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Cu(I)-carbenoid- and Ag(I)-Lewis acid-catalyzed asymmetric intermolecular insertion of α-diazo compounds into N–H bonds

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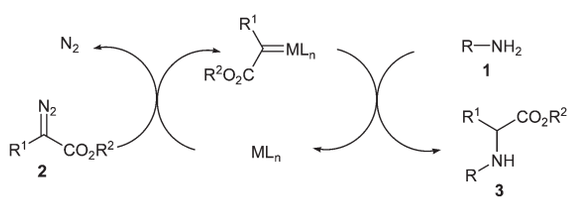
Chiral Cu(I)-bisoxazoline- and Cu(I)-PN-complexes were found to catalyze the intermolecular insertion of α-diazo compounds into N–H bonds. The insertion reactions proceed with enantioselectivities of up to 28% ee for the different α-diazo acetates into one of the N–H bonds of different amines. Analogous chiral Ag(I) complexes were found to give higher enantioselectivities of up to 48% ee, however, lower yields were obtained. There are indications, that the Ag(I)-mediated reactions follow a different reaction mechanism compared to the Cu(I)-catalyzed insertions. It is demonstrated that different α-amino acid derivatives can be obtained *via* this approach in good yields and with low to moderate enantioselectivities. However, the results obtained are the highest asymmetric inductions obtained for an intermolecular N–H insertion *via* chiral carbene complexes or chiral Lewis acid catalysis.

Introduction

The catalytic insertion of α-diazo compounds into X–H bonds (X=C, N, O, S) is a very powerful organic transformation,[1] due to the potential in forming highly versatile building blocks. The N–H insertion pathway (Scheme 1) provides access to *e.g.* proteinogenic and non-proteinogenic α-amino acid derivatives. Therefore, a lot of efforts have been devoted to the development of catalytic intra- and intermolecular N–H insertion reactions.[2]



Scheme 1 Intermolecular N–H insertion *via* a metal-catalyzed decomposition of diazo acetates.

Early work concerning a catalytic N–H insertion presented by Yates was based on copper catalysts.[3] This concept was continued later by Saegusa *et al.*[4] and Kagan *et al.*,[5] and the latter developed a diastereoselective CuCN-catalyzed reaction with chiral amines or chiral diazo acetates resulting in up to 26% de.[5] After the emergence of $[Rh_2(OAc)_4]$ as a highly efficient catalyst (in low catalyst loadings) for the insertion of α-diazo compounds into X–H (X=C, N, O, S) bonds,[6] the copper complexes were discarded as catalysts for this reaction type. Since then, $[Rh_2(OAc)_4]$ and its derivatives have been employed to induce inter- and intramolecular N–H insertions.[2,7,8]

Efforts in finding an asymmetric Rh(II)-catalyzed intermolecular reaction failed and the highest enantioselectivity obtained was 9% ee for different α-amino acid and α-amino phosphonic acid derivatives.[8] The lack of asymmetric induction was attributed to the fact that the nucleophilic amines strongly coordinate to the metal and poison the catalyst to a certain extent.[7a] However, the use of chiral amino acid derivatives as substrates resulted in a maximum diastereoselectivity of up to 37% de, but in general the yields were only moderate. Meanwhile, McKervey *et al.* developed an asymmetric intramolecular N–H insertion based on chiral Rh(II) catalysts.[9] They obtained up to 45% ee for the N–H insertion product. An asymmetric synthesis of optically active proline derivatives *via* a $[Rh_2(OAc)_4]$-catalyzed intramolecular N–H insertion, using chiral auxiliaries has also been described recently.[2j] An elegant new approach towards the synthesis of a variety of diamines in a three-component reaction, involving a Rh(II)-catalyzed intermolecular, achiral N–H insertion was developed by Doyle *et al.*[2k] The same authors also recently showed the potential of metal-carbenoid reactions with an efficient synthesis of *t*-RNA synthase inhibitors *via* carbonyl ylides. Cu(I)- and Cu(II)-complexes were tested as well, but were found to be less efficient.[10]

The Cu(I)-catalysts were rediscovered recently by Diaz-Requejo *et al.* using an achiral Cu(I)-homoscorpionate system. Different amines could be converted into the corresponding α-amino acid derivatives in excellent yield (90%) by N–H insertion with different α-diazo acetates.[11]

Although the concept of metal-carbenoid insertions into N–H bonds has been known for more than three decades, to our surprise and to the best of our knowledge, no efficient asymmetric version has been developed until now. Based on the fact that Cu(I)-complexes are potential candidates for insertion reactions of α-diazo compounds into N–H bonds, we tried to develop an asymmetric Cu(I)-based method. Therefore different Cu(I)-, but also Ag(I)-catalysts, have been screened. The Cu(I)-complex acts probably as a carbene-transfer catalyst, while the Ag(I)-complex is rather a Lewis acid catalyst.

Results and discussion

Cu(I)-catalyzed asymmetric N–H insertion

We initialized our investigations with a screening of well defined Cu(I)-complexes, including chiral ligands such as diphosphines, diamines, diimines, bisoxazolines or P–N ligands. Aniline **1a** and ethyl α-methyl diazo acetate **2a** were chosen as model reagents for the screening (Scheme 2). The diphosphine based systems, *e.g.* (*R*,*R*)-BINAP or (*R*,*R*)-tolyl-BINAP gave acceptable yields of up to 50%, however, no enantioselectivity was observed. Similar results were obtained with ligand **5** (Fig. 1, Table 1, entry 1). Interestingly, the Cu-(**6**)PF_6 system is highly effective and 81% of product **3a** was isolated. To our delight we found a minor asymmetric induction of 13% ee (entry 2). The enantioselectivity could be improved to 18% ee by using ligand **7**, however, a low yield of 13% of **3a** was obtained (entry 3). The use of bisoxazoline ligands resulted in good to high yields. With ligand **8a**, product **3a** was isolated in 52% yield and 22% ee (entry 4). It was found that the manner of addition of the diazo compound slightly affects the yield and the enantioselectivity of **3a**. The addition of the diazo acetate as a solution in CH_2Cl_2 over

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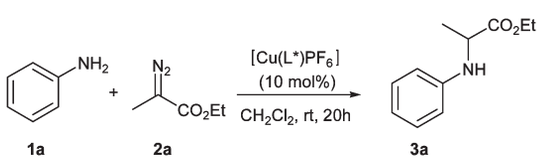
Table 1 Initial screening for the insertion of **2a** into one N–H bond of **1a**[a]

Entry	Catalyst	Solvent	Yield [%][b]	ee [%][c]
1[d]	Cu(**5**)PF_6	CH_2Cl_2	52	Rac
2[d]	Cu(**6**)PF_6	CH_2Cl_2	81	13
3[d]	Cu(**7**)PF_6	CH_2Cl_2	13	18
4[d]	Cu(**8a**)PF_6	CH_2Cl_2	52	22
5	Cu(**8a**)PF_6	CH_2Cl_2	62	20
6[d]	Cu(**8b**)PF_6	CH_2Cl_2	54	28
7	Cu(**8b**)OTf	CH_2Cl_2	33	Rac
8	Cu(**8b**)PF_6	Toluene	17	22
9	Cu(**8b**)PF_6	$MeNO_2$	<5	nd
10	Cu(**8b**)PF_6	MeCN	12	Rac
11	Cu(**8c**)PF_6	CH_2Cl_2	64	8
12	Cu(**8d**)PF_6	CH_2Cl_2	56	Rac
13[d]	Cu(**9**)PF_6	CH_2Cl_2	52	26
14[d]	Cu(**10**)PF_6	CH_2Cl_2	64	4
15	Cu(**11**)PF_6	CH_2Cl_2	41	14
16[d]	Cu(**12a**)PF_6	CH_2Cl_2	62	12
17	Cu(**12b**)PF_6	CH_2Cl_2	95	5
18	Cu(**12c**)PF_6	CH_2Cl_2	75	26

[a] For reaction conditions see Experimental section. [b] Isolated yield after FC. [c] The enantiomeric excess was determined by HPLC on a Chiralpak AS column. [d] The diazo acetate was added as a solution in CH_2Cl_2 (1 mL) *via* syringe pump over 1 h to the reaction mixture.

1 h or even longer *via* syringe pump to prevent dimerisation of the diazo compound gave a lower yield (entry 4) than addition of the undiluted diazo compound dropwise over 3–5 minutes (entry 5). We attribute this observation more to a dilution effect than to the slow addition.



Scheme 2 Model system for N–H insertion *via* Cu(I)-carbene complexes.

The addition of the diazo compound and the amine as a solution in CH_2Cl_2 over 1 h improved the yield to 75% in combination with 20% ee as observed for **3a**.[12] Due to the fact that this procedure is not a proper catalytic system, but rather a stoichiometric transformation we decided to continue by adding the diazo compound dropwise over a few minutes.

The nature of the counterion has a significant effect on the enantioselectivity. Stronger coordinating counterions, such as OTf^- compared to the weakly coordinating PF_6^- gave lower yields and no chiral induction was obtained (entries 6 *vs.* 7). The influence of different solvents, such as toluene, CH_3CN or CH_3NO_2 was investigated and for all solvents except CH_2Cl_2 low yields and a drop in enantioselectivity was observed (entries 8–10). It is notable that in THF no product was formed at all. With the other bisoxazolines **8c**,**d** or **11**, low enantioselectivities were obtained (entries 11, 12, 15), whereas the indane-derived ligand **9** gave a similar enantioselectivity as ligand **8b** (entry 13). Interestingly, the binding angle of the ligand to the Cu(I)-centre seems to be important and with ligand **10** no enantioselectivity was obtained (entry 14). We recently reported the versatility of Cu(I)-PN systems for the asymmetric half-transamination,[13] and indeed these complexes also perform asymmetric N–H insertions. Interestingly, the steric bulk of the substituents on the phosphorus atoms seems to have a major influence on the enantioselectivity, a fact already observed for transamination reactions.[13] In general, these Cu(**12**)PF_6 systems were able to induce enantioselectivities in the same range as the bisoxazoline systems, however, a slight increase of reactivity (entries 16–18) was observed. A variety of other ligands such as DBFOX, (*R*,*R*)-pybox (1*R*,2*R*)-*N*,*N*′-bis[2(diphenylphosphino)-benzylidene]cyclohexane-1,2-diamine or (*R*,*R*)-*N*,*N*′-bis-(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine in combination with $CuPF_6$ induced low enantioselectivities combined with moderate to good yields.

Influence of the substituents on the diazo compound

The influence of α-substituents and ester size of the diazo compounds on the reactivity and the enantioselectivity of the N–H insertion have been investigated. Four diazo compounds with sterically and electronically different substituents R^1 and R^2 were chosen as shown in Table 2. Their synthesis was performed in analogy to a slightly modified literature procedure.[14] The use of Et_2O instead of THF allowed us to reduce the amount of TsN_3 from 1.6 to 1.2 equiv. and pure products were obtained without the need for further product purification by column chromatography. Furthermore, for the volatile compound **2a** the solvent could be more easily removed. These procedures gave moderate yields for compounds **2a**–**2c** and for **2e**, whereas for **2d** a good yield of 88% was obtained.

In Table 2 the results of the N–H insertion of different α-diazo acetates into one N–H bond of aniline are summarized. In contrast to Cu(I)-catalyzed cyclopropanations of olefins, where an increase in steric bulk at the ester moiety gave major improvements for the diastereo- and enantioselectivities,[15] we did not find such a positive effect using compound **2e** for the N–H insertion of aniline **1a** (entries 1, 2). It is obvious that the low reactivity of **2b** (entry 3) is due to steric hindrance. A cross-check experiment with $(Rh_2(OAc)_4$ (15% yield)[16] gave similar results.

For a variety of different bisoxazoline-Cu(I) catalysts enantioselectivities in the range of 13–27% ee were obtained using ethyl α-phenyl diazo acetate **2c** (entries 4–7). Especially ligands **8a** and **8b**, but also the PN system **12c** showed good activities and high yields of up to 82% were obtained (entries 4, 5, 8).

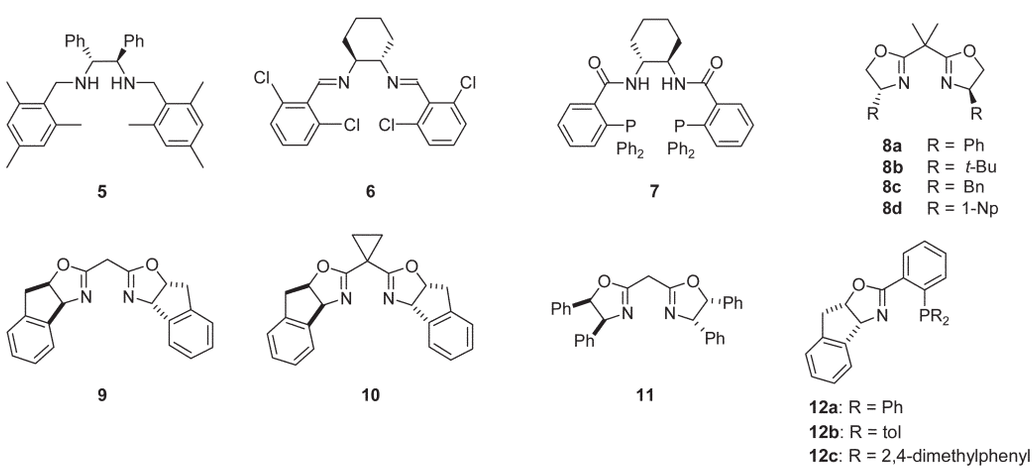
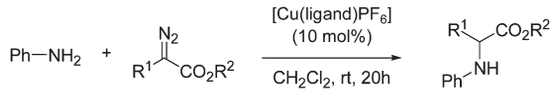


Fig. 1 Chiral ligands for the asymmetric N–H insertion of α-diazo compounds.

Table 2 Influence of different α-diazo acetates on N–H insertion[a]

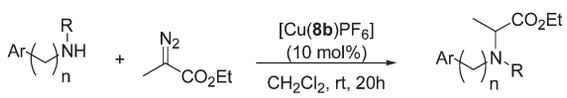


1a 2 3

Entry	Catalyst	Diazo	R^1	R^2	Product	Yield [%][b]	ee [%] [c]
1[d]	**8b**	**2e**	Me	*t*-Bu	**3e**	23	10
2[d]	**9**	**2e**	Me	*t*-Bu	**3e**	25	15
3	$CuPF_6$	**2b**	*i*-Pr	Et	**3b**	Traces	—
4	**8a**	**2c**	Ph	Et	**3c**	67	19
5	**8b**	**2c**	Ph	Et	**3c**	82	13
6	**9**	**2c**	Ph	Et	**3c**	33	15
7	**11**	**2c**	Ph	Et	**3c**	47	27
8	**12c**	**2c**	Ph	Et	**3c**	80	8
9	**8a**	**2d**	Bn	Et	**3d**	93	12
10	**8b**	**2d**	Bn	Et	**3d**	15	6
11	**11**	**2d**	Bn	Et	**3d**	89	Rac

[a] For reaction conditions see Experimental section. [b] Isolated yield after FC. [c] The enantiomeric excess was determined with a Chiralpak AS column. [d] The enantiomeric excess was determined with a Chiralpak AD column.

Table 3 Electronic effects for the insertion of **2a** into aniline derivatives **1**[a]



1 2a 4

Entry	Ar	R	*n*	Product	Yield [%][b]	ee [%][c]
1	2-Naphthyl **1b**	H	0	**4b**	27	24
2	4-OMe-C_6H_4 **1c**	H	0	**4c**	0	—
3	4-Me-C_6H_4 **1d**	H	0	**4d**	44	8
4	4-F-C_6H_4 **1e**	H	0	**4e**	40	20
5	4-CF_3-C_6H_4 **1f**	H	0	**4f**	57	7
6	2-OMe-C_6H_4 **1g**	H	0	**4g**	15	9
7	Ph **1h**	Me	0	**4h**	29	9
8	Ph **1i**	H	1	**4i**	27	10 (*R*)[d]

[a] For reaction conditions see Experimental section. [b] Isolated yield after FC. [c] The enantiomeric excess was determined with a Chiralpak AS column. [d] The absolute configuration was determined by optical rotation.

The use of the benzyl derived α-diazo compound **2d** gave a low yield with ligand **8b** and a very low enantioselectivity of only 6% ee (entry 10). Surprisingly, the yields were excellent using the ligands **8a** and **11** and enantioselectivities of up to 12% ee were found (entries 9, 11).

Scope of the system

After the initial screening with aniline we tried to apply the N–H insertion to different substrates using Cu(**8b**)PF_6 as the catalyst. First, we kept the electronic features of the amine but increased the steric bulk by using 2-aminonaphthalene **1b** as the substrate (Table 3, entry 1). This reaction provided 27% yield and 24% ee of **4b**. Compared to the related reaction with aniline (Table 1, entry 6), the yield decreased, but the enantioselectivity was in the same range. Therefore, it was decided to change the electronic properties of the aniline by varying the substituents in the 4-position of the aniline (entries 2–5). Electronic effects that follow a linear free energy relationship have been observed in diazo decomposition reactions, mainly in asymmetric metal-catalyzed cyclopropanations of olefins.[17] However, the electronic effects for the present asymmetric N–H insertion do not follow a linear free energy relationship. The enantioselectivities obtained for the electron-rich and electron-poor anilines (entries 2–5) were lower than for aniline itself (Table 1, entry 6). For 4-methyl- **1d**, 4-fluoro- **1e** and 4-trifluoromethylaniline **1f** similar reactivities compared to aniline **1a** were found. Interestingly, 4-methoxyaniline **1c** did not react at all using Cu(**8b**)PF_6 as the catalyst, while $CuPF_6$ without a chiral ligand as a catalyst gave only 6% yield.

In an attempt to investigate if the observation that the 4-methoxyaniline **1c** is not reacting due to electronic effects or to deactivation of the catalyst by coordination to the metal the reaction was also carried out using 2-methoxyaniline **1g**. In contrast to 4-methoxyaniline **1c**, this substrate (**1g**) gave 22% yield using $CuPF_6$ and 15% using the chiral catalyst Cu(**8b**)PF_6 (entry 6). However, no improvement in the enantioselectivity was achieved.[18] We attribute the reactivity of **1g** compared to **1c** to a coordinating effect of the methoxy group with the metal. This additional coordination binds the substrate in a preferred geometry to the metal center facilitating N–H insertion in low yields.

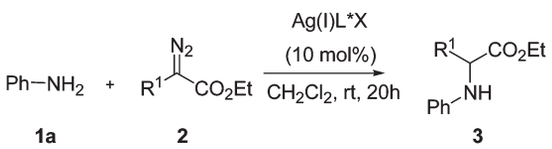
We proceeded, with *N*-methylaniline **1h**, to check whether secondary amines are useful substrates for the N–H insertion reaction. The additional substituent on the nitrogen atom is tolerated by the Cu(I)-catalyst to yield 29% of the product with 9% ee (entry 7), although, neither the reactivity, nor the enantioselectivity could be improved.

It has also been found that benzylamine **1i** is a suitable substrate for the N–H insertion, however, **1i** is less reactive than the aniline derivatives and also low enantioselectivities were obtained (entry 8). The reductive cleavage of the nitrogen protecting group followed by hydrolysis of the ester moiety provides access to free amino acids. The absolute configuration of **4i** was determined by optical rotation to be (*R*).[19]

Ag(I)-catalyzed asymmetric N–H insertion

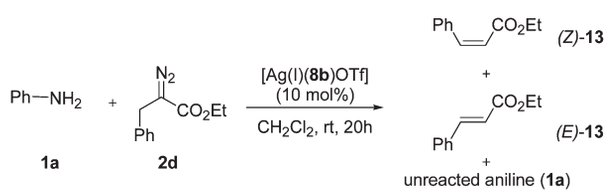
We continued our investigations by applying Ag(I)-complexes to the N–H insertion of diazo compounds into aniline.

Homogeneous Ag(I)-catalyzed reactions are rare and only a few recent examples are described in the literature,[20] and even less is known about Ag(I)-catalyzed decompositions of diazo compounds.[20f–h] Different Ag(I) salts in combination with different bisoxazoline ligands have been tested for this new approach (Scheme 3).



Scheme 3 Ag(I)-catalyzed insertion of different diazo acetates (**2**) into the N–H bond of aniline (**1a**).

The investigation was started with the application of the best ligand **8b** and diazo acetate **2b** found during the screening of the Cu(I)-catalyzed system in terms of reactivity and enantioselectivity. The first reaction with Ag(**8b**)SbF_6 gave only 8% isolated yield and 25% ee was found for the product **3a** (Table 4, entry 1). Although full consumption of the diazo compound was observed, no homologisation products (maleate or fumarate derivatives) were detected. This could indicate that the Ag(I)-catalysis follows a different pathway than the Cu(I)-catalysed reaction (*vide infra*). Interestingly, the Ag(I) system showed an opposite trend concerning the counterion to the Cu(I)-catalysts regarding the enantioselectivities. Catalyst Ag(**8b**)OTf also gave a very low yield of 5% (full conversion of the diazo compound) but 48% ee was obtained for product **3a** (entry 2). This is, according to our knowledge, the highest enantioselectivity ever observed for an intermolecular N–H insertion and is, despite the low yield, remarkable. The trend of the counterion is confirmed as Ag(**8b**)ClO_4 gives 48% ee for **3a** as well (entry 4). Not only the counterion, but also the solvent has an influence on the enantioselectivity.[13,21] In toluene only 20% ee was found (entry 3). The reactivity changed completely using **2c** instead of **2a** as the carbene source. In these reactions the yields were between 33 and 58%, but only a little asymmetric induction was obtained (entries 5–8). However, when diazo compound **2d** which gave excellent yields in the Cu(I)-catalyzed N–H insertions (*vide supra*) was used, product **3d** was not obtained but a side product was formed in 74% yield (Scheme 4).



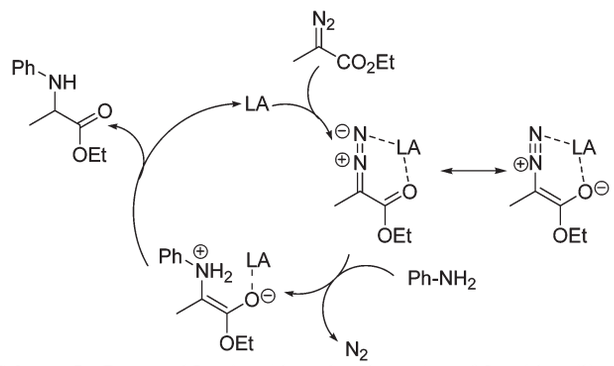
Scheme 4 Unpredicted side reaction in the N–H insertion with **2d**.

This side-product was found to be an elimination product and identified as a mixture of (*E*)- and (*Z*)-3-phenylacrylic acid ethyl esters **13**. With diazo compound **2b** an analogous elimination product was found with AgOTf as the catalyst. It should be noted that also in the Cu(I)-catalyzed asymmetric N–H insertion with **2d** traces of the elimination products (*E*,*Z*)-**13** were detected. Additionally, Ag(0) was found to catalyze the elimination reaction with **2d**. We therefore believe that either the Ag(I)-catalyst might be reduced to Ag(0) during the course of the reaction, which is then catalyzing the formation of the elimination products (*E*,*Z*)-**13**, or it might also be possible that silver hydrides are involved. More effort is needed to clearly determine the role of the Ag(I)/Ag(0) catalyst and to postulate a plausible catalytic cycle. However, these observations indicate that there are probably different reaction mechanisms apparent for the Ag(I)-mediated reactions compared to the Cu(I)-reactions. We postulate that there are probably two mechanisms taking place, one *via* a carbene intermediate (see Scheme 1) and a second pathway for the Ag(I)-mediated reaction as outlined in Scheme 5. Our experiments indicate that in the Cu(I)-case, the carbene pathway in Scheme 1 is probably predominant, whereas in the Ag(I)-case, the pathway in Scheme 5 might be favoured. This is supported by the fact that in the Cu(I)-reaction vigorous gas evolution can be observed, while for the Ag(I)-reaction only very slow release of nitrogen is found.

Table 4 Ag(I)-catalyzed N–H insertion with aniline (**1a**) and different α-diazo acetates[a]

Entry	Catalyst	Diazo	R^1	Product	Yield [%][b]	ee [%][c]
1	Ag(**8b**)SbF_6	**2a**	Me	**3a**	8	25
2	Ag(**8b**)OTf	**2a**	Me	**3a**	5	48
3	Ag(**8b**)OTf	**2a**	Me	**3a**	4	20
4	Ag(**8b**)ClO_4	**2a**	Me	**3a**	5	48
5	Ag(**8b**)SbF_6	**2c**	Ph	**3c**	33	13
6	Ag(**8b**)OTf	**2c**	Ph	**3c**	49	9
7	Ag(**8a**)OTf	**2c**	Ph	**3c**	58	9
8	Ag(**9**)OTf	**2c**	Ph	**3c**	58	Rac

[a] For reaction conditions see Experimental section. [b] Isolated yield after FC. [c] The enantiomeric excess was determined with a Chiralpak AS column. [d] Toluene as the solvent.



Scheme 5 Proposed Lewis acid catalysed reaction of **2a** with aniline.

Lewis acid-catalyzed N–H insertion

Finally, we performed a screening of different chiral Lewis acid catalysts for the asymmetric N–H insertion with aniline and **2a**. The use of Lewis acids in diazo decomposition reactions is a well known strategy,[22] but to the best of our knowledge no catalytic Lewis acid-catalyzed intermolecular N–H insertion has been described until now. We therefore screened a series of typical Lewis acids such as BCl_3, $Sn(OTf)_2$, $Zn(OTf)_2$, $Cu(OTf)_2$, $Sc(OTf)_3$, $La(OTf)_3$ and $RhCl(PPh_3)_3$ and found that La(III), Sc(III), Cu(II), Sn(II) and Rh(I) give moderate yields, whereas the other Lewis acids did not give any conversion.

Acceptable yields of up to 62% in CH_2Cl_2 or toluene were obtained, but all attempts to develop an asymmetric Lewis acid-catalyzed N–H insertion reaction failed and the enantioselectivity never exceeded 5% ee.

From the inspection of the proposed mechanism in Scheme 5 it is obvious that it will probably be difficult to obtain high enantioselectivity *via* a Lewis- acid catalysis, due to the fact that the asymmetric induction is probably built up during a protonation step.

Conclusion

We have developed the first asymmetric carbenoid intermolecular N–H insertion of different primary and secondary amines. Good to excellent yields and enantioselectivities of up to 48% ee could be obtained with different Cu(I)- and Ag(I)-complexes. Indications have been found that two different reaction mechanisms are operative. For Cu(I)-catalysts, the carbene pathway is predominant, whereas for the Ag(I) systems an elimination reaction seems to be dominant over the carbene one. Anyway, the formed elimination products **13** in the Cu(I)-catalyzed reactions and the relatively high enantioselectivity in the Ag(I)-reactions let us conclude that both pathways can be

apparent for both metals. A Lewis acid-catalyzed version of the reaction was investigated as well, giving moderate yields with low enantioselectivities.

Experimental

General

The ^{1}H and ^{13}C NMR spectra were measured on a Varian Mercury spectrometer at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to $CHCl_3$ (δ = 7.26) for ^{1}H NMR and relatively to the central $CDCl_3$ resonance (δ = 77.0) for ^{13}C NMR. All solvents used were of p.a. quality and were dried according to standard procedures. Flash chromatography (FC) was carried out using Merck silica gel 60 (230–400 mesh). The ee was determined by HPLC using a Chiralpak AS column with *i*-PrOH–hexane as eluent. All carbenoid transformations have been carried out in the absence of light. All catalytic reactions have been carried out under an atmosphere of N_2 or Ar.

Materials

All commercially available compounds were used without further purification. The diazo compounds were synthesized according to a modified literature procedure (see below).[14]

Ethyl α-diazo methyl acetate 2a

To a suspension of NaH (5.5 g, *ca.* 13.5 mmol) in dry Et_2O (10 mL) was added a solution of ethyl-2-methyl acetoacetate (1.0 g, 6.95 mmol) in Et_2O (2 mL) over a period of 5 min. The solution was cooled in a water bath and TsN_3 (1.05 g, 8.1 mmol) was added dropwise over 5 min. The reaction mixture was diluted with Et_2O (10 mL), stirred for 45 min and the precipitate was filtered off. The filtrate was extracted with H_2O (100 mL), the organic layer was dried over $MgSO_4$, filtered and the removal of the solvent yielded the pure title compound. Yield: 420 mg (47%). ^{1}H NMR δ 4.15 (q, 2H, J = 6.8 Hz, CH_2O), 1.90 (s, 3H, CH_3), 1.21 (t, 3H, J = 7.6 Hz, CH_3).

Ethyl α-diazo *iso*-propyl acetate 2b

The title compound was synthesized as described above starting from ethyl-2-*iso*-propyl acetoacetate (3.82 mmol scale). Yield: 225 mg (38%). ^{1}H NMR δ 4.22 (q, 2H, J = 7.2 Hz, CH_2O), 2.75 (sep, 1H, J = 7.2 Hz, CH), 1.27 (t, 3H, J = 7.2 Hz, CH_3), 1.14 (d, 6H, J = 7.2 Hz, CH_3).

Ethyl α-diazo phenyl acetate 2c

The title compound was synthesized as described above starting from ethyl-2-phenyl acetoacetate (4.85 mmol scale). Yield: 400 mg (43%). ^{1}H NMR δ 7.50 (d, 2H, J = 2.8 Hz, arom.), 7.39 (t, 2H, J = 8.4 Hz, arom.), 7.18 (m, 1H, arom.), 4.34 (q, 2H, J = 7.2 Hz, CH_2O), 1.34 (t, 3H, J = 7.2 Hz).

Ethyl α-diazo benzyl acetate 2d

The title compound was synthesized as described above starting from ethyl-2-benzyl acetoacetate (4.53 mmol scale). Yield: 812 mg (88%). ^{1}H NMR δ 7.26–7.16 (m, 5H, arom.), 4.18 (q, 2H, J = 7.2 Hz, CH_2O), 3.56 (s, 2H, CH_2), 1.21 (t, 3H, J = 6.8 Hz, CH_3).

tert-Butyl α-diazo methyl acetate 2e

The title compound was synthesized as described above starting from 2-methyl-3-oxopentanoic acid *tert*-butyl ester (5.00 mmol scale). Yield: 170 mg (22%). ^{1}H NMR δ 1.85 (s, 3H), 1.40 (s, 9H).

General procedure for the enantioselective Cu(I)- or Ag(I)-catalyzed insertion of α-diazo compounds into N–H bonds

The metal salt (25 μmol, 10 mol%) and the chiral ligand (27.5 μmol, 11 mol%) were stirred under vacuum in a flame-dried Schlenk tube for 1 h. Then the solvent (1 mL) was added and the catalyst solution was stirred for 30 min under an Ar or N_2 atmosphere, followed by the addition of the substrate (0.25 mmol, 1 equiv.) and the diazo compound (0.25 mmol, 1 equiv.). The α-diazo compound was added dropwise over a period of 3 min to the reaction mixture. The resulting mixture was stirred for 20 h and the product was isolated by FC over silica with CH_2Cl_2–Et_2O (9 : 1).

N-Phenylalanine ethyl ester 3a[23]

HRMS (TOF ES$^+$) calcd for $C_{11}H_{15}NO_2$ [M + Na]$^+$ 216.1000, found 216.0999. The ee was determined on a Chiralpak AS column using hexane–*i*-PrOH (98 : 2) as eluant. R_t/min: 6.4 (enantiomer-1) and 7.2 (enantiomer-2).

N-Phenylphenylalanine ethyl ester 3c

^{1}H NMR δ 7.54 (d, 2H, J = 7.6 Hz, arom.), 7.38 (m, 3H, arom.), 7.15 (t, 2H, J = 7.2 Hz, arom.), 6.73 (dt, 1H, J = 0.8 and 8.0 Hz, arom.), 6.60 (d, 2H, J = 8.4 Hz, arom.), 5.11 (d, 1H, J = 6.0 Hz, CH), 5.02 (br d, 1H, J = 6.0 Hz, NH), 4.27 (m, 1H, CH_2O), 4.16 (m, 1H, CH_2O), 1.24 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 171.7, 145.9, 137.6, 129.1, 128.7, 127.1, 117.9, 113.3, 61.7, 60.7, 14.0; HRMS (TOF ES$^+$) calcd for $C_{16}H_{17}NO_2$ [M + Na]$^+$ 278.1157, found 278.1153. The ee was determined on a Chiralpak AS column using hexane–*i*-PrOH (98 : 2) as eluant. R_t/min: 6.5 (enantiomer-1) and 7.8 (enantiomer-2).

N-Phenylbenzylalanine ethyl ester 3d

^{1}H NMR δ 7.3–7.0 (m, 7H, arom.), 6.66 (t, 1H, J = 7.6 Hz, arom.), 6.53 (d, 2H, J = 8.0 Hz, arom.), 4.27 (m, 1H, CH), 4.09 (br d, 1H, J = 9.6 Hz, NH), 4.04 (q, 2H, J = 7.6 Hz, OCH_2), 3.05 (dd, 2H, J = 3.6 and 6.4 Hz, CH_2), 1.09 (t, 3H, J = 6.8 Hz, CH_3); ^{13}C NMR δ 173.1, 146.3, 136.3, 129.3, 128.4, 126.9, 118.3, 113.5, 64.0, 57.6, 38.6, 14.1; HRMS (TOF ES$^+$) calcd. for $C_{17}H_{19}NO_2$ [M + Na]$^+$ 292.1313, found 292.1318. The enantiomeric excess was determined on a Chiralpak AS column using hexane–*i*-PrOH (98 : 2) as eluant. R_t/min: 6.1 (enantiomer-1) and 8.3 (enantiomer-2).

N-Phenylalanine *tert*-butyl ester 3e

^{1}H NMR δ 7.10 (t, 2H, J = 8.0 Hz, arom.), 6.65 (t, 1H, J = 7.3 Hz, arom.), 6.54 (d, 2H, J = 8.4 Hz, arom.), 4.15 (br s, 1H, NH), 4.01 (m$_c$, 1H, CH), 1.48–1.39 (m, 12H, *t*-Bu, CH_3), ^{13}C NMR ($CDCl_3$) δ 174.1, 147.0, 129.5, 118.3, 113.6, 81.7, 52.8, 31.2, 28.3, 19.1. MS (TOF ES$^+$) m/z (%) = 166 (50), 154 (30), 120 (100). The ee was determined on a Chiralpak AD column using hexane–*i*-PrOH (98 : 2) as eluant. R_t/min: 6.1 (enantiomer-1) and 7.6 (enantiomer-2).

N-[2]Naphthylalanine ethyl ester 4b

^{1}H NMR δ 7.60 (m, 2H, arom.), 7.60 (d, 2H, J = 8.2 Hz, arom.), 7.36 (t, 1H, J = 7.5 Hz, arom.), 7.21 (d, J = 7.5 Hz, arom.), 6.92 (dd, J = 8.7 and 2.2 Hz, arom.), 6.78 (br s, 1H, arom.), 4.40–4.11 (m, 4H, OCH_2, NH, CH), 1.54 (d, 3H, J = 6.9 Hz, CH_3), 1.27 (t, 3H, J = 7.0 Hz, CH_3); ^{13}C NMR δ 174.5, 144.2, 134.9, 129.1, 127.8, 127.6, 126.3, 126.0, 122.3, 118.1, 105.4, 61.2, 52.0, 18.8, 14.2; HRMS (TOF ES$^+$) calcd for $C_{15}H_{17}NO_2$ [M + Na]$^+$ 266.1157, found 266.1150. The ee was determined on a Chiralpak AS column using hexane–*i*-PrOH (98 : 2) as eluant. R_t/min: 6.6 (enantiomer-1) and 7.7 (enantiomer-2).

N-(4-Methylphenyl)alanine ethyl ester 4d

^{1}H NMR δ 8.08 (d, 2H, J = 5.2 Hz, arom.), 6.54. (d, 2H, J = 5.2 Hz, arom.), 5.05 (br d, 1H, J = 7.2 Hz, NH), 4.25 (m, 3H, OCH_2 and CH), 1.52 (d, 3H, J = 7.2 Hz, CH_3), 1.29 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR δ 174.6, 144.3, 129.8, 129.2, 113.6, 61.0, 52.3, 19.0, 15.9, 14.2. The ee was determined on a

Chiralpak AS column using hexane–*i*-PrOH (98 : 2) as eluant. R_t/min: 5.0 (enantiomer-1) and 5.5 (enantiomer-2).

_N_-(4-Fluorophenyl)alanine ethyl ester 4e

^{1}H NMR δ 6.87 (t, 2H, J = 8.8 Hz, arom.), 6.54 (m, 2H, arom.), 4.18 (q, 2H, J = 6.8, OCH_2), 4.05 (m, 2H, NH and CH), 1.45 (d, 3H, J = 6.4 Hz, CH_3), 1.23 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR δ 174.5, 115.8, 115.6, 114.6, 114.4, 61.1, 52.7, 18.8, 12.7; HRMS (TOF ES$^+$) calcd for $C_{11}H_{14}FNO_2$ [M + Na]$^+$ 234.0906, found 234.0818. The ee was determined by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program: isotherm at 140 °C for 12 min. R_t/min: 10.5 (enantiomer-1); 10.8 (enantiomer-2).

_N_-(4-Trifluoromethylphenyl)alanine ethyl ester 4f

^{1}H NMR δ 7.40 (d, 2H, J = 8.4 Hz, arom.), 6.60 (d, 2H, J = 8.4 Hz, arom.), 4.54 (br d, 1H, J = 8.0 Hz, NH), 4.20 (q, 2H, J = 6.8, CH_2O), 4.16 (dd, 1H, J = 8.0 and 14.8 Hz, CH), 1.49 (d, 3H, J = 6.8 Hz, CH_3), 1.24 (t, 3H, J = 7.12 Hz); ^{13}C NMR δ 173.9, 149.0, 126.6, 119.4, 115.2 112.5, 61.4, 51.4, 18.6, 14.1; HRMS (TOF ES$^+$) calcd for $C_{12}H_{14}F_3NO_2$ [M + Na]$^+$ 284.0874, found 284.0906. The ee was determined by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program: from 70 °C to 200 °C at a rate of 10 °C min^{-1}. R_t/min: 11.4 (enantiomer-1); 11.5 (enantiomer-2).

_N_-(2-Methoxyphenyl)alanine ethyl ester 4g

^{1}H NMR δ 6.76 (t, 1H, J = 7.5 Hz, arom.), 6.71 (d, 2H, J = 7.8 Hz, arom.), 6.63 (t, 1H, J = 7.7 Hz, arom.), 6.45 (d, 1H, J = 7.8 Hz, arom.), 4.70 (br s, 1H, NH), 4.12 (q, 2H, J = 7.1 Hz, CH_2O), 4.24–4.06 (m, 1H, CH), 3.85 (s, 3H, OCH_3), 1.43 (d, 3H, J = 6.9 Hz, CH_3), 1.18 (t, 3H, J = 7.1 Hz, CH_3); ^{13}C NMR δ 174.6, 147.0, 136.5, 121.1, 117.4, 110.3, 109.6, 61.0, 55.4, 51.7, 18.9, 14.2; HRMS (TOF ES$^+$) calcd. for $C_{12}H_{17}NO_2$ [M + Na]$^+$ 246.1106, found 246.1112. The ee was determined on a Chiralpak AD column using hexane–*i*-PrOH (98 : 2) as eluant. R_t/min: 6.4 (enantiomer-1) and 6.7 (enantiomer-2).

_N_-Methyl-_N_-phenylalanine ethyl ester 4h[23]

HRMS (TOF ES$^+$) calcd for $C_{12}H_{17}NO_2$ [M + Na]$^+$ 230.1157, found 230.1159. The ee was determined by GC on a Astec G-TA column. Temperature program: isotherm at 120 °C for 25 min. R_t/min: 23.6 (enantiomer-1); 24.3 (enantiomer-2).

_N_-Benzylalanine ethyl ester 4i[24]

The ee was determined on a Chiralpak AD column using hexane–*i*-PrOH (98 : 2) as eluant. R_t/min: 5.8 (enantiomer-1) and 6.4 (enantiomer-2). The absolute configuration was determined by optical rotation and compared to described literature values.[19]

Acknowledgements

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