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Ruthenium Catalyzed Direct Asymmetric Reductive Amination of Simple Aliphatic Ketones using Ammonium Iodide and Hydrogen

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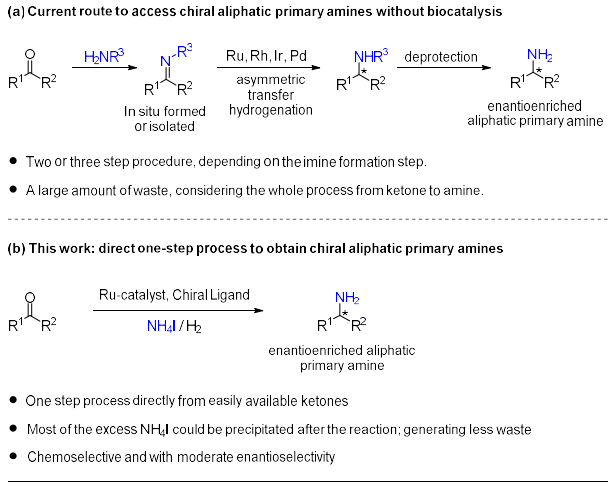
Abstract: The direct conversion of ketones into chiral primary amines is a key transformation in chemistry. Here, we present a ruthenium catalysed asymmetric reductive amination (ARA) of purely aliphatic ketones with good yields and moderate enantioselectivity: up to 99% yield and 74% *ee*. The strategy involves $[Ru(PPh_3)_3H(CO)Cl]$ in combination with the ligand (*S*,*S*)-*f*-binaphane as the catalyst, NH_4I as the amine source and H_2 as the reductant. This is a straightforward and user-friendly process to access industrially relevant chiral aliphatic primary amines. Although the enantioselectivity with this approach is only moderate, to the extent of our knowledge, the maximum *ee* of 74% achieved with this system is the highest reported till now apart from enzyme catalysis for the direct transformation of ketones into chiral aliphatic primary amines.

Optically active amines are ubiquitous in pharmaceuticals, agrochemicals and widely used in organic synthesis.[1] Among all the amines, chiral primary amines are extremely valued as they are very important building blocks for active ingredients in medicine, biology and materials.[2] In many cases, the pharmacological activities of these amines depend on the absolute configuration of the stereocenter.[3] Therefore, practical synthesis of chiral primary amines by imine hydrogenation, enamine hydrogenation, reductive amination, oxime hydrogenation, alcohol amination has gained remarkable attention in the past few decades.[4] However, most of the existing processes to obtain unprotected chiral primary amines involve multistep procedures with protected imine intermediates (*in situ* formed or isolated), followed by asymmetric hydrogenation and then deprotection leading to the unprotected amines (**Scheme 1a**). In this respect, in 2018, we have reported an atom-efficient approach to obtain optically pure aryl-alkyl amines from the corresponding prochiral ketones using ammonia and hydrogen.[5] Shortly afterwards, Xumu Zhang *et. al.* reported a similar approach to asymmetric reductive amination by using stoichiometric amounts of ammonium salt and hydrogen.[6] These two methods were very effective for aryl-alkyl ketones, but when applied to alkyl-alkyl ketones, the enantioselectivity achieved was less than 20%. In 2014, Guijarro *et. al.* reported microwave-assisted asymmetric transfer hydrogenation of *N*-(*tert*-butylsulfinyl)imines to obtain primary amines as the HCl salts in good yield and enantiomeric excess (*ee*). In contrast, they had to prepare and isolate the *N*-(*tert*-butylsulfinyl)imines from the corresponding ketones using the Ellman-reagent[7a] before the asymmetric transfer hydrogenation followed by desulfinylation to obtain the amine.'This adds up two more steps to obtain the amines from the ketone.[7b] Similarly, in 2003, Kadyrov *et. al.* reported one example of an aliphatic ketone (2-octanone) in an asymmetric version of the Leuckart-Wallach-reaction with very low conversion and 24% *ee* with the undesired formation of formylated amine as intermediate, ultimately requiring an additional hydrolysis step.[8] On the other hand, in the past years, several biocatalytic approaches have been reported involving kinetic resolution, deracemization of racemic amines, alcohol amination and transamination using enzymes to obtain chiral aliphatic primary amines.[9] Despite all those advances, a simple and dedicated method for the direct one-step synthesis of solely aliphatic chiral primary amines from prochiral ketones without enzymatic processes, has not been reported yet.

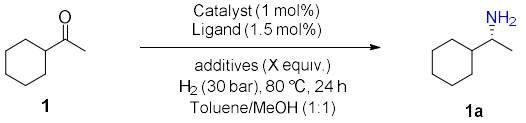
Scheme 1. Comparison of transition metal catalyzed ARA to access pure aliphatic chiral primary amines



Herein, we report an update on our ongoing investigation of ARA of purely aliphatic ketones using $[Ru(PPh_3)_3H(CO)Cl]$ in combination with the ligand (*S*,*S*)-*f*-binaphane as the catalyst, ammonium iodide and hydrogen with good yield and moderate enantioselectivity (**Scheme 1b**). In our previous findings in 2018, we have reported an *ee* of 14% for the asymmetric amination of 2-heptanone,[5] which in our present work increased to 32%. In this work, we could achieve an *ee* of up to 74% for chiral aliphatic primary amines. This, to the best of our knowledge, is by far the highest reported *ee* for an aliphatic amine obtained directly from a ketone without using biocatalysis.

Considering the limitations in the enantioselectivity of ARA of alkyl-alkyl ketones, we started our investigation by employing cyclohexyl methyl ketone (**1**) under the optimized reaction conditions from our previous report[5] on the ARA using NH_3 (4 bar) and H_2 (40 bar), with 1 mol% $[Ru(PPh_3)_3H(CO)Cl]$, 1.1 mol% (*S*,*S*)-*f*-binaphane, 2 mol% $NaPF_6$ and 10 mol% NH_4I in toluene at 120 °C for 16h. We achieved 74% of the amine with 45% *ee* (see the Supporting Information, **Scheme S1**). To improve the enantioselectivity, we started optimizing the reaction conditions using cyclohexyl methyl ketone (**1**) as the model substrate and the results are summarized in Table 1. The yields were determined by GC/FID with *n*-dodecane as the internal standard, after 24h reaction in a HEL CAT-7 autoclave (see the Supporting Information, **Fig. S1** for details on this autoclave)). We began our exploration with 1 mol% $[Ru(PPh_3)_3H(CO)Cl]$, 1.5 mol% (*S*,*S*)-*f*-binaphane and 2.5 equiv. of ammonium iodide in toluene at 100 °C, as the reaction was too slow at 80 °C in toluene. A low conversion of 15% to 1-cyclohexylethylamine (**1a**) was observed, but with an enhanced *ee* of 63% (Table 1, entry 1). Using MeOH as the reaction solvent at 80 °C, the conversion was increased to 88% but the *ee* was decreased to 55% (Table 1, entry 2). Then our immediate thought was to use a (1:1) mixture of toluene and MeOH, which to our delight, gave rise to 84% of **1a** with 68% *ee* (Table 1, entry 3). Using NH_4OAc instead of NH_4I or commercially available $[Ru(OAc)_2$(S)-Segphos] as the catalyst did not improve the result (Table 1, entries 4-5). A series of other Ru-catalysts as well as 21 other chiral phosphine ligands were tested which is summarized in the Supporting Information (**Table S1**). Among all the other ligands, only (4*S*,5*S*)-(+)-DIOP and (*S*,*S*)-BDPP resulted in a promising *ee* of 52% and 61% respectively (Table 1, entries 6-7). Comparing entries 8-9 with entry 3 in Table 1, it is evident that 2.5 equiv. of NH_4I is optimal for the reaction condition. Addition of ammonia or iodine diminished the enantioselectivity (Table 1, entries 10-11). To facilitate the stability of the imine we added different acids, which did not have a positive effect on the enantioselectivity (Table 1, entries 12-14). Although a 1:1 mixture of toluene and MeOH was optimal for our system, we have tested different other solvents and solvent-mixtures, which is summarized in the Supporting Information (**Table S2**). A mixture of toluene/EtOH (1:1) provided an *ee* similar to that in toluene/MeOH but with a lower reaction rate (Table 1, entry 15). Toluene/*i*PrOH (1:1) was the best choice of solvent (73% *ee* at 80 °C), but only 40% conversion to **1a** was observed (Table 1, entry 16). By increasing the reaction temperature to 100 °C, we achieved a good conversion of 81% but the *ee* was reduced to 65% (Table 1, entry 17). After having established the optimal reaction conditions, we intended to scale up our reaction from 0.2 mmol scale in a HEL CAT-7 autoclave to 1 mmol scale in a Premex autoclave (see the Supporting Information, **Fig. S2** for details on this autoclave). The amine (**1a**) was isolated in a free, unprotected form in 78% yield with 74% *ee* (Table 1, entry 18). It is worth mentioning that while transferring the optimal reaction conditions from HEL CAT-7 autoclave to a Premex autoclave, the reaction time was extended to 36h to achieve a better conversion, and as a matter of fact, the *ee* was improved by 4-7% for all the substrates.

Table 1. Optimization of reaction conditions [a]

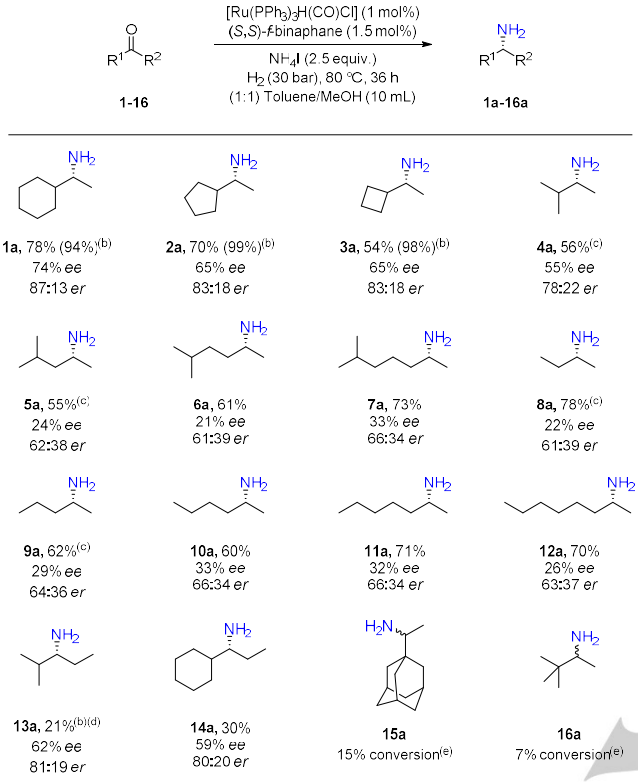


Entry	Catalyst	Ligand	Solvent	Additives (equiv.)	Yield of **1a** (%)[b]	*ee* (%)[c]	*er* [R/S][d]
1[e]	[Ru(PPh$_3$)$_3$H(CO)Cl]	(*S*,*S*)-*f*-binaphane	Toluene	NH_4I (2.5)	15	63	82/18
2	[Ru(PPh$_3$)$_3$H(CO)Cl]	(*S*,*S*)-*f*-binaphane	MeOH	NH_4I (2.5)	88	55	77/23
3	[Ru(PPh$_3$)$_3$H(CO)Cl]	(*S*,*S*)-*f*-binaphane	Toluene/MeOH (1:1)	NH_4I (2.5)	84	68	84/16
4	[Ru(PPh$_3$)$_3$H(CO)Cl]	(*S*,*S*)-*f*-binaphane	Toluene/MeOH (1:1)	NH_4OAc (2.5)	40	62	81/19
5	[Ru(OAc)$_2$(S)-Segphos]	-	Toluene/MeOH (1:1)	NH_4I (2.5)	86	31	35/65
6	[Ru(PPh$_3$)$_3$H(CO)Cl]	(4*S*,5*S*)-(+)-DIOP	Toluene/MeOH (1:1)	NH_4I (2.5)	70	52	76/24
7	[Ru(PPh$_3$)$_3$H(CO)Cl]	(*S*,*S*)-BDPP	Toluene/MeOH (1:1)	NH_4I (2.5)	32	61	20/80
8	[Ru(PPh$_3$)$_3$H(CO)Cl]	(*S*,*S*)-*f*-binaphane	Toluene/MeOH (1:1)	NH_4I (1.0)	52	69	84/16
9	[Ru(PPh$_3$)$_3$H(CO)Cl]	(*S*,*S*)-*f*-binaphane	Toluene/MeOH (1:1)	NH_4I (2.0)	74	68	84/16
10	[Ru(PPh$_3$)$_3$H(CO)Cl]	(*S*,*S*)-*f*-binaphane	Toluene/MeOH (1:1)	NH_3(4 bar); NH_4I (2.5)	82	37	69/31
11	[Ru(PPh$_3$)$_3$H(CO)Cl]	(*S*,*S*)-*f*-binaphane	Toluene/MeOH (1:1)	I_2 (1.0); NH_4I (2.5)	50	51	76/24
12	[Ru(PPh$_3$)$_3$H(CO)Cl]	(*S*,*S*)-*f*-binaphane	Toluene/MeOH (1:1)	AcOH (1.0); NH_4I (2.5)	80	68	84/16
13	[Ru(PPh$_3$)$_3$H(CO)Cl]	(*S*,*S*)-*f*-binaphane	Toluene/MeOH (1:1)	$Zn(OTf)_2$ (1.0); NH_4I (2.5)	56	65	83/17
14	[Ru(PPh$_3$)$_3$H(CO)Cl]	(*S*,*S*)-*f*-binaphane	Toluene/MeOH (1:1)	$Ti(O^iPr)_4$ (1.0); NH_4I (2.5)	75	66	83/17
15	[Ru(PPh$_3$)$_3$H(CO)Cl]	(*S*,*S*)-*f*-binaphane	Toluene/EtOH (1:1)	NH_4I (2.5)	62	67	84/16
16	[Ru(PPh$_3$)$_3$H(CO)Cl]	(*S*,*S*)-*f*-binaphane	Toluene/^{i}PrOH (1:1)	NH_4I (2.5)	40	73	87/13
17[e]	[Ru(PPh$_3$)$_3$H(CO)Cl]	(*S*,*S*)-*f*-binaphane	Toluene/^{i}PrOH (1:1)	NH_4I (2.5)	81	65	83/17
18[f]	[Ru(PPh$_3$)$_3$H(CO)Cl]	(*S*,*S*)-*f*-binaphane	Toluene/MeOH (1:1)	NH_4I (2.5)	78[g]	74	87/13

[a]Optimization of reaction conditions: in HEL CAT-7 autoclave; cyclohexyl methyl ketone (0.2 mmol), catalyst (1 mol%), ligand (1.5 mol%), additives (equiv.), H_2 (30 bar), (1:1) toluene/MeOH (2 mL), 80 °C, 24 h. [b]GC/FID determined yield with *n*-dodecane as internal standard. [c]The *ee* values were determined by chiral HPLC after benzoylation. [d]Enantiomeric ratio (*er*) of [*R*] and [*S*] enantiomers of **1a**. [e]Reactions were performed at 100 °C; [f] reaction was performed in a Premex autoclave; cyclohexyl methyl ketone (1.0 mmol), [Ru(PPh$_3$)$_3$H(CO)Cl] (1 mol%), (*S*,*S*)-*f*-binaphane (1.5 mol%), NH_4I (2.5 equiv.), H_2 (30 bar), (1:1) toluene/MeOH (10 mL), 80 °C, 36 h. [g] Isolated yield of **1a**.

To demonstrate the utility of our method, we started to screen different alkyl-alkyl ketones under the optimized reaction conditions in a Premex autoclave under 30 bars of H_2 at 80 °C for 36h (**Table 2**). A wide range of simple aliphatic amines were obtained with moderate enantioselectivity and good to excellent yield. The enantioselectivity of the reactions was determined after benzoylation of the products using chiral HPLC. As mentioned before, the model substrate (**1**) was reductively aminated in 78% isolated yield and 74% *ee*. The absolute configuration of the product (**1a**) was determined by comparing with commercially available enantiomers of **1a**. Similarly, **2a** and **3a** were obtained in 70% yield, 66% *ee* and 54% yield, 65% *ee* respectively. Our primary goal was to isolate the aliphatic amines in an unprotected form, but because of the volatility of amines (especially for compound **3a**) we obtained lower yields. So, we carried out separate reactions to isolate several of the amines as their corresponding HCl salts to show that the amines can also be isolated in excellent yields as the hydrochloride, when needed. For example, **1a**, **2a** and **3a** were isolated in 94%, 99% and 98% respectively as their corresponding HCl salts. In addition to that, in the process of isolating the amines as their HCl salt, 40% of the used NH_4I in the reaction (2.5 equiv.) was precipitated and could be reused in further reactions, reducing the waste to a minimum amount. We believe that for most of the

Table 2. Substrate Scope [a]



[a]Reaction conditions: in a Premex autoclave; ketones **1-16** (1.0 mmol), $[Ru(PPh_3)_3H(CO)Cl]$ (1 mol%), (*S*,*S*)-*f*-binaphane (1.5 mol%), NH_4I (2.5 equiv.), H_2 (30 bar), (1:1) toluene/MeOH (10 mL), 80 °C, 36 h. [b]In the parentheses: isolated yield of the amine as HCl salt from an independent reaction. [c]GC/FID determined yield with *n*-decane as internal standard. [c]The *ee* values were determined by chiral HPLC after benzoylation. [d]Reaction was carried out for 48h. [e]Reactions were performed at 100 °C.

other amines it would be possible to achieve better yields when isolated as HCl salts. Amines **4a**, **5a**, **7a** and **8a** were too volatile to be isolated as free amines on our scale; so, GC/FID determined yields are reported using *n*-decane as the internal standard. When the α-position of the ketone is a secondary carbon atom, 55-74% *ee* was obtained. On the other hand, when the steric bulk due to the secondary carbon atom shifts to β-, γ- or δ- position (**5a**-**7a**) from the carbonyl carbon, or when it is a linear *n*-alkyl chain (**8a**-**12a**), the enantioselectivity dropped significantly, varying from 21-33% *ee*. Keeping a secondary carbon atom on one side, when R^2 is changed from Me- to an Et-group, the reaction rate was reduced (**13a** and **14a**), but the enantioselectivity was maintained at 64% and 59% *ee* respectively. In the case of **13a**, due to low conversion and high volatility, we have isolated the product as its HCl salt in 21% yield, and the reaction time was extended to 48h. But unfortunately, in case of a tertiary carbon atom at the α-position of the ketone, the reaction was strongly impeded, and the conversion was only 15% (**15a**) and 7% (**16a**) even at 100 °C. We have also considered whether the hydrogenation of oximes, obtained from the corresponding ketones, would increase the enantioselectivity. However, with the oximes **1b** and **8b** derived from ketones **1** and **8** respectively, we could only achieve a similar yield or enantioselectivity compared to the current result (see the Supporting Information, **Table S3**). Moreover, we had to increase the reaction temperature to 100-120 °C as the oximes were less reactive compared to the ketones. With the optimized reaction conditions, we have also tested acetophenone (**17**), to compare the results with our previous system[5] of ARA using NH_3 and H_2. In this case, the reaction yield was lower than our previous system, providing 65% of the corresponding amine (**17a**) but with an increased *ee* of 93% (see the Supporting Information, **Scheme S2**).

In summary, we report an update on our ongoing research activities for the ARA of aliphatic ketones using a simple method and a versatile range of substrates. Using a 1:1 mixture of toluene/MeOH as the reaction solvent and NH_4I as the ammonia source was the key to improve the yield as well as the enantioselectivity. As for the aryl-alkly-ketones, the Ru-(*S*,*S*)-*f*-binaphane catalysts provided the highest *ee* compared to all the other tested systems Although the enantioselectivity is only moderate, we believe that these are the highest reported *ee* values for aliphatic amines directly obtained from corresponding ketones apart from biocatalysis. Although the reaction doesn't work well for α-tertiary ketones, for secondary ones it works well with moderate *ee* values of 55-74% and for linear *n*-alkyl ketones, the *ee* is in the range of 21-33%. We believe that to further improve the *ee* of this system, we need to find and design new catalysts, as it seems that the available catalyst/ligand systems are not able to deliver higher *ee* than the ones reported here. Overall, ARA of aliphatic ketones remains challenging but attractive.

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Keywords: Asymmetric reductive amination (ARA), chiral, aliphatic, primary amines, enantioselectivity.

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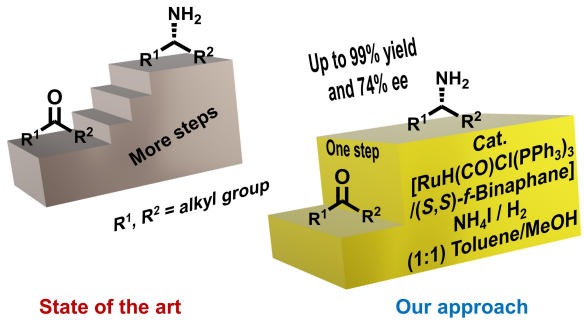

On the direct asymmetric reductive amination of aliphatic ketones to primary amines: By using Ru-Binaphane as catalyst and NH_4I as the amine source, it is possible to aminate prochiral aliphatic ketones with moderate ee´s up to 74%.

Key topic: Asymmetric Amination

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