = Cl, Ar = C_6F_5
3b: L = Cl, Ar = C_6H_5

Figure 1

The current investigations started by comparing rhodium acetate and the corrole complexes **1a** and **2** as catalysts for the following addition and insertion reactions of EDA (Scheme 2): (a) NH insertion, (b) OH insertion, (c) C=C addition, and (d) competitive C=C addition and CH insertion.



Scheme 2

The results obtained with the different catalysts under otherwise identical reaction conditions revealed remarkable differences (Table 1). Rhodium acetate is apparently an excellent catalyst for the reactions of olefins and an alco-

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hol, but not for NH insertion. The reactions of EDA with ethanol, styrene, and cyclohexene were complete within minutes, while much of the EDA was not consumed even after 26 hours with 4-chloroaniline. A similar trend was revealed for the rhodium corrole **2**, except that it is a less active catalyst in general. Iron corrole **1a** displayed very different catalytic properties. EDA was fully consumed within one hour regardless of the substrate, but the selectivity varied significantly. The desired products from the reactions of cyclohexene, ethanol, and styrene were formed in yields of 0%, 30%, and 91%, respectively, accompanied by 100%, 70%, and 9% of EDA coupling products (diethyl maleate and fumarate). The results obtained with 4-chloroaniline show that **1a** is an excellent NH insertion catalyst; the reaction was complete within one minute, with 100% selectivity for **4a**. Importantly, practically identical results were obtained with the other iron corrole **1b** and the iron porphyrins **3a** and **3b**, but the iron–salen complex was completely unreactive.[11]

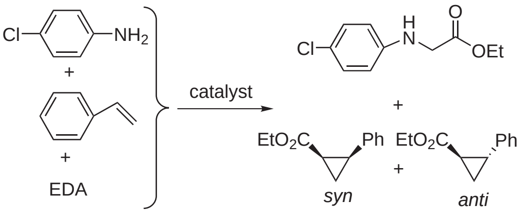
Table 1 Reaction Times for the Full Consumption of EDA in the Reactions Described in Scheme 2[a]

Catalyst	Reaction time, selectivity			
	4a	**5**	**8**	**6** and **7**
Fe(tpfc)Cl (**1a**)	1 min, 100%	1 h, 30%	1 h, 91%	1 h, 0%
Rh(tpfc)PPh$_3$ (**2**)	26 h, 100%[b]	10 h, 96%	15 min, 100%	30 min, 68% **6**, 7% **7**
Rh$_2$(OAc)$_4$	26 h, 100%[b]	5 min, 100%	5 min, 100%	5 min, 97% **6**, 3% **7**

[a] Catalyst/EDA/substrate, 1:100:1000 with 0.4–0.5 mM of catalyst at r.t. in CH$_2$Cl$_2$. Reactions were allowed to proceed until TLC indicated the full consumption of EDA or for 26 hours. The undesired byproducts formed were maleate and fumarate esters.

[b] Complete consumption of EDA was not attained.

The surprising differences in catalyst selectivity were further investigated by carrying out competition reactions between styrene and 4-chloroaniline (Scheme 3), with limited amounts of EDA. The advantage of this investigation is that it takes into account that coordination of the amine to the metal center could be a major factor in affecting reactivity and/or selectivity, which was indeed proven to be the case for both rhodium complexes (Table 2). One significant result is that EDA was not fully consumed even after 24 hours when both the olefin and the amine were present (Table 2). As rhodium-catalyzed cyclopropanation of styrene required only 5–15 minutes in the absence of 4-chloroaniline (Table 1) this clearly shows that the amine reduces the reactivity of the system. The selectivity of NH vs. C=C activation under the conditions described in Table 2 were about 1:3 and 10:1 for **2** and Rh$_2$(OAc)$_4$, respectively. However, both catalysts are of no practical utility under these conditions, as the reactions were not complete even after 24 hours. On the other hand, the reactivity of the iron complexes **1a**, **3a**, and **3b** was not affected by the large excess of amine, in fact, their selectivity towards NH activation remained absolute and reactions were complete within one minute.



Scheme 3

Table 2 Intermolecular Competition between NH and C=C Activation[a]

Catalyst	Insertion/ cyclopropanation	Reaction time
Fe(tpfc)Cl (**1a**)	100:0	1 min, complete
Fe(tpfpp)Cl (**3a**)	100:0	1 min, complete
Fe(tpp)Cl (**3b**)	100:0	1 min, complete
Rh(tpfc)PPh$_3$ (**2**)	23:77	24 h, incomplete
Rh$_2$(OAc)$_4$	91:9	24 h, incomplete

[a] Catalyst/EDA/substrate A/substrate B, 1:50:500:500 with 0.4–0.5 mM catalyst at r.t. in CH$_2$Cl$_2$. EDA and the substrates were added together in one portion. The relative yields of insertion and cyclopropanation products were determined by GC analysis.

To determine the synthetic utility of the reactions, several ring-substituted anilines were reacted with EDA in the presence of 0.1 mol% catalyst at >0.5 M concentration of reagents. The results shown in Table 3 report isolated yields of the corresponding glycine product obtained by simultaneous addition of equimolar amounts of amine and EDA to the pre-dissolved catalyst. Intense emission of nitrogen gas started almost instantaneously, reactions were complete in a few minutes except for the least reactive amine (4-cyanoaniline), and turnover numbers up to 900 were obtained in all cases. Diethyl ether was found to be a particularly practical solvent; both the reactants and the catalyst are very soluble, while in some cases the pure product precipitated.[12] This highly facile catalytic NH activation by **1a** is also shared by the analogous iron porphyrin **3a** (Figure 1), but in that case the desired product **4a** was contaminated by **4b**. This is reminiscent of results obtained with copper-based catalysts,[2d] emphasizing the advantage of iron corroles in being more selective to single NH insertion. Nevertheless, both iron complexes were found to catalyze the transformation of isolated **4a** into **4b** via the reaction of the former with EDA. This was not the only example of secondary amines:[14] morpholine was also reactive under the same reaction conditions (reaction time of 1.5 hours), with the corresponding product being obtained in 92% yield with 0.1% mol **3a** as catalyst.

Table 3 NH-Activation of Ring-Substituted Anilines and Morpholine by EDA[a]

Catalyst	Substrate	Reaction time (min)	Yield
Fe(tpfc)$(OEt_2)_2$ (**1b**)	4-Cl-$C_6H_4NH_2$	3	92%
Fe(tpfc)Cl (**1a**)	3-CN-$C_6H_4NH_2$	5	94%
Fe(tpfc)Cl (**1a**)	4-CN-$C_6H_4NH_2$	40	93%
Fe(tpfc)$(OEt_2)_2$ (**1b**)	$C_6H_4NH_2$	3	93%
Fe(tpfc)$(OEt_2)_2$ (**1b**)	4-OMe-$C_6H_4NH_2$	2	95%
Fe(tpfc)$(OEt_2)_2$ (**1b**)	4-Me-$C_6H_4NH_2$	2	90%
Fe(tpfpp)Cl (**3a**)	4-Cl-$C_6H_4NH_2$	3	94%
Fe(tpp)Cl (**3b**)	4-Cl-$C_6H_4NH_2$	3	95%
Fe(tpfpp)Cl (**3a**)	morpholine	90	92%

[a] Catalyst/EDA/substrate, 1:1000:1000, with 0.5–0.75 mM catalyst at r.t. in Et_2O. EDA and the substrate were added together in one portion and the reported yields are of isolated products.[13]

This work demonstrates that iron corroles and porphyrins catalyze the NH insertion of EDA into anilines very efficiently, leading to their full conversion into N-substituted glycine ethyl esters within minutes upon addition of the substrates together in one portion to the catalyst at room temperature. Only the copper-based catalysts developed by Perez et al. come close to these results, but gradual addition of primary amines was still required and reaction times were longer, despite the 4 mol% of catalyst employed.[2d,6a] The most outstanding features of the current catalytic system are: a) very large selectivity toward NH insertion, b) operation at 0.1 mol% catalyst loading, c) very high yields with very short reaction times, and d) non-poisoning by a very large excess and high concentration of amines (0.5–0.75 M). These remarkable differences relative to other catalysts suggest the operation of a different reaction mechanism in the iron-based catalysts. Detailed mechanistic aspects are out of the scope of this report and will certainly require further investigation, but several observations suggest that metallocarbenoid intermediates might not be involved. The strongest indications are the very fast emission of nitrogen gas only when amines are used as substrates and that Fe(tpp)Cl (**3b**) is an excellent NH insertion catalyst, although it does not catalyze cyclopropanation of olefins by EDA.[15] Future investigations will focus on mechanistic aspects, applications to more complex systems, and attempts to solve the open challenge of developing catalysts for asymmetric intermolecular NH insertion reactions.[6b]

Acknowledgment

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(12) **Quantitative reactions of amines with EDA**: To a solution of catalyst (1 mg, 1–1.5 μmol) in argon-purged Et_2O (1.5 mL), a solution of EDA and substrate (1–1.5 mmol each) in Et_2O (0.5 mL) was added at once. The 4-Cl-, 4-CN-, and 3-CN-substituted products precipitated from the reaction mixture, while the products of other amines were obtained by evaporating the solvent and treatment of the solid material with cold Et_2O. Reported yields are of isolated products (0.2–0.3 g); their purity was checked by GC analysis (> 99% for all the products) and their identity was confirmed by NMR spectroscopy and comparison with published data.[2d,6a,13]

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