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Ru-Catalyzed highly diastereoselective hydrogenation of *N-tert*-butylsulfinyl ketimines for the synthesis of aryl glycine derivatives†

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A ruthenium pincer catalyst has been shown to be highly efficient for the hydrogenation of a wide range of α-ketimino esters derived from α-keto esters and chiral 2-methylpropyl-2-sulfinamide, affording chiral aryl glycine derivatives with high yields and diasteroselectivities (20 examples, dr values up to 99 : 1).

Chiral α-amino acids and their derivatives are important molecules that are widely used as building blocks in chemical, pharmaceutical and biological syntheses.[1,2] Among these building blocks, chiral α-aryl glycines are of particular importance for some significant drugs, including glycopeptide antibiotics, β-lactam antibiotics, antihypertensive agents, cardiovascular agents and polymerase inhibitors (Fig. 1).[3] In these cases, the chirality of the compounds was found to affect the relevant bioactivity.

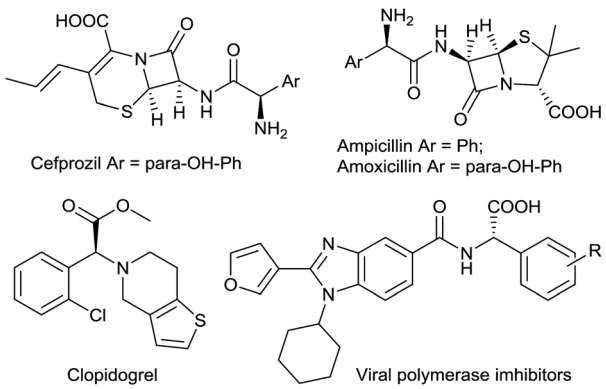

Fig. 1 Important drugs containing chiral aryl glycine derivatives.

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Traditional methods for obtaining optically active glycine compounds are by resolution of the racemate with chiral resolution reagents or enzymes.[4] Considering the call for atom economy, asymmetric synthesis may afford a more efficient route for chiral glycines. Indeed, over the past three decades, a variety of methodologies based on chiral catalysts have been explored to synthesize chiral aryl glycines,[5–7] including asymmetric amino-hydroxylation of aryl alkenes,[6a] asymmetric amination of enolate substrates,[6b] asymmetric Strecker reaction,[6c–h] asymmetric hydrogenation,[6i] transfer hydrogenation of α-imino esters,[6j–m] asymmetric Friedel–Crafts reaction,[6n–p] asymmetric N–H insertion reactions,[6q] silylation reaction of *N*-sulfonylimines,[6r] aryl boronic addition,[7a–d] and dynamic kinetic resolution.[7e–g]

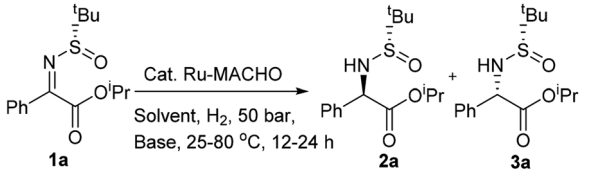
Apart from these asymmetric reactions effected with chiral catalysts, the chiral substrate-controlled asymmetric synthesis of aryl glycines has attracted much attention. Some important chiral auxiliaries, including chiral amino alcohols,[8] chiral amines,[9] and chiral 2-methylpropylsulfinamide,[10] have been investigated widely, providing an alternative to synthesizing chiral aryl glycines. Among these chiral auxiliaries, 2-methylpropylsulfinamide has been extensively used for the preparation of chiral amines[11] and chiral aryl glycines, probably due to such notable features as easy commercial availability, low price, excellent diastereofacial selectivity, high stability of the corresponding imine substrates, mild conditions for its cleavage and easy recycling.[12] The first example of the asymmetric synthesis of phenyl glycine using 2-methylpropylsulfinamide was reported by Davis in 1999,[10c] affording a moderate diastereomeric ratio (84 : 16 dr) and 70% yield. The asymmetric Strecker reaction involving chiral imines has also been carried out, which gave a moderate diastereoselectivity (83 : 17 dr) for ketimines;[10d] but for aldimines,[10e] high diastereoselectivities (>97 : 3 dr) were obtained in the presence of triflate salts. A significant breakthrough in the asymmetric synthesis of chiral aryl glycines was achieved by Ellman,[10f] who reported a rhodium-catalyzed addition reaction of arylboronic acids with *N-tert*-butylsulfinyl aldimino esters, affording excellent results in both yield (61–90%) and diastereoselectivities (dr values up

to 99 : 1). Later, this method was extended to a cationic palladium-catalyzed reaction by Lu, giving aryl glycine derivatives in good yields (57–90%) and high diastereoselectivities (>96 : 4 dr).[10g]

The diastereoselective reduction of *N-tert*-butylsulfinyl ketimino esters would afford a direct route for the preparation of chiral aryl glycine. The ketimino esters can be synthesised in high yield *via* the condensation of α-ketoesters[13] with chiral 2-methylpropylsulfinamide. Although some excellent reaction systems have been reported for the diastereoseletive reduction of *N-tert*-butylsulfinyl ketimines,[10h,11] examples of highly diastereoselective reduction of ketimino esters are rare. Only one efficient asymmetric reduction of *N-tert*-butylsulfinyl ketimino esters, with one equivalent of L-selectride as a reductant added slowly at −78 °C, was reported by Reddy, giving 85–94% yields and good diastereoselectivities (≥98 : 2 dr) (Fig. 2, ref. 10*h*). Later, the hydrosilylation of only one phenyl ketimino ester substrate catalyzed by zinc acetate was also reported, but affording only 54% yield and a moderate diastereoselectivity (<88 : 12) in 72 hours (Fig. 2, ref. 10*i*). From the viewpoint of both atom economy and practical application, hydrogenation with cheap H_2 would be a more attractive method for the reduction of *N-tert*-butylsulfinyl ketimino esters. Herein, we report our results on the first hydrogenation of this kind of substrates to access chiral aryl glycine derivatives.

Recently, we reported an efficient method for the chemoselective hydrogenation of α-ketoesters with a pincer Ru-MACHO catalyst,[14a] which is readily available and displays high catalytic activity for some reduction reactions under mild reaction conditions.[14] Therefore, an initial attempt to carry out a reaction using (*S*, *Z*) phenyl α-ketimino ester (**1a**)[15] was conducted in MeOH with 1 mol% of Ru-MACHO catalyst under our previously optimized conditions. Unfortunately, no reduced product but only a transesterification product was obtained (Table 1, entry 1). After the evaluation of several solvents (Table 1, entries 2–5), the use of toluene as a solvent gave the hydrogenation product **2a** with 82% conversion and 84 : 16 dr value. Next, a range of bases was examined (Table 1, entries 6–11), and the results demonstrated that the use of NaOMe gave satisfying conversion and diastetereoselectivity (Table 1, entry 5). Lowering the reaction temperature to 40 °C and 25 °C resulted in 96 : 4 and 99 : 1 dr values, respectively, and eroded the activities (Table 1, entries 12–14). Lowering of the H_2 pressure from 50 bar to 30 bar led to the decrease of both the conversion and diastereoselectivity (Table 1, entry 15). Additionally, decreasing the base loading also led to a lower conversion but the diastereoselectivity remained unchanged (Table 1, entry 16).

Table 1 Optimization of reaction conditions for the hydrogenation of phenyl α-ketimino ester **1a**[a]



1a 2a 3a

Entry	Solvent/base/cat.	Conv.[b] (%)	2a : 3a[c]
1	MeOH/$NaOCH_3$/1%	0	ND
2	^{i}PrOH/$NaOCH_3$/1%	55	51 : 49
3	THF/$NaOCH_3$/1%	42	63 : 37
4	CH_3CN/$NaOCH_3$/1%	32	79 : 21
5	Toluene/$NaOCH_3$/1%	82	84 : 16
6	Toluene/No base/1%	0	ND
7	Toluene/KO^{t}Bu/1%	49	65 : 35
8	Toluene/NaOH/1%	18	85 : 15
9	Toluene/KOH/1%	42	64 : 36
10	Toluene/K_2CO_3/1%	60	52 : 48
11	Toluene/NaO^{t}Bu/1%	37	59 : 41
12[d]	Toluene/NaOMe/1%	75	96 : 4
13[d,e]	Toluene/NaOMe/2%	96	95 : 5
14[e,f]	Toluene/NaOMe/2%	96	>99 : 1
15[e,f,g]	Toluene/NaOMe/2%	85	96 : 4
16[f,h]	Toluene/NaOMe/2%	26	>99 : 1

[a] Reaction conditions: **1a** (0.15 mmol), Ru-MACHO (0.0015 mmol, 1 mol%), base (0.03 mmol, 20 mol%), solvent (0.7 mL), H_2 (50 bar), 80 °C, 12 h. [b] The conversions were determined by ^{1}H NMR. [c] The ratios of **2a** : **3a** were determined by HPLC. [d] The reaction was carried out at 40 °C. [e] The reaction time was 24 h. [f] The temperature was 25 °C. [g] 30 bar H_2. [h] 10 mol% NaOMe was used.

Having established conditions for the highly diastereoselective hydrogenation of **1a**, we subsequently turned to exploring the scope of the Ru-MACHO-catalyzed diastereoselective hydrogenation of substituted *N-tert*-butylsulfinyl ketimino esters under optimized conditions. The results are listed in Table 2. As can be seen, all the substrates were smoothly hydrogenated with high diastereoselectivities and good to excellent isolated yields. It is found that the reaction proceeds well with different ester groups, with all affording both high diastereoselectivities and isolated yields (Table 2, entries 1–3).

Regarding the aryl groups, the reaction appears somewhat sensitive to the substituent position. Thus, a higher reaction temperature was needed for substrates bearing an *ortho*-substituent for satisfying yields (Table 2, compare entry 4 with entries 5–6 and entry 7 with entries 8–9). For the *para*-substituted aryl ketimino esters, the hydrogenation reactions worked very well, regardless of the substituent being electron-donating or electron-withdrawing (Table 2, entries 6, 9, 11, 13 and 15); excellent yields and diastereoselectivities were obtained in all

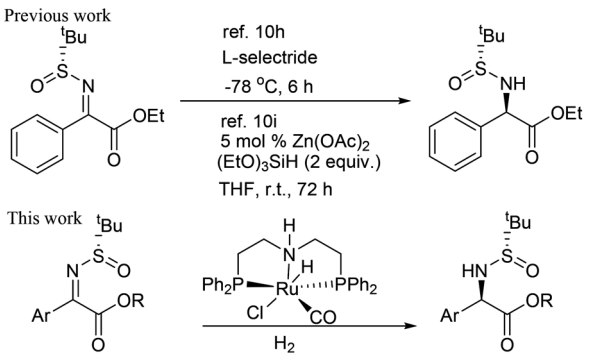
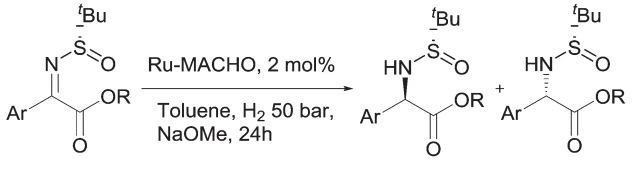
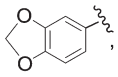


Fig. 2 Asymmetric reduction of *N-tert*-butylsulfinyl ketimino esters.

Table 2 Diastereoselective hydrogenation of substituted ketimino esters **1**[a]



1a: Ar = Ph, R = ^{i}Pr; **1b**: Ar = Ph, R= Et; **1c**: Ar = Ph, R = Me; **1d**: Ar = *o*-Me-C_6H_4, R = ^{i}Pr; **1e**: Ar = *m*-Me-C_6H_4, R = ^{i}Pr; **1f**: Ar = *p*-Me-C_6H_4, R = ^{i}Pr; **1g**: Ar = *o*-MeO-C_6H_4, R = ^{i}Pr; **1h**: Ar = *m*-MeO-C_6H_4, R = ^{i}Pr; **1i**: Ar = *p*-MeO-C_6H_4, R = ^{i}Pr; **1j**: Ar = *o*-F-C_6H_4, R = ^{i}Pr; **1k**: Ar = *p*-F-C_6H_4, R = ^{i}Pr; **1l**: Ar = *m*-Cl-C_6H_4, R = ^{i}Pr; **1m**: Ar = *p*-Cl-C_6H_4, R = ^{i}Pr; **1n**: Ar = *m*-Br-C_6H_4, R = ^{i}Pr; **1o**: Ar = *p*-Br-C_6H_4, R = ^{i}Pr; **1p**: Ar = 3,5-diMe-C_6H_3, R = ^{i}Pr; **1q**: Ar = 2,4-diMe-C_6H_3, R = ^{i}Pr; **1r**: Ar =  , R = ^{i}Pr; **1s**: Ar = 2-Naphthyl, R = ^{i}Pr; **1t**: Ar = 9-phenanthyl, R = ^{i}Pr;

Entry	Substrate	*T* (°C)	Yield[b] (%)	**2 : 3**[c,d]
1	**1a**	25	96	>99 : 1
2	**1b**	25	92	>99 : 1
3	**1c**	25	93	>99 : 1
4	**1d**	40	72	97 : 3
5	**1e**	30	95	>99 : 1
6	**1f**	25	96	99 : 1
7	**1g**	40	96	86 : 14
8	**1h**	30	95	>99 : 1
9	**1i**	25	96	>99 : 1
10	**1j**	25	94	>98 : 2
11	**1k**	25	95	99 : 1
12	**1l**	30	95	>97 : 3
13	**1m**	25	93	>99 : 1
14	**1n**	25	97	96 : 4
15	**1o**	25	92	>99 : 1
16	**1p**	25	94	97 : 3
17	**1q**	40	76	>99 : 1
18	**1r**	25	93	>98 : 2
19	**1s**	30	90	95 : 5
20	**1t**	40	85	>99 : 1

[a] Reaction conditions: **1** (0.15 mmol), Ru-MACHO (0.003 mmol, 2 mol%), NaOMe (0.03 mmol, 20 mol%), toluene (0.7 mL), H_2. [b] Isolated yield. [c] The ratios of **2 : 3** were examined by HPLC. [d] The configuration of products was confirmed by comparison with **5i** deriving from product **2i**.

cases. For the multi-substituted aryl ketimino esters **1p–1r** (Table 2, entries 16–18), the reactions also worked well with high diastereoselectivities, although the *ortho*-methyl substituted **1q** gave a lower yield compared with the other two substrates **1p** and **1r**. Additionally, two substrates containing fused aromatic rings **1s** and **1t** were also hydrogenated smoothly with good isolated yields and excellent diastereoselectivities (Table 2, entries 19 and 20).

Finally, we applied this new protocol to the synthesis of the chiral amino alcohol **5i** (Fig. 3), an important building block for the preparation of an inhibitor of phosphodiesterase (**A**).[16] Under our optimized conditions, the diastereoselective hydrogenation of substrate **1i** was carried out on a gram scale,

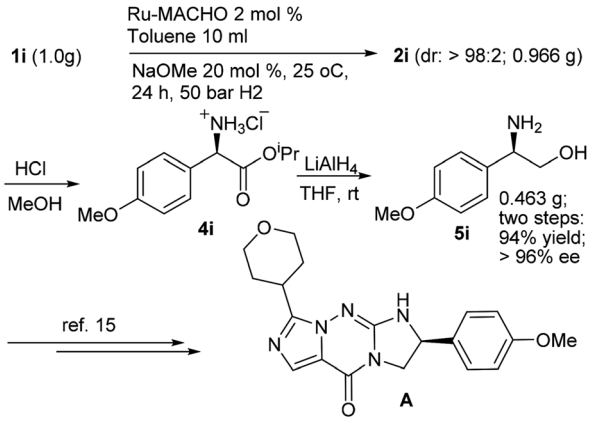


Fig. 3 An example of the application of the protocol developed.

providing the product **2i** in 96% isolated yield with more than 98 : 2 diastereoselectivity. A standard transformation of the sulfinyl amine with a saturated HCl solution in methanol, followed by the reduction with $LiAlH_4$ in THF, afforded the chiral amino alcohol (*R*)-**5i** in total 90% yield with more than 96% ee value. The absolute configuration of **5i** has been confirmed by the comparison of optical rotation.[17]

Conclusions

We have developed a practical and efficient method for the preparation of chiral aryl glycine derivatives *via* the diastereoselective hydrogenation of *N-tert*-butylsulfinyl α-ketimino esters catalyzed by the pincer Ru-MACHO catalyst. The method demonstrates excellent diastereoselectivities for a wide range of substrates. The resulting aryl glycine derivatives could be transformed easily to chiral aryl glycines and chiral amino alcohols for practical applications.

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