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Enantioselective carbene insertion into the N–H bond of benzophenone imine†

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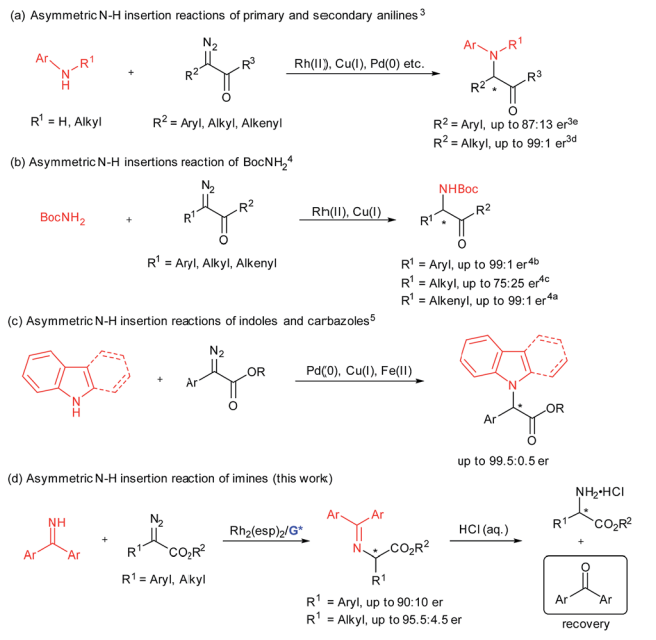
Efficient enantioselective insertion of α-diazoesters into the N–H bond of *N*-sp^2-hybridized benzophenone imine was realized by using $Rh_2(esp)_2$ and chiral guanidine cooperative catalysis. Both aliphatic and aromatic substituted α-amino esters were obtained in high yields (up to 99%) and good enantioselectivities (up to 95.5 : 4.5 er) under mild reaction conditions.

Introduction

Efficient synthesis of enantiomerically enriched α-amino acids and their derivatives remains a hot topic in synthetic organic chemistry and biology.[1] The transition-metal-catalyzed enantioselective insertion of an α-diazocarbonyl compound into an N–H bond represents a potentially attractive route to chiral α-amino acid derivatives.[2] Significant progress has been made on asymmetric insertion reactions of *N*-sp^3-hybridized N–H sources including primary and secondary anilines (Scheme 1a),[3] as well as those of *tert*-butyl carbamate[4] (Scheme 1b). Recently, enantioselective carbene insertion into the N–H bond of C3-substituted indoles and carbazoles was achieved (Scheme 1c).[5] With regard to the chiral catalyst variety, different transition metal complexes have proven to be useful, including chiral dirhodium(II) prolinates by McKervey,[6] copper complexes with chiral ligands, such as bisoxazoline by Jørgensen,[3i] spiro bisoxazolines by Zhou,[3h] bpy* by Fu,[4d] 2,2′-biimidazole by Zhou,[5a] a BINOL derivative by our group,[3g] chiral palladium complexes liganded with guanidine by our group,[3a] and PyBox by Vranken.[5b] In addition, cooperative catalytic systems of dirhodium(II) carboxylates with cinchona alkaloids[3f] or chiral phosphoric acids[4c] were well applied to the asymmetric N–H bond insertion reaction and others.[3b,i,4e,5a] In these cases, the coupling of α-diazo compounds and N–H sources is interesting. It seems that insertion of alkyl α-diazoesters into anilines[3] and aryl α-diazocarbonyl compounds into *tert*-butyl carbamate[4] and carbazoles[5] yielded higher enantioselectivity than the opposite cross combination. This might be due to the nucleophilicity of the nitrogen sources and the stability of the carbene intermediates. This indicates one limitation of these developed catalytic systems.

Benzophenone imine, which is industrially produced by condensation of benzophenone and ammonia, could serve as an ammonia carrier and has been successfully applied to many asymmetric catalytic amination reactions.[7] The amination products could be transformed into *N*-unprotected amino compounds conveniently by one step acidic hydrolysis, and the ammonia carrier precursor benzophenone could be recovered and reused. We became interested in catalytic asymmetric carbene insertion into the N–H bond of *N*-sp^2-hybridized benzophenone imines because the products could be readily transformed into optically active *N*-unprotected amino acids (Scheme 1d).



Scheme 1 Asymmetric N–H insertion reactions.

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Previously, our group demonstrated enantioselective insertion of α-diazocarbonyl compounds into the O–H bond of carboxylic acids by the use of cooperative catalysis of $Rh_2(OAc)_4$ and a chiral guanidine.[8] In this case, the chiral guanidine salt of the carboxylic acid could act as a proton shuttle[9] for the enantioselective proton shift. In view of the strong basicity of guanidine[10] and the acidity of the N–H bond of benzophenone imines albeit weak, we plan to extend the cooperative catalysis of the dirhodium(II) complex and chiral guanidine to asymmetric carbene insertion into the N–H bond of benzophenone imine. In this text, we reported the details of such a process which enables the convenient generation of both alkyl and aryl substituted amino acetates in high yield and good enantioselectivities under mild reaction conditions. With regard to reaction partners and the type of proton-transfer carrier, this method complements the studies of Fu[4d] and Zhou,[4a–c] using either a chiral copper complex or dirhodium/chiral phosphoric acids for enantioselective N–H insertion of *tert*-butyl carbamate (Scheme 1b).

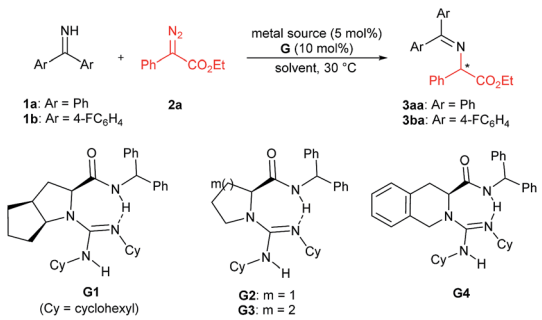
Results and discussion

We initially chose benzophenone imine **1a** and ethyl 2-diazo-2-phenylacetate **2a** as the model substrate to optimize the reaction conditions (Table 1). Several metal sources (see the ESI† for details) were screened in the presence of chiral guanidine **G1**[11] in CH_2Cl_2 at 30 °C, and it was found that $Rh_2(OAc)_4$ could promote the reaction to give the N–H insertion product **3aa** in good yield with low enantioselectivity (84% yield, 75 : 25 er, Table 1, entries 1–3). The combination of chiral guanidine with Pd(0), which was efficient in the asymmetric carbene insertion reaction of primary and secondary anilines,[3a] was completely inefficient in this reaction (entry 1). Next, we used $Rh_2(OAc)_4$ to explore different chiral guanidines. After exploring chiral guanidines derived from various amino acids, such as L-proline derived **G2**, L-pipecolic acid derived **G3** and (*S*)-tetrahydroisoquinoline-3-carboxylic acid derived **G4**, we obtained enantiomerically enriched products only in the presence of L-ramipril derived **G1** (Table 1, entry 3 *vs.* entries 4–6). The addition of 4 Å molecular sieves slightly benefited the improvement of the yield (Table 1, entry 7). After careful screening of the solvents, $CHCl_3$ was proven to be the best choice, and the N–H insertion product could be obtained in 87% yield and 82 : 18 er (Table 1, entry 8). $Rh_2(esp)_2$ exhibited higher activity, with which a yield of 93% with 82 : 18 er could be obtained at a reduced reaction temperature (Table 1, entries 9–11). The different substituents on phenyl of benzophenone imines were evaluated (see the ESI† for details), and in the presence of bis(4-fluorophenyl)methanimine **1b** as the model substrate and 1 mol% of $Rh_2(esp)_2$, the product **3ba** could be obtained in 96% yield and 90 : 10 er (Table 1, entries 12 and 13).

With the optimized reaction conditions in hand, we turned to evaluating the scope of α-diazoesters of this protocol. A variety of α-aryl α-diazoesters **2** were investigated. As shown in Table 2, α-diazoesters bearing halo-substituted phenyl groups at different positions could be smoothly converted to the corresponding products **3bb–3bg** in 96%–99% yields with 85 : 15 to 90 : 10 er, except for the 2-fluorophenyl substituted one. Generally, substrates with a halogen at the *meta*- and *para*-position obviously gave higher enantioselectivity than substrates with a halogen at the *ortho*-position. Electron-donating groups were tolerated in this reaction, and the desired products **3bh–3bj** were generated in 98–99% yields with 84 : 16 to 88 : 12 er. 2-Naphthyl or heteroaromatic substituted α-diazoesters were also suitable substrates, affording the related products **3bk–3bm** with moderate to good results (93–99% yields, 78 : 22 to 90 : 10 er). It is noteworthy that ethyl (*E*)-2-diazo-4-phenylbut-3-enoate **2n**, which contains an alkenyl substituent, underwent the reaction smoothly, but the product **3bn** *via* [1,4]-H transfer was obtained. This result is different from that of dirhodium(II) carboxylate/chiral spirophosphoric acid cooperatively promoted N–H insertion of vinyl diazoacetates with *tert*-butyl carbamate in Zhou's work.[4a]

Excited by the expected reaction profile, we next examined the attractive scenario of preparing alkyl substituted amino acids which are less enantioselective in the insertion reaction of *tert*-butyl carbamate.[4c] We reoptimized the reaction conditions between fluoro-containing benzophenone imine **1b** and 2-diazopropanoate (see the ESI† for details). To our delight, the

Table 1 Optimization of the reaction conditions[a]



Entry	Metal source	G	Solvent	Yield[b] (%)	er[c]
1	$Pd_2(dba)_3$	**G1**	CH_2Cl_2	N.R.	—
2	$AgNTf_2$	**G1**	CH_2Cl_2	83	50 : 50
3	$Rh_2(OAc)_4$	**G1**	CH_2Cl_2	84	75 : 25
4	$Rh_2(OAc)_4$	**G2**	CH_2Cl_2	82	50 : 50
5	$Rh_2(OAc)_4$	**G3**	CH_2Cl_2	88	50 : 50
6	$Rh_2(OAc)_4$	**G4**	CH_2Cl_2	89	50 : 50
7[d]	$Rh_2(OAc)_4$	**G1**	CH_2Cl_2	96	75 : 25
8[d]	$Rh_2(OAc)_4$	**G1**	$CHCl_3$	87	82 : 18
9[d]	$Rh_2(oct)_4$	**G1**	$CHCl_3$	88	74 : 26
10[d,e]	$Rh_2(esp)_2$	**G1**	$CHCl_3$	90	74 : 26
11[d,f]	$Rh_2(esp)_2$	**G1**	$CHCl_3$	93	82 : 18
12[d,f,g]	$Rh_2(esp)_2$	**G1**	$CHCl_3$	96	90 : 10
13[d,g,h]	$Rh_2(esp)_2$	**G1**	$CHCl_3$	96	90 : 10

[a] Unless otherwise noted, all reactions were carried out with metal source (5 mol%), **G** (10 mol%), **1a** (0.1 mmol), and **2a** (0.12 mmol) in the solvent (0.5 mL) at 30 °C for 5 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 4 Å MS (30 mg) was added. [e] The reaction time was 10 min. [f] At 0 °C for 8 h. [g] **1b** (0.1 mmol) was used. [h] $Rh_2(esp)_2$ (1 mol%) at 0 °C for 24 h.

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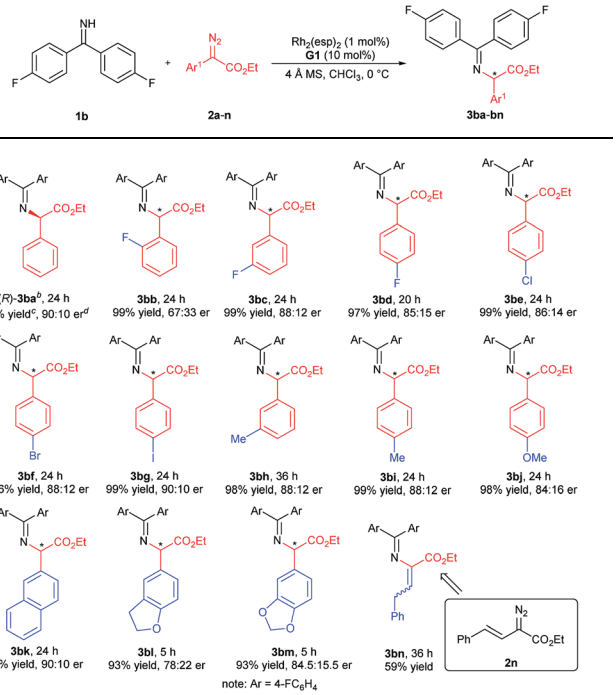
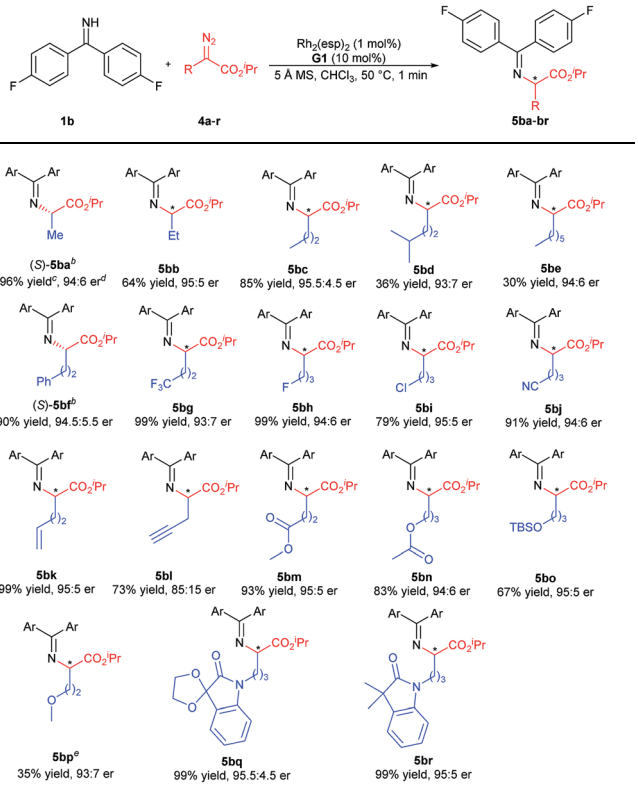
Table 2 Substrate scope of α-aryl α-diazoesters[a]



[a] Unless otherwise noted, all reactions were carried out with $Rh_2(esp)_2$ (1 mol%), **G1** (10 mol%), 4 Å MS (30 mg), **1b** (0.1 mmol), and **2** (1.2 equiv.) in $CHCl_3$ (0.5 mL) at 0 °C for 24 h. [b] The absolute configuration of the product **3ba** was determined to be *R* after the transformation into the corresponding *N*-Boc-protected amine **7ba**.[12] [c] Isolated yield. [d] Determined by chiral HPLC analysis.

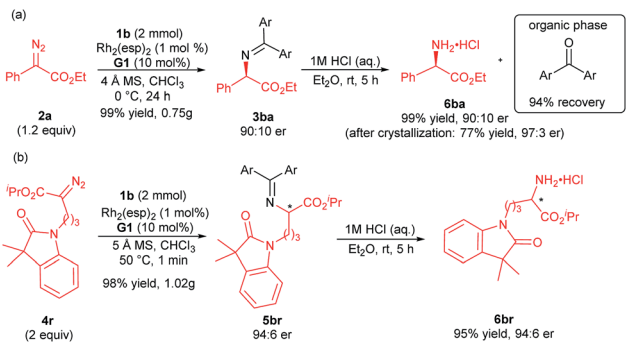
cooperative catalysis of $Rh_2(esp)_2$ and chiral guanidine **G1** occurred much more efficiently for alkyl substituted diazoesters than for aryl substituted ones. All the reactions were completed within one minute at increased reaction temperatures. Thus, we examined the reaction of benzophenone imine **1b** with various α-alkyl α-diazoesters **4**, with the results listed in Table 3. It was found that the length of the α-alkyl chain attached to α-diazoesters had a limited influence on the enantioselectivity (93 : 7 to 95.5 : 4.5 er) but the yield dramatically varied (30–96% yields) due to the formation of β-H elimination byproducts.[3d,15] The reaction was also tolerable to α-alkyl α-diazoesters with important functional groups, including phenyl, halogen, nitrile, alkenyl, propargyl, ester, silyl ester, and ether, and the corresponding products **5bf–5bp** were obtained in moderate to good yields (35–99% yields) with high enantioselectivities (85 : 15 to 95 : 5 er). Generally, the use of substrates with electron-withdrawing groups gave obviously higher yields than the use of those with electron-donating groups (**5bf–5bn** *vs.* **5bo–5bp**) because α-alkyl α-diazoesters containing electron-donating groups easily underwent β-H eliminate to form the corresponding olefins. Notably, the protected isatin and oxindole derived substrates could undergo the reaction smoothly and afforded the desired products **5bq** and **5br** with excellent results (99% yield, 95 : 5 and 95.5 : 4.5 er, respectively).

Table 3 Substrate scope of α-alkyl α-diazoesters[a]



[a] Unless otherwise noted, all reactions were carried out with $Rh_2(esp)_2$ (1 mol%), **G1** (10 mol%), 5 Å MS (30 mg), **1b** (0.1 mmol), and **4** (2.0 equiv.) in $CHCl_3$ (0.5 mL) at 50 °C for 1 min. [b] The absolute configuration of the products **5ba** and **5bf** was determined to be *S* after further transformation into known compounds[13,14] (see the ESI for details). [c] Isolated yield. [d] Determined by chiral HPLC analysis. [e] **4p** (4.0 equiv.) was added.

Furthermore, the synthetic utility of this reaction was investigated. A gram-scale synthesis of the products **3ba** and **5br** was carried out as shown in Scheme 2. Under the standard reaction conditions, the corresponding product **3ba** was generated in 99% yield and 90 : 10 er (Scheme 2a). The optically active *N*-unprotected 2-amino-2-phenylacetate **6ba** could be obtained easily by one step acidic hydrolysis in excellent yield



Scheme 2 Scaled-up version and further transformation.

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and enantioselectivity after recrystallization. Meanwhile, the benzophenone could be recovered in high yield from the organic phase. The absolute configuration of the product **3ba** was determined to be *R* after the transformation into the corresponding *N*-Boc-protected amine **7ba**, whose structure was determined by X-ray crystal analysis.[12] It is noteworthy that the absolute configuration of the products **5ba** and **5bf** was determined to be mainly *S* in comparison with the known chiral compounds after transformation (see the ESI† for details). An enantiodivergent phenomenon[16] was observed from the substrate variation in these cases (**3ba**/**5ba**/**5bf**). Similarly, the alkyl substituted amino acetate **6br** was afforded at a gram-scale with maintained enantioselectivity (Scheme 2b, 93% total yield, 94 : 6 er). This N–H insertion reaction of benzophenone imine provides a new convenient route to various chiral α-amino acids.

Conclusions

We have developed the first catalytic asymmetric N–H insertion of α-diazoesters with benzophenone imines. A cooperative catalytic system of a dirhodium(II) complex and chiral guanidine showed high efficiency. Both aryl and alkyl substituted α-amino esters were prepared in high yields and with good enantioselectivities under mild reaction conditions. In particular, this method complements the substrate limitation in N–H insertion of *tert*-butyl carbamate. We are currently extensively studying the mechanism and the use of chiral guanidine for other asymmetric reactions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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