COMMUNICATION

Insertion of ethyl diazoacetate into N–H and S–H bonds catalyzed by ruthenium porphyrin complexes

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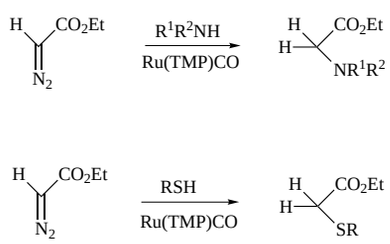
Ruthenium porphyrin complexes catalyze insertion of ethyl diazoacetate into sulfur–hydrogen and nitrogen–hydrogen bonds under mild conditions and with reasonable to very good yields.

The insertion of diazo compounds into heteroatom–H bonds remains of considerable importance in organic synthesis.[1] After the pioneering work of Yates on the copper-catalyzed decomposition of diazo ketones in the presence of thiophenol and aniline,[2] little work was done in this area until Paulissen *et al.* discovered the high catalytic activity of rhodium(II) acetate.[3] While the intramolecular version of the insertion has found the widest use in synthesis, with notably a new approach to bicyclic β-lactams,[4] intermolecular reactions are still interesting, particularly as a versatile route to α-amino carboxylic derivatives.[5,6] Recently, rhodium porphyrin complexes have been found to be very effective catalysts for the insertion of ethyl diazoacetate (EDA) into hydroxylic bonds.[7,8] Having established that ruthenium porphyrin complexes are very active catalysts in the cyclopropanation of olefins,[9] we now report their catalytic properties toward EDA insertion into S–H and N–H bonds.

The complex Ru^{II}(TMP)CO,†[10] in catalytic amounts, reacts with ethyl diazoacetate in the presence of thiols‡ to give α-thio ethyl esters (Scheme 1). Both aromatic and aliphatic thiols



Scheme 1

can be used as substrates (Table 1). The insertion process is regiospecific since dithiothreitol reacts to give the S–H insertion product without any trace of the ether compound. The main advantage of this system over rhodium(II) acetate[3] is the SH/OH selectivity. This regiospecificity also offers a quick route to ethyl 2-(2-hydroxyethylthio)acetate, which is useful in the building of organic donors for conducting cation radical salts.[11] In this case, 2-mercaptoethanol and EDA were used as starting materials. Extension of the insertion process to α-methyl-α-diazo esters is also possible; treatment of ethyl 2-diazopropionate[12] with thiophenol, in the presence of the ruthenium porphyrin catalyst at room temperature, afforded the corresponding α-thio ethyl ester with moderate yield (71%) (solvent: toluene, 3 h). This insertion reaction can be developed to investigate further the possibility of diastereoselectivity in the S–H insertion of ruthenium carbenoids, using chiral thiols or chiral diazo esters[5] as substrates.

Having established the S–H insertion reactions of diazo esters as a simple route to α-thio ethyl ester derivatives, we next investigated the corresponding reactions of N–H insertion. The complex Ru^{II}(TMP)CO,†[10] in catalytic amounts, reacts with ethyl diazoacetate in the presence of alkyl and aromatic amines‡ to give the corresponding *N*-substituted glycine ethyl esters (Scheme 1). The reaction proceeds under mild conditions with reasonable to very good yields (Table 2). Both primary and secondary amines react with EDA. However reaction conditions are different from those described in the Ru^{II} porphyrin catalyzed S–H insertion reactions, since it is necessary to add simultaneously the diazo ester and the substrate into the solution to avoid too large an excess of amine in the presence of the catalyst. Indeed, the nucleophilic amines clearly coordinate to the ruthenium[13] and to a certain extent poison the catalyst. Accordingly, secondary amines are better substrates than primary: a higher yield and a shorter reaction time are observed when diethylamine is used instead of *n*-propylamine.

The difference in reactivity of the catalyst toward R_2NH and RNH_2 is imputable to the less bulky primary amine which is a better ligand for the metal than the secondary amine. Indeed, when Ru(TMP)CO is stirred with an excess of diethylamine, the

Table 1 Yields of α-thio ethyl esters obtained from the reaction of thiols and EDA in the presence of Ru(TMP)CO

RSH	Product	Yield[a] (%)
PhSH	$PhSCH_2CO_2Et$	<95
$(p\text{-}ClC_6H_4)SH$	$(p\text{-}ClC_6H_4)SCH_2CO_2Et$	<95
Bu^tSH	$Bu^tSCH_2CO_2Et$	<95
$HOCH_2CH_2SH$	$HOCH_2CH_2SCH_2CO_2Et$	90
$HSCH_2CH(OH)$-$CH(OH)CH_2SH$	$EtO_2CCH_2SCH_2CH(OH)$-$CH(OH)CH_2SCH_2CO_2Et$	87

[a] Yields determined by NMR analysis.

Table 2 Yields of *N*-substituted glycine ethyl esters obtained from the reaction of amines and EDA in the presence of Ru(TMP)CO

R^1R^2NH	Product	Yield[a] (%)
Et_2NH	$Et_2NCH_2CO_2Et$	81
$Pr^i{}_2NH$	$Pr^i{}_2NCH_2CO_2Et$	75
PhMeNH	$PhMeNCH_2CO_2Et$	72
Bu^tNH_2	$Bu^tNHCH_2CO_2Et$	76
Pr^nNH_2	$Pr^nNHCH_2CO_2Et$	63
$(p\text{-}MeC_6H_4)NH_2$	$(p\text{-}MeC_6H_4)NHCH_2CO_2Et$	64

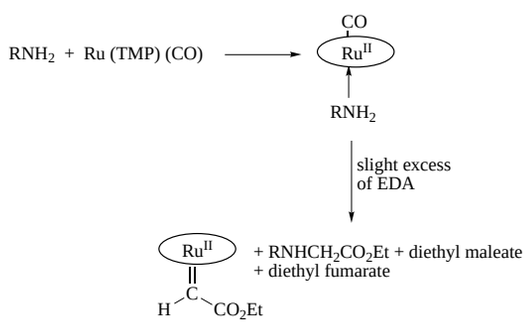
[a] Yields determined by NMR analysis.

† TMP = 5,10,15,20-tetramesitylporphyrin dianion.

‡ *General procedures.* α-Thio ethyl esters: EDA (0.439 mmol) was slowly added (1.5 h) at room temperature and under inert atmosphere to a vigorously stirred solution of thiol (0.571 mmol) and catalyst (4.4 μmol) in dry toluene. The reaction mixture was then stirred for 30 min. The products were identified by comparison with data in the literature.[15]

N-Substituted glycine ethyl esters: a solution of EDA (0.439 mmol) and amine (0.658 mmol) was slowly added (2.5 h) at room temperature and under inert atmosphere to a vigorously stirred solution of catalyst (4.4 μmol) in dry benzene. The reaction mixture was then stirred for 3 to 18 h (stirring for secondary amine: 2 h). The products were identified by comparison with data in the literature.[15]

complex Ru(TMP)CO(Et_2NH)§ is isolated, but the Ru–N bond is quite weak. Thus, addition of 4 equiv. of *n*-propylamine is sufficient to remove completely in 10 min the diethylamino ligand to give Ru(TMP)CO(Pr^nNH_2).§ Substitution of propylamine in the latter complex is much more difficult. The reverse reaction of Ru(TMP)CO(Pr^nNH_2) with 4 equiv. of diethylamine does not proceed to any observable extent after 1 h. After long reaction times (>5 h) we have found, however, that the reaction allows the observation of Ru(TMP)-CO(Et_2NH) in low yield (15%). Such a poisoning has already been reported with another catalyst.[6] In contrast, no detectable coordination occurs with thiols as substrates, and the reaction quickly reaches completion. We presume that the active intermediate in the catalyzed ethyl diazoacetate insertion into the S–H or N–H bond is a carbene complex. Thus addition of a slight excess of EDA to a solution of Ru(TMP)CO(Pr^nNH_2) leads to the formation of a new red complex and to the expected glycine ester together with diethyl maleate and fumarate (Scheme 2). The ^{1}H NMR data of this complex indi-



Scheme 2

cate the presence of a carbene fragment ligated to the ruthenium,[14] as previously detected in the cyclopropanation reaction.¶[9]

We conclude that ruthenium porphyrins efficiently catalyze the carbene insertion into N–H and S–H bonds by use of ethyl diazoacetate. Mechanistic and preparative implications of these results are under investigation in our laboratory.

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§ Ru(TMP)CO(Et_2NH): δ_H($CDCl_3$, *J*/Hz) 8.34 (s, 8H, H_β), 7.24 (s, 4H, H_m), 7.21 (s, 4H, $H_{m'}$), 2.58 (s, 12H, *p*-Me), 1.97 (s, 12H, *o*-Me), 1.77 (s, 12H, *o*′-Me); amine: −1.79 (t, 6H, *J* 7.15, CH_3), −2.68 (m, 4H, CH_2), −6.31 (m, 1H, NH).

Ru(TMP)CO($Pr^n{}_2NH$): δ_H($CDCl_3$, *J*/Hz) 8.34 (s, 8H, H_β), 7.22 (s, 4H, H_m), 7.20 (s, 4H, $H_{m'}$), 2.57 (s, 12H, *p*-Me), 1.87 (s, 12H, *o*-Me), 1.86 (s, 12H, *o*′-Me); amine: −0.96 (t, 3H, *J* 7.30, CH_3), −1.33 (m, 2H, CH_2), −3.03 (m, 2H, CH_2), −5.75 (m, 2H, NH).

¶ However there is no evidence for a CO ligand, as erroneously suggested in our previous paper.[9]