Asymmetric Catalysis

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Asymmetric N–H Insertion of Secondary and Primary Anilines under the Catalysis of Palladium and Chiral Guanidine Derivatives**

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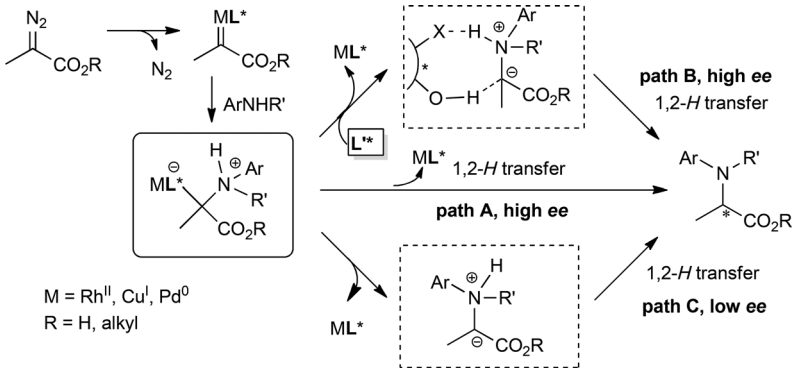
Abstract: *Efficient enantioselective N–H insertion reactions of secondary and primary anilines were catalyzed by palladium(0) in combination with chiral guanidine derivatives. A broad range of substituted anilines were tolerated, and the corresponding products were obtained in high yield (up to 99%) with good enantioselectivity (up to 94% ee) under mild reaction conditions. The N–H insertion mechanism was examined by the study of kinetic isotope effects, control experiments, HRMS, and spectroscopic analysis.*

The enantioselective insertion of metal carbenes into N–H bonds[1] provides an attractive route for the synthesis of chiral α-amino acids.[2] Remarkable progress on asymmetric N–H insertion reactions of primary amines with α-diazoesters[3] has been made.[4] Copper(I) and dirhodium(II) complexes are the most widely used catalysts for this type of reaction. A pioneering study of McKervey and co-workers demonstrated the ability of chiral rhodium(II) carboxylates to catalyze asymmetric intramolecular N–H insertion reactions.[4a] Copper complexes of well-defined chiral ligands, such as spiro bisoxazolines,[5] bipyridines,[6] and binol derivatives,[7] were later developed to achieve high enantioselectivity (Scheme 1, path A). Recently, intriguing strategies involving the cooperative catalysis of dirhodium(II) carboxylates with cinchona alkaloids[8a] or chiral spiro phosphoric acids[9] were also exploited (Scheme 1, path B). A further, earlier example of a silver(I)-mediated reaction proceeded with moderate enantioselectivity.[4b] Although palladium has been applied increasingly in carbenoid chemistry,[10] its use in catalytic asymmetric X–H insertion reactions (X = heteroatom) has rarely been reported.[1f,11,12]

The general consensus on the N–H insertion mechanism is that the electron-deficient metal carbene inserts into the N–H bond according to a stepwise ylide-generation/proton-shift process (Scheme 1).[13] Only when the stereodetermining 1,2-*H* shift occurs in a concerted manner or in a metal-associated-ylide pathway[4b,5–7] (path A) or is assisted by a chiral proton-transfer shuttle[9] (path B) can high enantioselectivity be achieved. Alternatively, the intermediacy of a free ylide from which the chiral catalyst has dissociated would result in low enantioselectivity (path C).[1c,5b] As compared with the reaction of primary amines, the N–H insertion of secondary amines, such as *N*-alkyl anilines, would generate a more stable ylide intermediate bearing alkyl/aryl substituents at the nitrogen atom. It is reasonable to hypothesize that the relatively high stability of ammonium ylides might facilitate the degeneration of the catalyst-associated ylide to a free ylide and thus lead to poor enantioselectivity.[5b] On the other hand, the more nucleophilic nitrogen atom is inclined to coordinate strongly with the metal center, which may lead to the inactivation of the catalyst. Less asymmetric N–H insertion of secondary amines[14] with α-diazoesters has yet been developed with satisfactory enantioselectivity.[4a,b,5a,7] The highest enantioselectivity observed for the asymmetric N–H insertion of *N*-methylaniline was the formation of the product with 70% *ee*.[7] Thus, the development of a new and efficient catalytic system for the asymmetric N–H insertion of secondary amines is of interest and is challenging.



Scheme 1. Possible mechanisms of the asymmetric N–H insertion reaction.

Chiral guanidine derivatives have been developed as useful organocatalysts in recent years.[15] Our research group has dedicated itself to the design of bifunctional chiral guanidine–amide organocatalysts and has thereby discovered several efficient reactions.[16] Guanidine has abundant coordination modes with various metals;[17] however, neutral guanidine derivatives have been overlooked as ligands and have received a disproportionately low amount of attention.[18] In 2005, Anders and co-workers reported a unique example of an asymmetric Henry reaction promoted by a chiral guanidine–zinc(II) complex; however, the product

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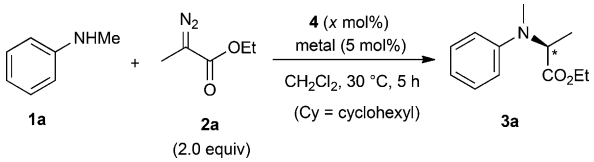
was formed with only 2% *ee*.[19a,b] Herein, we report our preliminary results on the combination of chiral guanidine derivatives with Pd^0 as catalysts for asymmetric N–H insertion reactions of both secondary and primary amines. Good yields and enantioselectivities were observed for the synthesis of various substituted anilines.

The insertion of ethyl 2-diazopropanoate (**2a**) into the N–H bond of *N*-methylaniline (**1a**) in dichloromethane at 30°C was chosen as the model reaction. We initiated our investigation with a screening of several metal catalysts in the presence of chiral guanidine **4a** derived from (*S*)-tetrahydroisoquinoline-3-carboxylic acid (Table 1, entries 1–4). With CuCl, product **3a** was obtained with acceptable enantioselectivity (71% *ee*) in up to 99% yield (Table 1, entry 1). Whereas $Rh_2(OAc)_4$ gave comparable enantioselectivity to

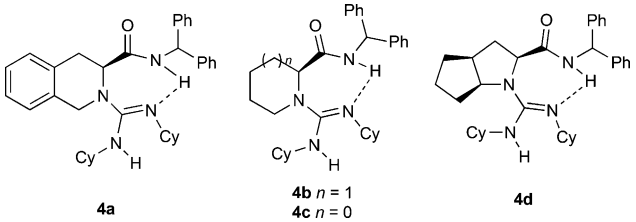
Table 1: Effect of various reaction parameters.[a]



1a **2a** (2.0 equiv) **3a**

Entry	Metal precursor	4	*x*	Yield [%][b]	*ee* [%][c]
1[d]	CuCl	**4a**	10	99	71
2	$Rh_2(OAc)_4$	**4a**	10	60	70
3[d]	$Fe(ClO_4)_2{\cdot}6H_2O$	**4a**	10	99	0
4	$[Pd_2(dba)_3]$	**4a**	10	86	88
5	$[Pd_2(dba)_3]$	**4b**	10	75	72
6	$[Pd_2(dba)_3]$	**4c**	10	74	86
7	$[Pd_2(dba)_3]$	**4d**	10	75	88
8	$[Pd_2(dba)_3]$	**4a**	2	86	90 (*S*)[e]
9	$[Pd_2(dba)_3]$	**4a**	1	86	87

[a] Unless otherwise noted, reactions were carried out with the metal precursor (5 mol%), **4** (*x* mol%), **1a** (0.10 mmol), and **2a** (0.20 mmol, 2.0 equiv) in CH_2Cl_2 (1.0 mL) at 30°C for 5 h. [b] Yield of the isolated product as based on aniline **1a**. [c] The *ee* value was determined by HPLC analysis on a chiral stationary phase. [d] The amount of the metal precursor was 10 mol%. [e] The absolute configuration of **3a** was determined by comparison of the optical rotation with that given in Ref. [20], as shown in the Supporting Information. dba = dibenzylideneacetone.

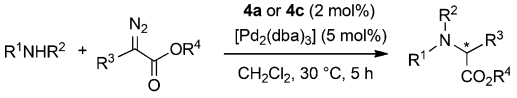


4a **4b** *n* = 1, **4c** *n* = 0 **4d**

CuCl, but a lower yield, $Fe(ClO_4)_2{\cdot}6H_2O$ showed excellent reactivity, but the product was obtained as a racemate (Table 1, entries 2 and 3). A remarkable improvement in enantioselectivity was observed when $[Pd_2(dba)_3]$ was used as the metal precursor (86% yield, 88% *ee*; Table 1, entry 4). Although L-ramipril-derived guanidine **4d** was superior to L-pipecolic acid derived **4b** and L-proline-derived **4c**, no improvement in enantioselectivity or yield was observed as compared with **4a** (Table 1, entries 5–7). Intriguingly, a decrease in the amount of guanidine **4a** to 2 mol% led to slightly higher enantioselectivity without loss of yield (90% *ee* and 86% yield; Table 1, entry 8). The requirement of an excess amount of palladium might be partly attributable to deactivation by the precipitation of Pd^0. Further lowering of the amount of the guanidine derivative to 1 mol% led to the formation of the insertion product in maintained yield but with a somewhat lower *ee* value (87% *ee*; Table 1, entry 9).

Various substituted secondary anilines were tested in the asymmetric N–H insertion reaction under the optimized conditions (Table 1, entry 8). The influence of the electronic properties of the *N*-methylaniline on the enantioselectivity of the reaction was evaluated by varying the substitution of the aryl group. Generally, the use of substrates with electron-withdrawing groups gave slightly higher enantioselectivities than the use of those with electron-donating groups (Table 2, entries 1–6 and 12 versus entries 7–11). The position of the substituent on the aryl group had no clear influence on the enantioselectivity of the reaction. Moreover, *N*-methylnaphthalen-1-amine, *N*-ethylaniline, *N*-allylaniline, and *N*-benzylaniline were well tolerated in terms of enantioselectivity when the L-proline-derived guanidine **4c** was used (Table 2,

Table 2: Scope of the N–H insertion of secondary anilines.[a]



1 **2** (2.0 equiv) **3**

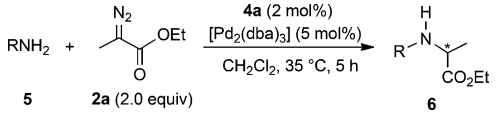
Entry	R^1	R^2	R^3	R^4	Yield [%][b]	*ee* [%][c]
1	$2\text{-}FC_6H_4$	Me	Me	Et	77 (**3b**)	88
2	$3\text{-}FC_6H_4$	Me	Me	Et	77 (**3c**)	91
3	$4\text{-}FC_6H_4$	Me	Me	Et	80 (**3d**)	91
4	$3\text{-}ClC_6H_4$	Me	Me	Et	82 (**3e**)	93
5	$4\text{-}ClC_6H_4$	Me	Me	Et	75 (**3f**)	92
6	$4\text{-}BrC_6H_4$	Me	Me	Et	80 (**3g**)	92
7	$3\text{-}MeC_6H_4$	Me	Me	Et	70 (**3h**)	90
8	$4\text{-}MeC_6H_4$	Me	Me	Et	75 (**3i**)	87
9[d]	$2\text{-}MeOC_6H_4$	Me	Me	Et	65 (**3j**)	92
10	$3\text{-}MeOC_6H_4$	Me	Me	Et	82 (**3k**)	90
11[e]	$4\text{-}MeOC_6H_4$	Me	Me	Et	91 (**3l**)	87
12	$4\text{-}CF_3OC_6H_4$	Me	Me	Et	93 (**3m**)	93
13[d]	1-naphthyl	Me	Me	Et	59 (**3n**)	88
14[d]	Ph	Et	Me	Et	60 (**3o**)	92
15[d,f]	Ph	Et	Me	Me	24 (**3p**)	94
16[d,g]	Ph	allyl	Me	Et	66 (**3q**)	85
17[d]	Ph	Bn	Me	Et	50 (**3r**)	92
18[d]	Ph	Me	Et	Et	55 (**3s**)	90
19[d]	Ph	Me	*n*Pr	Et	20 (**3t**)	90
20[f]	Ph	Me	Me	Me	75 (**3u**)	90
21[d]	Ph	Me	Me	*t*Bu	79 (**3v**)	81
22[d]	Ph	Me	Me	Bn	85 (**3w**)	93
23[h]	Ph	Me	Me	Et	85 (**3a**)	90

[a] Unless otherwise noted, reactions were carried out with $[Pd_2(dba)_3]$ (5 mol%), **4a** (2 mol%), **1** (0.10 mmol), and **2** (0.20 mmol, 2.0 equiv) in CH_2Cl_2 (1.0 mL) at 30°C for 5 h. [b,c] See Table 1. [d] Guanidine **4c** was used. [e] The reaction was carried out at 15°C. [f] The reaction was carried out in CH_2Cl_2 (2.0 mL). [g] The reaction was carried out at 35°C. [h] The reaction was carried out with $[Pd_2(dba)_3]$ (5 mol%), **4a** (2 mol%), **1a** (7.0 mmol), and **2a** (14.0 mmol, 2.0 equiv) in CH_2Cl_2 (70 mL) at 30°C for 12 h. Bn = benzyl.

entries 13–17). The lower yields might be due to an adverse effect of steric hindrance on nucleophilic addition to the electron-deficient carbene intermediate. Next, the substituents on the α-diazoester were investigated (Table 2, entries 18–22). The length of the α-alkyl group had a remarkable effect on the yield. When ethyl α-diazobutyrate was used, the N–H insertion product was obtained in 55% yield with 90% *ee* (Table 2, entry 18). A low yield was observed for the corresponding reaction with ethyl 2-diazopentanoate, although the enantioselectivity was maintained (90% *ee*, 20% yield; Table 2, entry 19). The ester group could be changed from an ethyl to a methyl group without deterioration of the enantioselectivity (Table 2, entry 20). The reaction of *tert*-butyl-substituted 2-diazopropanoate proceeded well in 79% yield with 81% *ee* (Table 2, entry 21). Furthermore, benzyl 2-diazopropanoate was transformed into the corresponding product with excellent results (93% *ee*, 85% yield; Table 2, entry 22). Unfortunately, in attempts at the N–H insertion of α-aryl- and other α-alkyl-substituted diazoesters, the aniline substrate was not consumed under the present conditions. A gram-scale synthesis was performed under the optimized reaction conditions, and the desired product **3a** was obtained without loss of yield or enantioselectivity (Table 2, entry 23; 85% yield, 90% *ee*).

Subsequently, we examined the asymmetric N–H insertion reactions of several primary anilines with the catalytic system of $[Pd_2(dba)_3]$ and guanidine **4a**. Most of the substituted anilines in Table 3 could be smoothly converted into the corresponding products in good yields (83–98%) with high *ee* values (87–92%; Table 3, entries 1–6). In the case of 2-bromoaniline, an excellent yield was observed with slightly lower enantioselectivity (99% yield, 82% *ee*; Table 3, entry 7). Interestingly, the correlation of the log(*er*) values (*er* is the ratio of enantiomers) of the products with the Hammett substituent constants[22] of the corresponding *para*-substituted aniline followed a linear relationship, but an opposite trend between secondary and primary amines was observed (see the Supporting Information for details).

Table 3: Scope of the N–H insertion of primary anilines.[a]

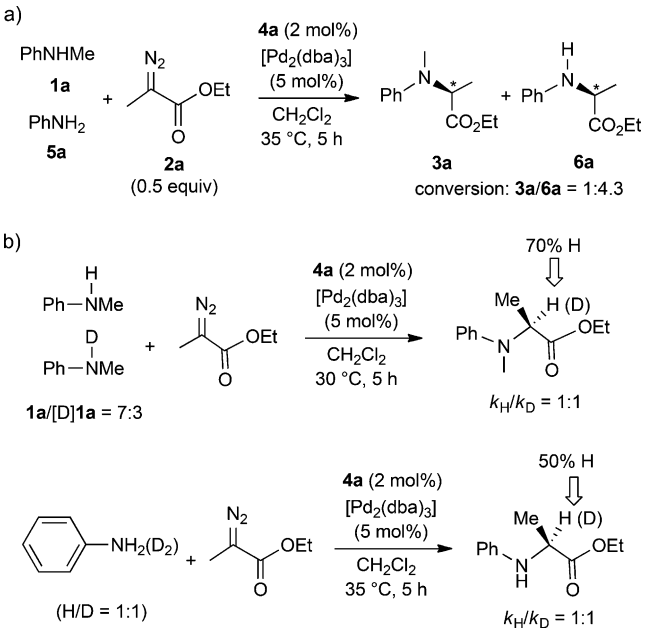


5 2a (2.0 equiv) 6

Entry	R	Yield [%][b]	*ee* [%][c]
1	Ph	98 (**6a**)	90 (*S*)[d]
2	4-MeC_6H_4	97 (**6b**)	92
3	4-MeOC_6H_4	83 (**6c**)	92
4	4-FC_6H_4	85 (**6d**)	90
5	4-ClC_6H_4	88 (**6e**)	87
6	4-BrC_6H_4	96 (**6f**)	88
7	2-BrC_6H_4	99 (**6g**)	82

[a] Reactions were carried out with $[Pd_2(dba)_3]$ (5 mol%), **4a** (2 mol%), **5** (0.10 mmol), and **2a** (0.20 mmol, 2.0 equiv) in CH_2Cl_2 (2.0 mL) at 35 °C for 5 h. [b,c] See Table 1. [d] The absolute configuration of **6a** was determined by comparison of the optical rotation with that given in Refs. [5a, 21].

A competition experiment between aniline and *N*-methylaniline under identical reaction conditions indicated a much higher reactivity of aniline (Scheme 2a). We speculated that the steric hindrance of the secondary amine was disadvantageous for nucleophilic addition to carbene species; thus, the yield was lower than that observed for the primary amine



Scheme 2. Control experiments.

(Table 2 versus Table 3). No kinetic isotope effect ($k_H/k_D = 1.0$) was detected in the guanidine–palladium(0)-catalyzed N–H insertion reaction of α-diazoester **2a** with either *N*-methylaniline (**1a**)[23] or aniline (**5a**; Scheme 2b), in contrast to the N–H insertion of anilines with a chiral copper(I) catalyst.[5b,6] This result implied that a proton transfer was not involved in the rate-limiting step in the current system. Decomposition of the α-diazoester and nucleophilic addition of the amine to the metal carbene might account for the reaction process. Hence, high enantioselectivity was gained through simultaneous intramolecular 1,2-proton transfer[14c,24] and dissociation of the chiral catalyst. Otherwise, a stabilized free ammonium ylide and oxygen-associated intermediate would cause formation of the N–H insertion product with lower enantioselectivity.

The detailed mechanism of the N–H insertion catalyzed by the combination of a guanidine derivative and palladium is not yet clear, but some observations may offer insight. Considering the strong Brønsted basicity of guanidine,[15b,f,25] we suspected that it could coordinate with Pd[19c] instead of acting as a chiral proton-transfer shuttle.[9] The action of palladium was probed by ESI HRMS analysis. MS peaks observed at *m*/*z* 206.9566, 441.0638, and 655.2812 corresponded to $[Pd^0 + (\mathbf{2a}-N_2) + H^+]^+$, $[Pd^0 + (\mathbf{2a}-N_2) + dba + H^+]^+$ and $[Pd^0 + \mathbf{4a} + H^+]^+$, respectively, and confirmed the generation of palladium–carbene species and the coordination of the guanidine with Pd^0. Next, the catalytically active oxidation state of palladium in the system was investigated

through additional control experiments. In the presence of guanidine **4a**, palladium(II) compounds, such as $PdCl_2$, $Pd(OAc)_2$, $[PdCl_2(CH_3CN)_2]$, and $[Pd_2Cl_2(allyl)_2]$, promoted the reaction of **1a** with **2a** either in poor yield or with low enantioselectivity. Taking these results together, we identified the Pd^0 complex as the active species.

Fluorescence and UV/Vis absorption spectroscopy experiments were also used to analyze the catalytic species. Complete fluorescence quenching was observed upon the addition of $[Pd_2(dba)_3]$ to the solution of **4a** (Figure 1a). CuCl and $Rh_2(OAc)_4$ lowered the fluorescence intensity to a certain

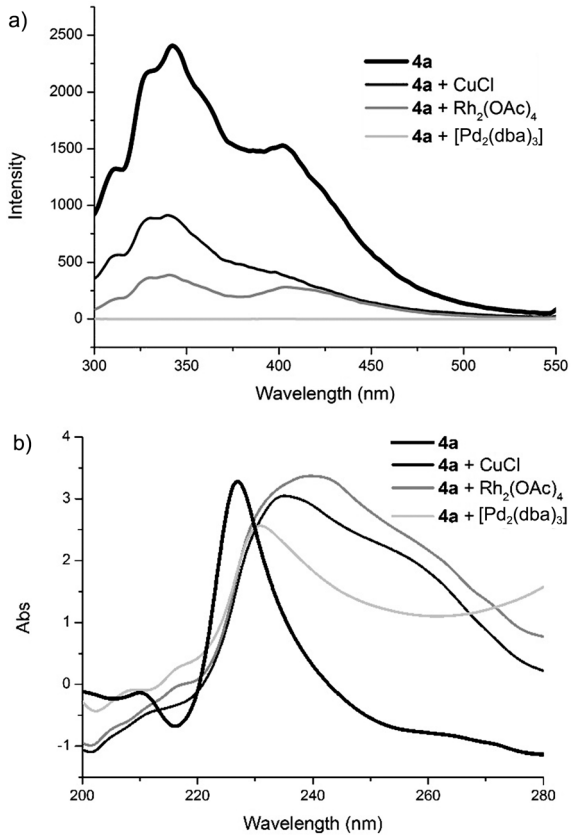


Figure 1. a) Fluorescence spectra of **4a** at 4×10^{-3} M with or without a metal precursor (4×10^{-3} M) in CH_2Cl_2; b) UV spectra of **4a** at 2×10^{-3} M with or without a metal precursor (2×10^{-3} M) in CH_2Cl_2.

degree. Furthermore, the maximum UV absorption wavelength of the mixture of **4a** and $[Pd_2(dba)_3]$ was shifted toward a longer wavelength (from 226 nm for **4a** to 230 nm), and the addition of CuCl or $Rh_2(OAc)_4$ to **4a** uniformly led to a redshift (Figure 1b). These observations indicated that there must be an interaction between the chiral guanidine and the effective metal precursor used.[26]

In summary, we have developed a new kind of chiral complex catalyst for the highly enantioselective N–H insertion of α-diazoesters. Our results clearly showed that palladium(0) could also be active in the asymmetric N–H insertion. Moreover, a chiral guanidine derivative was for the first time successfully developed as a fascinating ligand, although a detailed study of the catalyst structure is still highly desired. The catalytic system is based on the unique properties of the chiral guanidine ligand and palladium–carbene chemistry, and provides new opportunities for novel transformations. Further study of the reaction mechanism and extensive exploration of the use of the catalyst system for other asymmetric reactions are under way.

Experimental Section

General procedure: A mixture of $[Pd_2(dba)_3]$ (4.6 mg, 0.005 mmol, 5 mol%) and guanidine **4a** (1.1 mg, 0.002 mmol, 2 mol%) was weighed into a test tube under an inert atmosphere. CH_2Cl_2 (1.0 mL) was then added, followed by *N*-methylaniline (**1a**; 10.8 μL, 10.7 mg, 0.1 mmol) and then α-diazoester **2a** (24.0 μL, 25.6 mg, 0.2 mmol). The resulting mixture was stirred for 5 h at 30 °C, and the product **3a** was purified by flash chromatography ($R_f = 0.5$, petroleum ether/Et_2O 4:1).

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[1] For representative reviews of the catalyzed N–H insertion of diazo compounds, see: a) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, **1998**, chap. 3 and 8; b) T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091–1160; c) C. J. Moody, *Angew. Chem.* **2007**, *119*, 9308–9310; *Angew. Chem. Int. Ed.* **2007**, *46*, 9148–9150; d) Z.-H. Zhang, J.-B. Wang, *Tetrahedron* **2008**, *64*, 6577–6605; e) S.-F. Zhu, Q.-L. Zhou, *Acc. Chem. Res.* **2012**, *45*, 1365–1377; f) D. Gillingham, N. Fei, *Chem. Soc. Rev.* **2013**, *42*, 4918–4931; for the first example of asymmetric vinylogous N–H insertion, see: g) X. F. Xu, P. Y. Zavalij, M. P. Doyle, *Angew. Chem.* **2012**, *124*, 9967–9971; *Angew. Chem. Int. Ed.* **2012**, *51*, 9829–9833.

[2] For selected reviews, see: a) R. M. Williams, in *Synthesis of Optically Active α-Amino Acids* (Ed.: J. E. Baldwin), Pergamon, Oxford, UK, **1989** (Organic Chemistry Series); b) C. Nájera, J. M. Sansano, *Chem. Rev.* **2007**, *107*, 4584–4671; c) M. Calmes, J. Daunis, *Amino Acids* **1999**, *16*, 215–250.

[3] For the preparation of α-diazoesters, see: a) D. F. Taber, R. B. Sheth, P. V. Joshi, *J. Org. Chem.* **2005**, *70*, 2851–2854; b) L. Huang, W. D. Wulff, *J. Am. Chem. Soc.* **2011**, *133*, 8892–8895.

[4] For early enantioselective N–H reactions of primary amines, see: a) C. F. García, M. A. McKervey, T. Ye, *Chem. Commun.* **1996**, 1465–1466; b) S. Bachmann, D. Fielenbach, K. A. Jørgensen, *Org. Biomol. Chem.* **2004**, *2*, 3044–3049; c) R. T. Buck, C. J. Moody, A. G. Pepper, *ARKIVOC* **2002**, viii, 16–33.

[5] a) B. Liu, S.-F. Zhu, W. Zhang, C. Chen, Q.-L. Zhou, *J. Am. Chem. Soc.* **2007**, *129*, 5834–5835; b) S.-F. Zhu, B. Xu, G.-P. Wang, Q.-L. Zhou, *J. Am. Chem. Soc.* **2012**, *134*, 436–442.

[6] E. C. Lee, G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 12066–12067.

[7] Z. R. Hou, J. Wang, P. He, J. Wang, B. Qin, X. H. Liu, L. L. Lin, X. M. Feng, *Angew. Chem.* **2010**, *122*, 4873–4876; *Angew. Chem. Int. Ed.* **2010**, *49*, 4763–4766.

[8] a) H. Saito, T. Uchiyama, M. Miyake, M. Anada, S. Hashimoto, T. Takabatake, S. Miyairi, *Heterocycles* **2010**, *81*, 1149–1155; for the N–H insertion of anilines under the catalysis of cinchona alkaloids without metals, see: b) H. Saito, D. Morita, T. Uchiyama, M. Miyake, S. Miyairi, *Tetrahedron Lett.* **2012**, *53*, 6662–6664.

[9] B. Xu, S.-F. Zhu, X.-L. Xie, J.-J. Shen, Q.-L. Zhou, *Angew. Chem.* **2011**, *123*, 11685 – 11688; *Angew. Chem. Int. Ed.* **2011**, *50*, 11483 – 11486.
[10] For representative reviews of palladium-catalyzed reactions of diazo compounds, see: a) Y. Zhang, J.-B. Wang, *Eur. J. Org. Chem.* **2011**, 1015 – 1026; b) Q. Xiao, Y. Zhang, J.-B. Wang, *Acc. Chem. Res.* **2013**, *46*, 236 – 247.
[11] a) D. F. Taber, J. C. Amedio, Jr., R. G. Sherrill, *J. Org. Chem.* **1986**, *51*, 3382 – 3384; b) D. Zhang, H. Qiu, L.-Q. Jiang, F.-P. Lv, C.-Q. Ma, W.-H. Hu, *Angew. Chem.* **2013**, *125*, 13598 – 13602; *Angew. Chem. Int. Ed.* **2013**, *52*, 13356 – 13360.
[12] For a recent example of a diastereoselective reaction, see: G. Liu, J. Li, L. Qiu, L. Liu, G. Y. Xu, B. Ma, J. T. Sun, *Org. Biomol. Chem.* **2013**, *11*, 5998 – 6002.
[13] a) Y.-H. Wang, Y.-X. Zhu, Z.-Y. Chen, A.-Q. Mi, W.-H. Hu, M. P. Doyle, *Org. Lett.* **2003**, *5*, 3923 – 3926; b) Y.-H. Wang, Z.-Y. Chen, A.-Q. Mi, W.-H. Hu, *Chem. Commun.* **2004**, 2486 – 2487; c) H.-X. Huang, Y.-H. Wang, Z.-Y. Chen, W.-H. Hu, *Adv. Synth. Catal.* **2005**, *347*, 531 – 534; d) Y.-G. Zhu, C.-W. Zhai, Y.-L. Yue, L.-P. Yang, W.-H. Hu, *Chem. Commun.* **2009**, 1362 – 1364.
[14] For selected examples of N–H insertion reactions of secondary amines to give racemic products, see: a) Q.-H. Deng, H.-W. Xu, A. W.-H. Yuen, Z.-J. Xu, C.-M. Che, *Org. Lett.* **2008**, *10*, 1529 – 1532; b) I. Aviv, Z. Gross, *Chem. Eur. J.* **2008**, *14*, 3995 – 4005; c) B. J. Anding, L. K. Woo, *Organometallics* **2013**, *32*, 2599 – 2607.
[15] For selected reviews about guanidine-catalyzed reactions, see: a) D. Leow, C.-H. Tan, *Chem. Asian J.* **2009**, *4*, 488 – 507; b) M. Terada, *J. Synth. Org. Chem. Jpn.* **2010**, *68*, 1159 – 1168; c) X. Fu, C.-H. Tan, *Chem. Commun.* **2011**, *47*, 8210 – 8222; d) T. R. M. Rauws, B. U. W. Maes, *Chem. Soc. Rev.* **2012**, *41*, 2463 – 2497; e) J. E. Taylor, S. D. Bull, J. M. J. Williams, *Chem. Soc. Rev.* **2012**, *41*, 2109 – 2121; f) P. Selig, *Synthesis* **2013**, *45*, 703 – 718.
[16] For selected examples from our research group, see: a) Z. P. Yu, X. H. Liu, L. Zhou, L. L. Lin, X. M. Feng, *Angew. Chem.* **2009**, *121*, 5297 – 5300; *Angew. Chem. Int. Ed.* **2009**, *48*, 5195 – 5198; b) S. X. Dong, X. H. Liu, X. H. Chen, F. Mei, Y. L. Zhang, B. Gao, L. L. Lin, X. M. Feng, *J. Am. Chem. Soc.* **2010**, *132*, 10650 – 10651; c) S. X. Dong, X. H. Liu, Y. Zhu, P. He, L. L. Lin, X. M. Feng, *J. Am. Chem. Soc.* **2013**, *135*, 10026 – 10029; for other examples, see: d) T. Naicker, P. I. Arvidsson, H. G. Kruger, G. E. M. Maguire, T. Govender, *Eur. J. Org. Chem.* **2012**, 3331 – 3337; e) L. Wu, G. X. Li, Q. Q. Fu, L. T. Yu, Z. Tang, *Org. Biomol. Chem.* **2013**, *11*, 443 – 447.
[17] For selected examples, see: a) R. Lee, Y. Y. Yang, G. K. Tan, C.-H. Tan, K.-W. Huang, *Dalton Trans.* **2010**, *39*, 723 – 725; b) I. M. Müller, R. Robson, *Angew. Chem.* **2000**, *112*, 4527 – 4530; *Angew. Chem. Int. Ed.* **2000**, *39*, 4357 – 4359; c) S. Aoki, K. Iwaida, N. Hanamoto, M. Shiro, E. Kimura, *J. Am. Chem. Soc.* **2002**, *124*, 5256 – 5257.
[18] For representative reviews, see: a) P. J. Bailey, S. Pace, *Coord. Chem. Rev.* **2001**, *214*, 91 – 141; b) M. P. Coles, *Dalton Trans.* **2006**, 985 – 1001; c) M. P. Coles, *Chem. Commun.* **2009**, 3659 – 3676.
[19] a) U. Köhn, W. Günther, H. Görls, E. Anders, *Tetrahedron: Asymmetry* **2004**, *15*, 1419 – 1426; b) U. Köhn, M. Schulz, H. Görls, E. Anders, *Tetrahedron: Asymmetry* **2005**, *16*, 2125 – 2131; c) S. H. Oakley, M. P. Coles, P. B. Hitchcock, *Inorg. Chem.* **2004**, *43*, 7564 – 7566.
[20] V. Camp, J. Ann, PCT Int. Appl. 2003099769, 04 Dec, **2003**.
[21] A. V. Kurkin, V. V. Nesterov, A. V. Karchava, M. A. Yurovskaya, *Chem. Heterocycl. Compd.* **2003**, *39*, 1466 – 1477.
[22] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165 – 195.
[23] For the preparation for deuterium-labeled *N*-methylaniline, see: D. C. Dittmer, A. F. Marcantonio, *J. Am. Chem. Soc.* **1964**, *86*, 5621 – 5626.
[24] J. Jiang, H.-D. Xu, J.-B. Xi, B.-Y. Ren, F.-P. Lv, X. Guo, L.-Q. Jiang, Z.-Y. Zhang, W.-H. Hu, *J. Am. Chem. Soc.* **2011**, *133*, 8428 – 8431.
[25] T. Ishikawa in *Superbases for Organic Synthesis* (Ed.: T. Ishikawa), Wiley, Chichester, **2009**, pp. 93 – 143.
[26] a) G. L. Geoffroy, H. Isci, J. Litrenti, W. R. Mason, *Inorg. Chem.* **1977**, *16*, 1950 – 1955; b) W. R. Mason III, H. B. Gray, *J. Am. Chem. Soc.* **1968**, *90*, 5721 – 5729; c) C. D. Cowman, C. J. Ballhausen, H. B. Gray, *J. Am. Chem. Soc.* **1973**, *95*, 7873 – 7875.

