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Enantioselective N–H Insertion Reaction of α-Aryl α-Diazoketones: An Efficient Route to Chiral α-Aminoketones**

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Abstract: *A highly enantioselective N–H insertion reaction of α-diazoketones was developed by using cooperative catalysis by dirhodium(II) carboxylates and chiral spiro phosphoric acids. The insertion reaction provides a new access route to diverse chiral α-aminoketones, which are versatile building blocks in organic synthesis, with fast reaction rates, good yields and high enantioselectivity under mild and neutral conditions.*

The construction of carbon–heteroatom bonds (C–X) is a central task for studies in organic synthesis.[1] C–X bonds can be formed directly by transition-metal-catalyzed insertion of carbenes into heteroatom–hydrogen bonds (X–H, where X = N, O, S, etc.).[2] Recently, significant progress in catalytic asymmetric X–H insertion reactions has been made, for example, high enantioselectivities have been achieved with carbene insertions into N–H, O–H, and S–H bonds, which all contain heteroatoms with lone-pair electrons.[3] However, α-diazoesters are the only carbene precursors that have been used for these asymmetric X–H insertion reactions, which produce chiral α-heteroatom-substituted esters. Therefore, the potential applications of these reactions are severely limited. α-Diazoketones, another readily available carbene precursor, have been used in a few rhodium-catalyzed asymmetric cyclopropanation reactions, in C–H and Si–H insertion reactions, and in tandem reactions involving ylides.[2,4] X–H insertion reactions of α-diazoketones produce α-heteroatom-substituted ketones, which are useful building blocks for organic synthesis. However, when we used 1-diazo-1-phenylpropan-2-one (**2a**) in the asymmetric insertion reaction with *tert*-butyl carbamate ($BocNH_2$) catalyzed by $[Rh_2(R\text{-DOSP})_4]$, $[Rh_2(S\text{-PTAD})_4]$, or a chiral copper complex with a spirobisoxazoline ligand (**4**; Figure 1), no enantioselectivity was observed (Table 1, entries 1–3).[5] The problem with the asymmetric insertion of α-diazoketones into X–H bonds in which X has lone-pair electrons is that the strongly electron-withdrawing carbonyl group promotes the formation of free ylide **III**[2,6] or enol **IV**,[7] and chiral catalyst is thus not present during the chirality-determining proton-transfer step (Scheme 1).

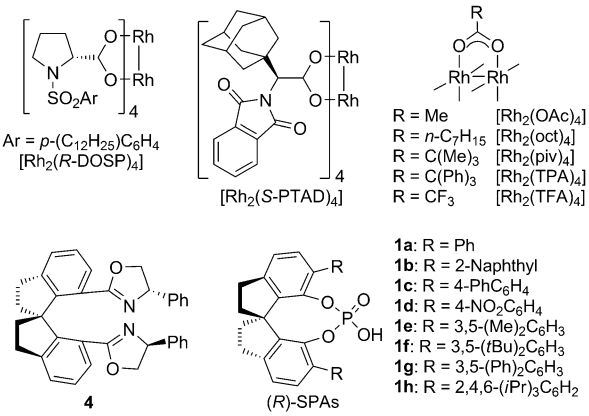
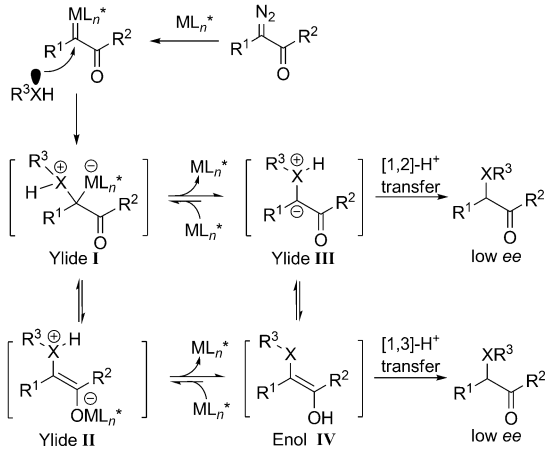


Figure 1. The catalysts and ligands used in this study.



Scheme 1. Proposed pathway of X–H insertions of α-diazoketones.

Herein, we report a highly enantioselective N–H insertion reaction of α-diazoketones co-catalyzed by dirhodium(II) carboxylates and chiral spiro phosphoric acids (SPAs, **1**), in which chiral induction was achieved in the proton-transfer step.[8] The mild, neutral conditions bring special advantages for the preparation of synthetically important chiral α-aminoketones,[9] which can epimerize under harsh conditions.

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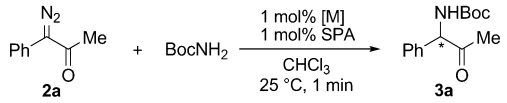
Initially, we performed the N–H insertion reaction of α-diazoketone **2a** with $BocNH_2$ by using 1 mol% $[Rh_2(OAc)_4]$ and 1 mol% SPA **1** as the catalysts (Table 1). SPAs with various substituents at the 6 and 6′ positions were evaluated (Table 1, entries 4–11), and the 6,6′-*di*-(4-PhC_6H_4)-substituted SPA **1c** afforded the highest enantioselectivity (52% *ee*; Table 1, entry 6). The type of dirhodium(II) complex strongly affected the enantioselectivity of the reaction (Table 1, entries 12–15). Specifically, when we used dirhodium(II) carboxylates, including $[Rh_2(TPA)_4]$, which gives the best results in the N–H insertion reaction of α-diazoesters,[8a] only moderate enantioselectivity was obtained. In sharp contrast, dirhodium(II) trifluoroacetate, a strong Lewis acid, significantly increased the enantioselectivity to 93% *ee* (Table 1, entry 15). The enantioselectivity was further improved to 96% *ee* by addition of the mixed solution of **2a** and $BocNH_2$ with a syringe pump over the course of 5 min (Table 1, entry 16). A control experiment showed that the SPA did not catalyze the insertion reaction in the absence of a dirhodium complex (Table 1, entry 17). Although the reaction afforded comparable enantioselectivity (93% *ee*) when it was performed without argon protection, the yield of desired N–H insertion product markedly decreased to 32%. The lower yield is attributed to significant dimerization of α-diazoketones.

Table 1: Enantioselective N–H insertion reaction of α-diazoketone **2a**: optimization of the reaction conditions.

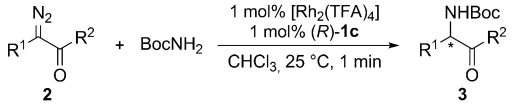


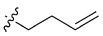
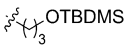
Entry[a]	[M]	SPA	Yield [%][b]	*ee* [%][c]
1[d]	Cu^I/**4**	none	78	0
2	$[Rh_2(R\text{-DOSP})_4]$	none	70	1
3	$[Rh_2(S\text{-PTAD})_4]$	none	72	1
4	$[Rh_2(OAc)_4]$	**1a**	79	14
5	$[Rh_2(OAc)_4]$	**1b**	76	50
6	$[Rh_2(OAc)_4]$	**1c**	85	52
7	$[Rh_2(OAc)_4]$	**1d**	84	25
8	$[Rh_2(OAc)_4]$	**1e**	88	37
9	$[Rh_2(OAc)_4]$	**1f**	75	17
10	$[Rh_2(OAc)_4]$	**1g**	85	8
11	$[Rh_2(OAc)_4]$	**1h**	76	4
12	$[Rh_2(oct)_4]$	**1c**	75	47
13	$[Rh_2(piv)_4]$	**1c**	89	58
14	$[Rh_2(TPA)_4]$	**1c**	87	67
15	$[Rh_2(TFA)_4]$	**1c**	85	93
16[e]	$[Rh_2(TFA)_4]$	**1c**	80	96
17[f]	none	**1c**	–	–

[a] Reaction conditions: [Rh]/SPA/**2a**/$BocNH_2$ = 0.002:0.002:0.21:0.2 (mmol) in 2 mL of $CHCl_3$ at 25 °C. [b] Yield of isolated product. [c] Determined by HPLC. [d] With 5 mol% catalyst, 4 h. [e] A mixed solution of two substrates was added over 5 min by a pump. [f] No insertion product was detected and **2a** was recovered in 93% yield.

Using the optimal reaction conditions, we investigated the substrate scope of the asymmetric N–H insertion reaction of diazoketones[10] (Table 2). All of the tested α-aryl-α-diazoacetones (**2a**–**2i**) reacted completely in 1 min to afford the corresponding chiral α-aminoketones **3a**–**3i** in good yields with high enantioselectivity (Table 2, entries 1–9). The electronic properties of the substituent at the *para* or *meta* position of the phenyl ring of the diazoketone affected the yields and enantioselectivity only slightly, whereas an *ortho*-fluoro substituent lowered the enantioselectivity slightly (86% *ee*; Table 2, entry 8). We also studied the effect of the R^2 substituent. Excellent enantioselectivity (92–98% *ee*) was obtained when R^2 was either an alkyl group (**2j**–**2o**; Table 2, entries 10–15) or an aryl group (**2p**–**2s**; Table 2, entries 16–19). The insertion reaction tolerated a range of functional groups, such as alkenyl, methoxy, silyloxy, and *N*-methyl pyrrole (Table 2, entries 13–15 and 19). In the reactions of **2m**, which has a terminal olefin, and **2n**, which has a methoxy group, the occurrence of side reactions (intramolecular cyclopropanation and C–H insertion) decreased the yields (Table 2, entries 13 and 14).

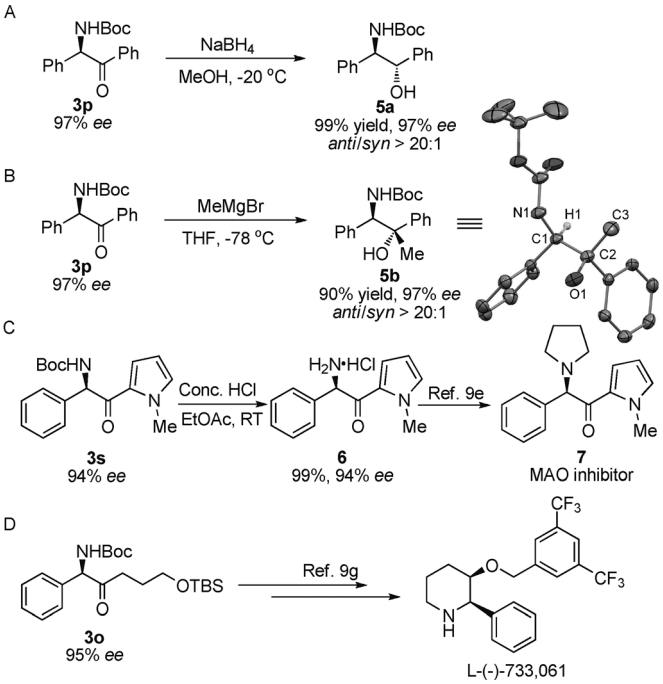
Table 2: Enantioselective N–H insertion reaction of α-diazoketones: substrate scope.



Entry	R^1	R^2	Product	Yield [%]	*ee* [%][11]
1	C_6H_5	Me	**3a**	80	96(*R*)
2	4-MeC_6H_4	Me	**3b**	79	94
3	4-BrC_6H_4	Me	**3c**	82	93
4	4-FC_6H_4	Me	**3d**	78	93
5	3-$MeOC_6H_4$	Me	**3e**	80	95
6	3-MeC_6H_4	Me	**3f**	82	96
7	3-FC_6H_4	Me	**3g**	75	90
8	2-FC_6H_4	Me	**3h**	86	86
9	2-Naph	Me	**3i**	95	97
10	C_6H_5	Et	**3j**	85	97(*R*)
11	C_6H_5	*n*Bu	**3k**	78	98(*R*)
12	C_6H_5		**3l**	82	96(*R*)
13	C_6H_5		**3m**	46	95(*R*)
14	C_6H_5		**3n**	56	92
15	C_6H_5		**3o**	85	95(*R*)
16	C_6H_5	C_6H_5	**3p**	85	96(*R*)
17	C_6H_5	4-$MeOC_6H_4$	**3q**	89	98
18	C_6H_5	4-FC_6H_4	**3r**	78	96
19	C_6H_5		**3s**	79	94

The reaction conditions and analysis method were the same as those described for Table 1, entry 16. All of the reactions had run to completion within 1 min after the addition of diazo compound **2**.

To demonstrate the utility of this asymmetric N–H insertion reaction of α-diazoketones, we carried out various reactions with the chiral α-aminoketone products (Scheme 2). Ketone **3p** could be reduced with $NaBH_4$ to chiral α-amino alcohol **5a** in quantitative yield with high stereoselectivity (*anti*/*syn* > 20:1, 97% ee; Scheme 2 A).[12] Upon addition of



Scheme 2. Transformations of the chiral α-aminoketone products.

a Grignard reagent, **3p** could also be easily converted to α-amino alcohol **5b**, which has a quaternary chiral center, in 90% yield and with excellent stereoselectivity (*anti*/*syn* > 20:1, 97% ee; Scheme 2B). The configuration of **5b** was determined to be (1*R*, 2*S*) by means of X-ray diffraction analysis of a single crystal.[13] Removal of the protecting group from **3s** afforded **6**, which is a key intermediate for the synthesis of monoamine oxidase inhibitor **7** (Scheme 2C).[9e] According to the reported procedure,[9g] chiral insertion product **3o** could be readily converted to (L)-(−)-733,061, which is a selective antagonist for the NK1 receptor (Scheme 2D).

In conclusion, we have described the first asymmetric N–H insertion reaction of α-diazoketones, which was achieved by cooperative catalysis by achiral dirhodium(II) carboxylates and chiral SPAs. This new reaction provides an efficient and straightforward route to synthetically important chiral α-aminoketones with good yields and high enantioselectivity. This study markedly broadens the scope of asymmetric X–H insertion reactions.

Experimental Section

The $[Rh_2(F_3CCO_2)_4]$ (1.3 mg, 0.002 mmol, 1 mol%) and (*R*)-**1c** (1.2 mg, 0.002 mmol, 1 mol%) were introduced into an oven-dried Schlenk tube in an argon-filled glovebox. After 2 mL $CHCl_3$ was injected into the Schlenk tube, the mixture was stirred at 25°C. A solution of 1-diazo-1-phenylpropan-2-one **2a** (33.6 mg, 0.21 mmol) and $BocNH_2$ (23.4 mg, 0.2 mmol) in 1 mL $CHCl_3$ was introduced into the mixture by a syringe pump over 5 min. The color of the diazo compound disappeared immediately after the addition. TLC showed that the reaction ran to completion as soon as the addition finished. The reaction mixture was then concentrated and purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 8:1) to give **3a** as a white solid.

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[13] CCDC 980485 (**5b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

