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ASYMMETRIC INTERMOLECULAR N–H INSERTION REACTION OF PHENYLDIAZOACETATES WITH ANILINES CATALYZED BY ACHIRAL DIRHODIUM(II) CARBOXYLATES AND CINCHONA ALKALOIDS

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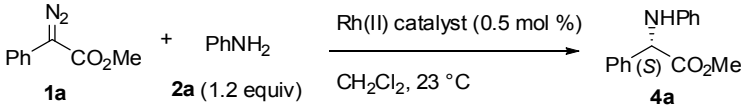
Abstract – Asymmetric N–H insertion of phenyldiazoacetates with anilines catalyzed cooperatively by achiral dirhodium(II) carboxylates and cinchona alkaloids is described. A new catalytic system of dirhodium(II) tetrakis(triphenylacetate), $Rh_2(TPA)_4$, and dihydrocinchonine provides phenylglycine derivatives in up to 71% ee.

The transition metal-catalyzed N–H insertion reaction of α-diazocarbonyl compounds, which features C–N bond formation with simultaneous creation of a stereogenic center, offers a potentially powerful strategy for the synthesis of nitrogen-containing compounds.[1] Consequently, much effort has been directed towards the development of an enantioselective version of this catalytic process.[2] While exceptionally high levels of enantiocontrol in C–H insertions of α-diazocarbonyl compounds have already been achieved by the device of well-defined dirhodium(II) carboxylates and carboxamidates as chiral catalysts,[3] it was not until recently that a highly enantioselective N–H insertion process was developed.[4–6] In 2007, Zhou and co-workers demonstrated the first successful examples of intermolecular N–H insertion of α-alkyl-α-diazoacetates with anilines (up to 98% ee) using a chiral copper(I)–spiro bis(oxazoline) catalyst.[7] Thereafter, Fu and Lee reported enantioselective N–H insertion reactions of *tert*-butyl aryldiazoacetates with benzyl or *tert*-butyl carbamates catalyzed by a planer-chiral copper(I)-bipyridine complex with up to 95% ee.[8]

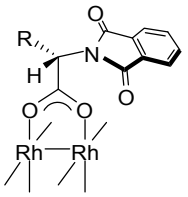
In recent years, we have achieved high levels of enantiocontrol in C–H[9] and Si–H[10] insertion reactions by developing dirhodium(II) carboxylate catalysts, which incorporate *N*-phthaloyl- or *N*-benzene-fused-phthaloyl-(*S*)-amino acids as bridging ligands. As a logical extension of our studies, we addressed the issue of enantiocontrol in Rh(II)-catalyzed N–H insertion reactions.

At the outset of this work, we explored the N–H insertion reaction of methyl phenyldiazoacetate (**1a**) with aniline (**2a**) in dichloromethane using 0.5 mol% of Rh_2(*S*-PTPA)$_4$ (**3a**). The reaction proceeded smoothly completion at room temperature within 1 h, giving phenylglycine derivative (**4a**) in 90% yield (Table 1, Entry 1). The enantioselectivity of this reaction was determined to be 14% ee by HPLC analysis (Daicel Chiralpak AD-H). The preferred absolute stereochemistry of **4a** [$[\alpha]^{22}_D$ +10.3° (*c* 2.16, THF) for 14% ee] was established as *S* by comparing the sign of the optical rotation with the literature value [lit.,[11] $[\alpha]^{26}_D$ +68.3° (*c* 0.32, THF) for > 98% ee of (*S*)-**4a**]. A survey of solvents revealed that dichloromethane was the optimal solvent for this transformation.[12] We next screened other chiral dirhodium(II) carboxylates, Rh_2(*S*-PTA)$_4$ (**3b**), Rh_2(*S*-PTV)$_4$ (**3c**), and Rh_2(*S*-PTTL)$_4$ (**3d**), derived from *N*-phthaloyl-(*S*)-alanine, -valine, and -*tert*-leucine, respectively. Although the reactions with **3b-d** afforded **4a** in high yields at similar reaction rates as those observed with **3a**, these catalysts led to much lower enantioselectivities than Rh_2(*S*-PTPA)$_4$ (Entries 2–4).

Table 1. Enantioselective N–H Insertion Reaction of Methyl Phenyldiazoacetate (**1a**) with Aniline (**2a**) Catalyzed by Chiral Rh(II) Carboxylates[a)]



Entry	Rh(II) catalyst	Time (h)	α-Amino ester **4a** Yield (%)[b)]	Ee (%)[c)]	Config[d)]
1	Rh_2(*S*-PTPA)$_4$ (**3a**)	1	90	14	*S*
2	Rh_2(*S*-PTA)$_4$ (**3b**)	1	83	7	*S*
3	Rh_2(*S*-PTV)$_4$ (**3c**)	1.5	86	1	*R*
4	Rh_2(*S*-PTTL)$_4$ (**3d**)	1	89	1	*S*

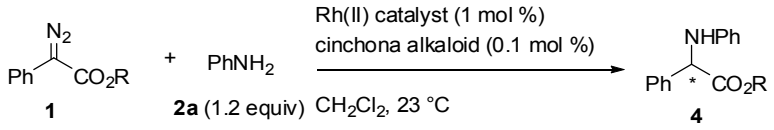


R = Bn: Rh_2(*S*-PTPA)$_4$ (**3a**)
R = Me: Rh_2(*S*-PTA)$_4$ (**3b**)
R = ^{i}Pr: Rh_2(*S*-PTV)$_4$ (**3c**)
R = ^{t}Bu: Rh_2(*S*-PTTL)$_4$ (**3d**)

[a)] The following procedure is representative (Entry 1): Rh_2(*S*-PTPA)$_4$ (**3a**) (1.4 mg, 0.001 mmol, 0.5 mol %) was added in one portion to a solution of phenyldiazoacetate (**1a**) (35 mg, 0.20 mmol) and aniline (**2a**) (22 mg, 0.24 mmol, 1.2 equiv) in CH_2Cl_2 (2 mL) at 23 °C. After 1 h of stirring, the mixture was concentrated and chromatographed on silica gel to afford **4a** (43.2 mg, 90%) as a colorless needle. [b)] Isolated yield. [c)] Determined by HPLC (Daicel Chiralpak AD-H). [d)] Determined by comparison of the sign of optical rotation with the literature value.

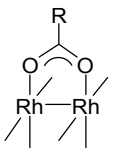
In order to further improve the enantioselectivity, our efforts were centered on a double asymmetric induction with the use of a chiral additive.[13,14] To this end, we explored the N–H insertion reaction of **1a** with **2a** in the presence of 1 mol % of **3a** as a catalyst and 0.1 mol % of cinchonine (**5a**) as a chiral additive. To our delight, the reaction proceeded at room temperature smoothly to provide (*R*)-**4a** in 86%

Table 2. Enantioselective N–H Insertion Reaction of Phenyldiazoacetates with Aniline (**2a**) Catalyzed by Rh(II) Carboxylates and Cinchona Alkaloids[a)]

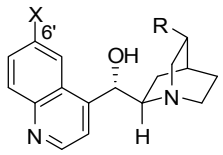


	Phenyldiazoacetates					α-Amino esters			
Entry		R	Rh(II) catalyst	Cinchona alkaloid	Time (h)		Yield (%)[b)]	Ee (%)[c)]	Confign[d)]
1	**1a**	CH_3	Rh_2(*S*-PTPA)$_4$ (**3a**)	cinchonine (**5a**)	2	**4a**	86	31	*R*
2	**1a**	CH_3	Rh_2(*S*-PTPA)$_4$ (**3a**)	cinchonidine (**5b**)	1	**4a**	87	37	*S*
3	**1a**	CH_3	Rh_2(TPA)$_4$ (**3e**)	cinchonine (**5a**)	12	**4a**	84	55	*R*
4	**1a**	CH_3	Rh_2(TPA)$_4$ (**3e**)	cinchonidine (**5b**)	12	**4a**	88	53	*S*
5	**1a**	CH_3	Rh_2(TPA)$_4$ (**3e**)	quinine (**5c**)	10	**4a**	86	<1	–[e)]
6	**1a**	CH_3	Rh_2(TPA)$_4$ (**3e**)	quinidine (**5d**)	10	**4a**	88	2	*S*
7	**1a**	CH_3	Rh_2(TPA)$_4$ (**3e**)	dihydrocinchonine (**5e**)	9	**4a**	94	59	*R*
8[f)]	**1a**	CH_3	Rh_2(TPA)$_4$ (**3e**)	dihydrocinchonine (**5e**)	22	**4a**	83	58	*R*
9	**1a**	CH_3	Rh_2(OAc)$_4$ (**3f**)	dihydrocinchonine (**5e**)	1	**4a**	84	36	*R*
10	**1a**	CH_3	Rh_2(oct)$_4$ (**3g**)	dihydrocinchonine (**5e**)	1	**4a**	91	24	*R*
11	**1a**	CH_3	Rh_2(piv)$_4$ (**3h**)	dihydrocinchonine (**5e**)	0.5	**4a**	83	36	*R*
12	**1b**	CH_2CH_3	Rh_2(TPA)$_4$ (**3e**)	dihydrocinchonine (**5e**)	10	**4b**	99	62[g)]	–[e)]
13	**1c**	$CH_2C(CH_3)_3$	Rh_2(TPA)$_4$ (**3e**)	dihydrocinchonine (**5e**)	30	**4c**	88	63[h)]	–[e)]
14	**1d**	$CH_2CH(CH_3)_2$	Rh_2(TPA)$_4$ (**3e**)	dihydrocinchonine (**5e**)	36	**4d**	93	67	–[e)]
15	**1e**	$CH(CH_3)_2$	Rh_2(TPA)$_4$ (**3e**)	dihydrocinchonine (**5e**)	120	**4e**	72	59	–[e)]

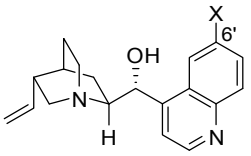
[a)] The following procedure is representative (Entry 14): A solution of **1d** (44 mg, 0.20 mmol) and **2a** (22 mg, 0.24 mmol, 1.2 equiv) in CH_2Cl_2 (1 mL) was added dropwise to a solution of Rh_2(TPA)$_4$ (**3e**) (2.8 mg, 0.002 mmol, 1 mol %) and dihydrocinchonine (**5e**) (0.06 mg, 0.0002 mmol, 0.1 mol %) in CH_2Cl_2 (1 mL) at 23 °C. After 36 h of stirring, the mixture was concentrated and chromatographed on silica gel to afford **4d** (53.3 mg, 93%) as a colorless needle. [b)] Isolated yield. [c)] Determined by HPLC (Daicel Chiralpak AD-H) unless otherwise stated. [d)] Determined by comparison of the sign of optical rotation with the literature value. [e)] Not determined. [f)] The reaction was carried out using 1 mol % of **5e**. [g)] Determined by HPLC (Daicel Chiralcel OJ-H). [h)] Determined by HPLC (Daicel Chiralpak AS-H).



R = Ph_3C: Rh_2(TPA)$_4$ (**3e**)
R = Me: Rh_2(OAc)$_4$ (**3f**)
R = C_7H_{15}: Rh_2(oct)$_4$ (**3g**)
R = ^{t}Bu: Rh_2(piv)$_4$ (**3h**)



R = CH_2=CH, X = H: cinchonine (**5a**)
R = CH_2=CH, X = MeO: quinine (**5c**)
R = Et, X = H: dihydrocinchonine (**5e**)



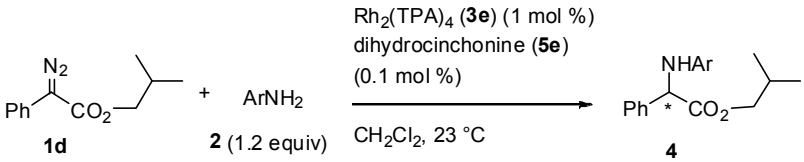
X = H: cinchonidine (**5b**)
X = MeO: quinidine (**5d**)

yield with 31% ee (Table 2, Entry 1). On the other hand, the use of cinchonidine (**5b**), a pseudo-enantiomer of **5a**, gave (*S*)-**4a** in 87% yield with 37% ee (Entry 2). Although the mechanistic profile is not clear at this time, these results suggest that the chirality of cinchona alkaloids rather than that of a dirhodium(II) catalyst dictates the stereochemical course of this process. Thus, we were intrigued by the possibility of the combined use of achiral dirhodium(II) carboxylate catalysts and cinchona alkaoids.[15] We were gratified to find that switching the Rh(II) catalyst to Rh_2(TPA)$_4$ (**3e**), a dirhodium(II) carboxylate complex incorporating bulky triphenylacetates as bridging ligands, gave even higher enantioselectivities than those found with Rh_2(*S*-PTPA)$_4$ (55% ee and 53% ee, Entries 3 and 4). A survey

of chiral additives revealed that dihydrocinchonine (**5e**) was the optimal additive for this transformation, giving (*R*)-**4a** in 94% yield with 59% ee (Entry 7). Quinine (**5c**) and quinidine (**5d**), 6'-methoxy substituted cinchona alkaloids, were not effective (Entries 5 and 6).[16] Interestingly, increasing the amount of **5e** to 1 mol % had no beneficial effect on enantioselectivity, but the reaction required a significantly longer time to reach completion (Entry 8).[17] Using **5e** as a chiral additive, we then evaluated the performance of other dirhodium(II) carboxylate catalysts, $Rh_2(OAc)_4$ (**3f**), $Rh_2(oct)_4$ (**3g**), and $Rh_2(piv)_4$ (**3h**). The reactions with the use of these catalysts (**3f-h**) proceeded to completion much faster than the catalysis with $Rh_2(TPA)_4$ (**3e**), although a considerable drop in enantioselectivity was observed (Entries 9–11). To further enhance the enantioselectivity, we examined the effect of an alkoxy group in the ester moiety on the enantioselectivity. Higher enantioselectivities were obtained by increasing the steric bulk of the ester alkyl group of phenyldiazoacetates (**1b-d**) with a significant reduction in the reaction rate (62–67% ee, Entries 12–14); however, with the more sterically demanding isopropyl ester (**1e**), further enhancement of enantioselectivity could not be attained (59% ee, Entry 15).[18] Eventually, we assessed the isobutyl ester (**1d**) as the ester of choice from the standpoint of enantioselectivity.

With optimized conditions in hand, we then investigated the scope of the reaction with respect to the aniline component (Table 3). High yields and good enantioselectivities were consistently observed with electron-withdrawing substituents such as chlorine and bromine at the *para*, *meta*, or *ortho* position on

Table 3. Enantioselective N−H Insertion Reaction of Isobutyl Phenyldiazoacetate (**1d**) with Anilines Catalyzed by $Rh_2(TPA)_4$ (**3e**) and Dihydrocinchonine (**5e**)



1d **2** (1.2 equiv) **4**

Entry	Aniline		Time (h)	α-Amino esters		
		R			Yield (%)[a]	Ee (%)[b]
1	**2b**	4-$CF_3C_6H_4$	2	**4f**	94	63
2	**2c**	4-FC_6H_4	30	**4g**	92	68
3	**2d**	4-ClC_6H_4	20	**4h**	93	70
4	**2e**	4-BrC_6H_4	20	**4i**	91	71
5	**2f**	4-IC_6H_4	8	**4j**	93	69
6	**2g**	3-ClC_6H_4	10	**4k**	92	67
7	**2h**	3-BrC_6H_4	3	**4l**	90	56
8	**2i**	2-ClC_6H_4	1	**4m**	98	55[c]
9	**2j**	2-BrC_6H_4	1	**4n**	91	56[c]
10	**2k**	4-MeC_6H_4	36	**4o**	91	64
11	**2l**	3-MeC_6H_4	72	**4p**	93	61
12	**2m**	2-MeC_6H_4	12	**4q**	91	56
13	**2n**	4-$MeOC_6H_4$	No reaction			

[a] Isolated yield. [b] Determined by HPLC (Daicel Chiralcel OD-H) unless otherwise stated.
[c] Determined by HPLC (Daicel Chiralcel OJ-H).

the benzene ring (Entries 1–9). It is notable that the enantioselectivity of 71% ee obtained with *p*-bromoaniline (**2e**) is the highest reported to date for dirhodium(II) complex-catalyzed N–H insertions (Entry 4).[4,5] The reaction with anilines **2k-m** bearing a methyl group at the *para*, *meta*, or *ortho* position also afforded the corresponding phenylglycine derivatives (**4o-q**) in high yields and good enantioselectivities (56–64% ee, Entries 10–12). However, no reaction occurred when *p*-anisidine (**2n**) bearing an electron-donating methoxy group was used (Entry 13).

In summary, we have demonstrated that a new catalytic system of $Rh_2(TPA)_4$ and dihydrocinchonine is effective for enantiocontrol in intermolecular N–H insertion reaction of phenyldiazoacetates with anilines. Mechanistic and stereochemical studies on the present N–H insertion reaction are currently in progress.

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16. The product yields and enantioselectivities obtained with other chiral additives are as follows: (–)-sparteine, 1.5 h, 82% yield, 5% ee (*S*); brucine, 22 h, 65% yield, 7% (*R*).
17. The reaction of **1a** with **2a** under identical conditions in the absence of $Rh_2(TPA)_4$ did not work even after 24 h.
18. The N–H insertion reaction of *tert*-butyl phenyldiazoacetate with aniline under the same conditions did not go to completion even after 1 week, and the corresponding phenylglycine derivative was obtained in 58% yield with 57% ee.