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Mechanistic investigation of imine formation in ruthenium-catalyzed N-alkylation of amines with alcohols

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Imines are observed frequently in ruthenium-catalyzed N-alkylation of amines with alcohols. Herein, nitrogen–phosphine functionalized carbene ligands were developed and used in ruthenium-catalyzed N-alkylation to explore the mechanism of imine formation. The results showed that strongly electron-donating ligands were beneficial for imine formation and alcohol dehydrogenation to generate acid. In addition, with an increase of electron density of nitrogen atom in substituted amines, the yield of imines in N-alkylation was improved. At the same time, with electron-rich imines as substrates, the transfer hydrogenation of imines became difficult. It is suggested that strongly electron-donating ligands and substrates caused an increase of electron density on the ruthenium center, which resulted in the elimination of hydrogen atoms in active species [$LRuH_2$] as hydrogen gas rather than transfer onto the imine coordinated with the ruthenium center.

KEYWORDS
dehydrogenation, imine, N-alkylation, ruthenium

1 | INTRODUCTION

Transition metal-catalyzed N-alkylation is an environmentally friendly method for providing primary, secondary and tertiary amines, and thus a plethora of Ru, Ir, Pd, Co, Pt, Fe and Mn complexes have been developed and used as catalysts for this reaction.[1–9] Among them, inexpensive ruthenium complexes show high reactivity and are widely applied in N-alkylation of amines with alcohols.[10–14] However, a ruthenium loading of 5% or more is usually required to achieve satisfactory yields. Recently, the catalyst loading has been significantly reduced (Figure 1) while ruthenium complexes bearing chelating ligands[15–18] and phosphine-functionalized carbene ligands[19–22] have been utilized in N-alkylation. Based on these results, a nitrogen–phosphine functionalized carbene ligand (L1; Figure 1) was developed and used in N-alkylation to achieve excellent conversion of amines when the catalyst loading was as low as 0.01%. This good result was attributed to the long lifetime of the catalytic active species bearing this chelating and hemilabile ligand.[23] However, imine formation was also observed in reaction condition screening. Especially, when alkylamines were used as substrates, imines were obtained as main products. Similarly, functionalized carbene in ruthenium-catalyzed N-alkylation systems also led to imines as main products.[13,14,19] Nevertheless, the reason for imine formation was undefined in the reported N-alkylation mechanisms.

In general, transition metal-catalyzed N-alkylation includes inter- and intramolecular mechanisms[1,2] (Figure 2). In the intramolecular mechanism, after an imine is generated on the active center (**D**), it does not depart from the metal center, and it subsequently accepts hydrogen atoms from the metal center to give a *sec*-amine. In this mechanism, the key point is that the imine does not depart from the metal center and no imine is detected at the end of the reaction. In the intermolecular mechanism, after an alcohol molecule is dehydrogenated to form an aldehyde (**B**), the aldehyde is immediately eliminated

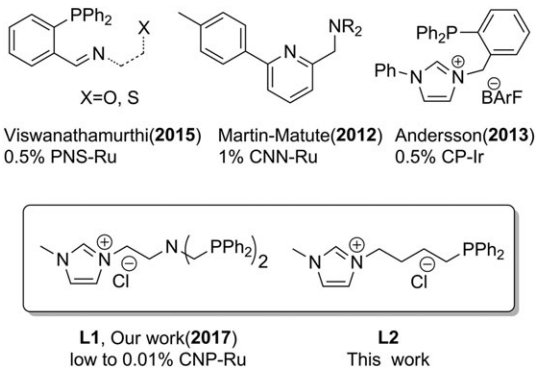


FIGURE 1 Ligands and their complexes for highly efficient N-alkylation of amines with alcohols

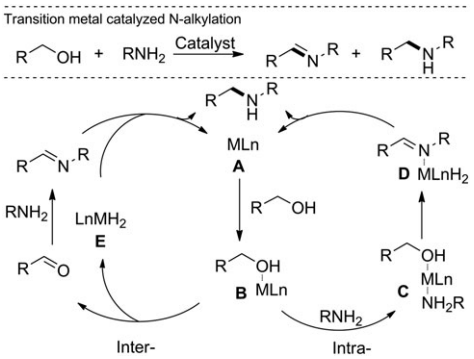


FIGURE 2 Mechanism of transition metal-catalyzed N-alkylation of amines

from the metal center and reacts with an amine to form an imine. And then the imine combines with metal species [$LRuH_2$] (**E**) and transfer hydrogenation occurs to give a *sec*-amine. For this mechanism, imines are often observed after the reaction is completed. Therefore, Ru–L1 mediated N-alkylation was judged to progress via the intermolecular mechanism and electronic factors of substrates showed a marked influence on imine formation.[23] However, to the best of our knowledge, the detailed mechanism of imine formation has not been proposed for the reported transition metal-catalyzed N-alkylation.

In order to explore the mechanism of imine formation in N-alkylation, Ru–L1 promoted N-alkylation of amines with alcohols and transfer hydrogenation of imines with various substituents were conducted in the work reported here. In addition, an electron-donating phosphine-functionalized carbene ligand (L2), having similar chelating effect and hemilability, was synthesized to investigate the effect of ligand structure on N-alkylation. The reaction results proved that electronic factors were vital for imine formation in N-alkylation and the mechanism of imine formation is proposed.

2 | EXPERIMENTAL

2.1 | General

All reactions were conducted under nitrogen atmosphere unless otherwise stated, and solvents were subjected to standard purification methods. Commercial reagents were purchased from suppliers and used as received. Moisture-sensitive compounds were stored and used in a glovebox. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded with a Bruker AVANCE III HD-400 MHz. GC analysis was performed with an Agilent 6890 N and Agilent 6890-GC/MSD (GC-MS). High-resolution MS was conducted with a Shimadzu LCMS-IT-TOF mass spectrometer. $[Ru(COD)Cl_2]_n$ and ligand L1 were prepared using reported protocols.[23]

2.2 | Synthesis of Ligand L2

2.2.1 | Synthesis of 3-(4-chlorobutyl)-1-methyl-1*H*-imidazol-3-ium chloride (1)

1,4-Dichlorobutane (10 ml) and 1-methylimidazole (1 ml, 1.1 g) were added into a two-necked flask under nitrogen, and then the mixture was heated to 80 °C with stirring overnight. At the end of the reaction, the mixture was cooled to room temperature and excessive reagent was distilled off to give a sticky solid. The solid was washed with acetone (2 × 5 ml) and dissolved in 60 ml of acetonitrile. The acetonitrile solution was cooled to −20 °C, whereupon some impurity was formed as a precipitate. The precipitate was filtered off and the filtrate was evaporated to dryness under reduced pressure to afford a light-yellow oil (1.0 g, 36% yield). ^{1}H NMR (400.1 MHz, DMSO-d_6, δ, ppm): 9.39 (s, 1H), 7.85 (t, 1H, J = 1.6 Hz), 7.78 (t, 1H, J = 1.6 Hz), 4.25 (t, 2H, J = 7.2 Hz), 3.87 (s, 3H), 3.69 (t, 2H, J = 6.4 Hz), 1.91 (m, 2H), 1.71 (m, 2H). ^{13}C NMR (100.6 MHz, DMSO-d_6, δ, ppm): 137.2, 124.1, 122.7, 48.4, 45.1, 36.2, 29.0, 27.4.

2.2.2 | Synthesis of 3-[4-(diphenylphosphino)butyl]-1-methyl-1*H*-imidazol-3-ium chloride (L2)

Triphenylphosphine (5 mmol, 1.31 g) and lithium (20 mmol, 0.12 g) were added into a 100 ml two-necked flask under nitrogen atmosphere. Then 20 ml of tetrahydrofuran (THF) was added with a syringe and the mixture solution was stirred at room temperature for 5 h. At the end of the reaction, the unreacted lithium was filtered off and *tert*-butyl chloride (5 mmol, 0.465 g) was added to the filtrate. The solution was stirred at room temperature for 30 min, and then an acetonitrile (5 ml) solution

of compound **1** (5.5 mmol, 1.15 g) was added into it in an ice bath. The resulting mixture was further stirred at room temperature overnight. After the reaction ended, all solvents were removed under reduced pressure and the residual solid was added to 10 ml of water. The aqueous solution was extracted with 30 ml of dichloromethane. The organic phase was separated, dried over $MgSO_4$ and filtered. The filtrate was evaporated to *ca* 5 ml under reduced pressure and 20 ml of ether was added to form an oil product. The product was separated, washed with ether (2 × 10 ml) and dried under vacuum to afford a pale yellow viscous liquid (0.56 g, 31% yield). ^{1}H NMR (400.1 MHz, DMSO-d_6, δ, ppm): 9.28 (s, 1H), 7.77 (s, 1H), 7.72 (s, 1H), 7.3–7.5 (m, 10H), 4.19 (t, 2H, J = 7.2 Hz), 3.84 (s, 3H), 2.12 (m, 2H), 1.91 (m, 2H), 1.31 (m, 2H). ^{13}C NMR (100.6 MHz, DMSO-d_6, δ, ppm): 138.7 (d, J = 13.3 Hz), 137.1, 132.8 (d, J = 18.4 Hz), 129.2, 129.0 (d, J = 6.6 Hz), 124.0, 122.7, 48.6, 36.2, 31.1 (d, J = 13.3 Hz), 26.3 (d, J = 11.1 Hz), 22.5 (d, J = 16.8 Hz). ^{31}P NMR (161.9 MHz, DMSO-d_6, δ, ppm): −17.8. High-resolution MS (ESI-TOF) m/z: $[M - Cl]^+$; calcd for $C_{20}H_{24}N_2P$ 323.1677, found 323.1679.

2.3 | Typical Procedure for N-alkylation and Transfer Hydrogenation

$[Ru(COD)Cl_2]_n$ (0.01 mmol Ru, 2.8 mg), ligand L1 (0.01 mmol, 5.6 mg) and KO^{t}Bu (1 mmol, 112 mg) were added into a dried reaction tube in a glovebox. Then, benzyl alcohol (1 mmol, 108 mg), aniline (1 mmol, 93 mg) and toluene (4 ml) were added into it successively and the mixture reacted at 100°C under stirring for 24 h. After the reaction ended, the mixture was cooled to room temperature and quenched with water (4 ml). Product was extracted with EtOAc (3 × 5 ml) and the combined organic phase was washed with saturated saline (3 × 25 ml), dried with $MgSO_4$ and analyzed using GC and GC-MS. Further purification was performed with column chromatography to give the corresponding pure product. The procedure for transfer hydrogenation of imines was the same as for N-alkylation, except for imines being used as substrates and alcohols as hydrogen sources.

3 | RESULTS AND DISCUSSION

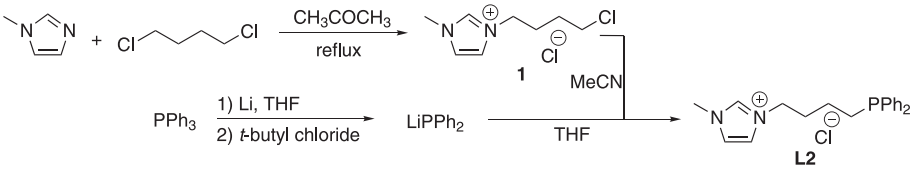
3.1 | Ligand Synthesis

Ligand L1 was prepared using a reported method.[23] Ligand L2 was prepared by reacting PPh_2Li with compound **1** (Scheme 1), which was formed by reacting 1-methylimidazole with 1,4-dicholobutane in refluxing acetone. L2 was obtained as an oily liquid and was very sensitive to air.

3.2 | Imine Formation in N-alkylation

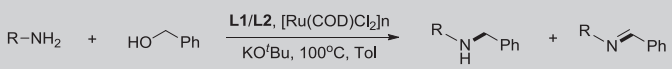
With ligands L1 and L2 in hand, we subsequently evaluated the catalytic reactivity of corresponding ruthenium complexes, formed *in situ*, for N-alkylation of benzyl alcohol with substituted amines. Firstly, it was found that L1 and L2 led to a marked difference in conversions (95 and 83%, respectively) when the ratio of aniline to benzyl alcohol was 1:1 (Table 1, entries 1 and 2). At the same time, the residual benzyl alcohol was not detected in GC analysis in both samples, so we suggest that some benzyl alcohol was transformed into other substances in the N-alkylation process. Obviously, this result may be attributed to be structural difference between ligands L2 and L1. Although ligand L1 contained C, P, P coordination atoms, the key catalytic species should be κ^2-C,P–Ru complex as two singlets, not doublets, were observed in the ^{31}P NMR spectrum *in situ* (Figure S1)[23] and coordination vacant site was necessary as well in N-alkylation. Moreover, both diphosphine (dppe) and N-heterocyclic carbene (MI) resulted in a worse result (Table 1, entries 11 and 12). These results implied both carbene and biphenylphoshpino moieties of ligand L2 might coordinate with the ruthenium center in N-alkylation. Hence, the active Ru intermediate bearing ligand L1 or L2 should be κ^2-C,P type Ru complex. Compared with the electron-rich alkyl linker in ligand L2, ligand L1 containing an electron-deficient N-containing alkyl linker showed a positive effect on the reaction.

Next, the amount of benzyl alcohol was increased to 2 eq. to exclude the effect of deficient alcohol as the side reaction of benzyl alcohol occurring. As expected, after the amount of alcohol was increased to 2 eq. (Table 1,



SCHEME 1 Synthesis of ligand L2

TABLE 1 Effect of ligand and substrate structure on imine formation of N-alkylation[a]



Entry	Ligand	Substrate (R)	Time (h)	Conv. (%)	Imine/amine (%)
1	L1/1%	Phenyl-	24	95	<1:99
2	L2/1%	Phenyl-	24	83	<1:99
3[b]	L1/1%	Phenyl-	24	>99	<1:99
4[b]	L2/1%	Phenyl-	24	>99	<1:99
5[b,c]	L1/1%	hexyl-	24	92	>99:1
6[b,c]	L1/1%	Cyclohexyl-	24	98	>99:1
7[b,c]	L1/1%	Dodecyl-	24	77	>99:1
8[b,c]	L1/1%	Benzyl-	24	>99	83:17
9[b]	L1/1%	Phenyl-	6	98	5:95
10[b]	L2/1%	Phenyl-	6	74	24:76
11[b]	dppe/1%	Phenyl-	6	71	64:36
12[b]	MI/2%	Phenyl-	6	44	71:29
13[b]	No ligand	Phenyl-	6	56	62:38
14[b]	L1/0.1%	4-Pyridyl-	24	96	3:97
15[b]	L1/0.1%	4-Fluorophenyl-	24	96	15:86
16[b]	L1/0.1%	Phenyl-	24	93	19:81
17[b]	L1/0.1%	4-Methoxylphenyl-	24	96	66:34

[a]Reaction conditions: benzyl alcohol (1 mmol, 108 mg), amine (1 mmol), KO^{t}Bu (1 mmol, 112 mg), ligand (0.01 mmol), $[Ru(COD)Cl_2]_n$ (0.01 mmol, 2.8 mg), toluene (4 ml), temperature 100 °C, time 24 h. GC and GC-MS analysis. dppe = 1,2-bis(diphenylphosphino)ethane; MI = 1,3-bis(2,4,6-trimethylphenyl) imidazolinium chloride.

[b]2 eq. of benzyl alcohol.

[c]120°C. Conversion was determined by GC with *N*-methylaniline as internal standard.

entries 3 and 4), both Ru–L1 and Ru–L2 catalytic systems gave excellent conversion (>99%) and selectivity to *sec*-amine (>99%). Interestingly, when the reaction time was shortened to 6 h, the conversion of aniline and selectivity to *sec*-amine for the Ru–L2 system were lower than those for the Ru–L1 system (Table 1, entries 9 and 10), which indicated that an increase of the electron-donating ability of the ligand caused a decrease in conversion of aniline and increase in selectivity of imine.

In addition, the electronic nature of substituents on aromatic amine also showed a significant influence on N-alkylation in the presence of 0.1% Ru–L1 (Table 1, entries 14–17). With an increase of the electron-donating ability of substituents, the selectivity to imines increased, but the conversions of substrates did not show any significant change. This suggested that the electronic nature of substituted aromatic amines only changed the selectivity to imines. And this result also indicated that the reaction progressed via the intermolecular mechanism. Moreover, when benzylamine and alkylamines were utilized as substrates, the conversions were satisfactory, but benzylamine only gave 17% *sec*-amine and all alkylamines gave imines as main products (Table 1, entries 5–7). Also, reacting alkyl alcohols with alkylamines containing O,S heterocycles gave low yields of products for the same conditions (Table S1). And all arylamines gave excellent yields of *sec*-amines in the presence of ligand L1 when the reaction time was extended to 48 h.[23] Interestingly, in the reported transition metal-catalyzed imine formation by reacting amines with alcohols,[24,25] the authors only used alkylamines as substrates rather than arylamines. Therefore, we suggest that the selectivity to imines is determined by the electron-donating ability of amines and both electron-rich ligands and amines are favorable for the formation of imines.

3.3 | Transfer Hydrogenation of Imines

In order to clarify why electron-rich amines gave imines as major products and electron-poor amines gave *sec*-amines as major products, we tried to explore the reason with transfer hydrogenation of substituted imines as it is a key step in N-alkylation according to the intermolecular mechanism (Figure 2). The results showed that the

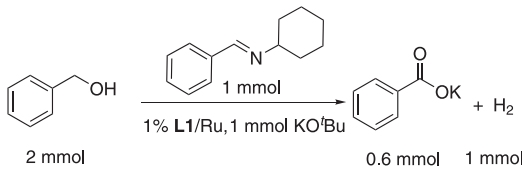
weakly electron-donating *N*-benzylidenebenzylamine only gave a low conversion of 34% (Table 2, entry 2). For the strongly electron-donating *N*-benzylidenecyclohexylamine, transfer hydrogenation did not occur (Table 2, entry 4). It is noteworthy that when 10 eq. of ^{i}PrOH was used as the hydrogen source, the conversion of *N*-benzylidenebenzylamine increased to 99% (Table 2, entry 3), but there was still no reaction for *N*-benzylidenecyclohexylamine (Table 2, entry 5). Therefore, these results further confirmed that the existence of strongly electron-donating substituents on nitrogen atom was beneficial for the formation of imines. Moreover, if transfer hydrogenation of imines was able to occur, excess alcohol would be favorable for obtaining *sec*-amines in high yields. In fact, in the presence of sufficient benzyl alcohol, these substituted anilines (Table 1, entries 14–17) could undergo N-alkylation to form *sec*-amines in high yields after the reaction time was extended to 48 h.[23] Consequently, we inferred that the formation of *sec*-amines and imines followed different and competing routes after the imines were formed by reacting aldehyde with amines. Meanwhile, the competing result was mainly determined by the electron-donating ability of substituents in different substrates. Obviously, this catalytic system showed a high selectivity to imines with alkylamines or electron-rich arylamines as substrates while *sec*-amines were formed with electron-poor arylamines as substrates.

3.4 | Dehydrogenation Oxidation of Alcohol

In the transfer hydrogenation of *N*-benzylenecyclohexylamine, NMR and GC analyses demonstrated that the imine was not hydrogenated, but most of the benzyl alcohol was consumed. After the resulting mixture was isolated and purified, we obtained about 0.6 eq. of benzoic acid. This result evidenced the dehydrogenation oxidation of alcohol occurring in the N-alkylation, which was further supported by the formation of *ca* 1 mmol of hydrogen gas in parallel experiment (Scheme 2). Therefore, the low conversion of aniline (Table 1, entry 2) was attributed to the dehydrogenation oxidation of benzyl alcohol, which caused the consumption of benzyl alcohol and led to deficient alcohol in the N-alkylation. Interestingly, a controlled experiment without addition of *N*-benzylenecyclohexylamine showed the dehydrogenation oxidation of benzyl alcohol was not obvious. This means that the addition of an electron-rich imine accelerated the dehydrogenation oxidation of benzyl alcohol. In fact, it proved that the dehydrogenation of alcohol would generate the key intermediate $RuLH_2$ in our previous work.[23] Hence, the generation of hydrogen gas was ascribed to hydrogen elimination from Ru–dihydride intermediate and hydrogen elimination was promoted by adding an electron-rich imine.

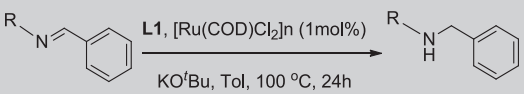
3.5 | Mechanism of Imine Formation in N-alkylation

According to the intermolecular mechanism of N-alkylation[1,2] and our previous results, in which we had confirmed the presence of aldehyde, Ru–OR complex (**I**), RuH_2 intermediate (**II**) and amine–RuH_2 complex (**V**) from NMR spectra *in situ*,[23] it is suggested that as soon



SCHEME 2 *N*-benzylidenecyclohexanamine-promoted dehydrogenation of benzyl alcohol

TABLE 2 Transfer hydrogenation of imines[a]



Entry	Substrate (R)	Alcohol	Conv. (%)
1	Phenyl	2 eq. BnOH	>99
2	Benzyl	2 eq. BnOH	34
3	Benzyl	10 eq. ^{i}PrOH	>99
4	Cylcohexyl	2 eq. BnOH	0
5	Cylcohexyl	10 eq. ^{i}PrOH	0

[a]Reaction conditions: imine (1 mmol), KO^{t}Bu (1 mmol, 112 mg), ligand L1 (0.01 mmol, 5.6 mg), $[Ru(COD)Cl_2]_n$ (0.01 mmol, 2.8 mg), toluene (4 ml), reaction stirred at 100 °C for 24 h under nitrogen. Reaction analyzed using GC.

as aldehyde was formed by the dehydrogenation of alcohol, it could not only react intermediately with amines to form imines, but it could also be dehydrogenated to produce acids as byproducts. At the same time, if an electron-poor imine coordinated with active $LRuH_2$ species to give the imine–$LRuH_2$ species, the coordinated imine would easily accept the hydrogen atoms from Ru–dihydride species to produce corresponding *sec*-amine. If the Ru species bears an electron-rich ligand and/or imine, the coordinated imine would with difficulty accept the hydrogen atoms from the ruthenium center and cause the decomposition of the imine–$LRuH_2$ species to release hydrogen gas and an imine. Similarly, when an electron-rich imine was used in the transfer hydrogenation, no *sec*-amine was detected, with a lot of hydrogen gas being released. Also, different ligands exhibited similar electronic effects. In a word, with an increase of electron-donating strength of substrates or ligands, the intermediate **III** was quickly decomposed.

Therefore, a detailed mechanism of imine formation in N-alkylation is proposed, as shown in Figure 3. (Catalyst activation and intermediate configuration are omitted for clarity. For related information, see Figure S2.) For an alkylamine, the formed imine would coordinate with $RuLH_2$ intermediate **II** to form active species **III**, and then it decomposes and releases hydrogen gas. After the alkylamine is completely transformed into the corresponding imine, the excess alcohol would be dehydrogenated into acid continuously. In the presence of an arylamine or benzylamine, the transfer hydrogenation from intermediate **III** to **V** is a key step to produce the corresponding *sec*-amine. An electron-donating substituent on imine would decrease the stability and lead to a fast decomposition of intermediate **III**, so that the hydrogenation transfer becomes difficult and a low yield of *sec*-amine is obtained.

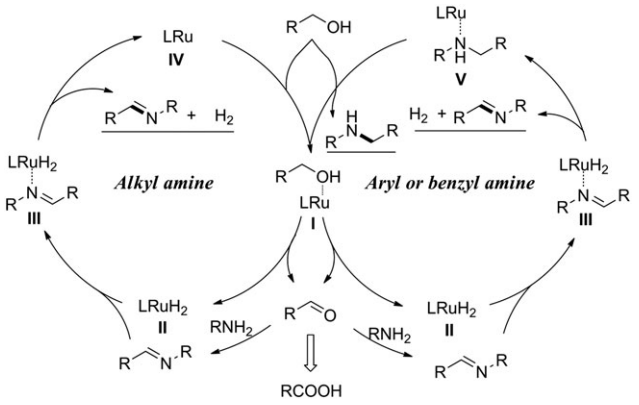


FIGURE 3 Mechanism of imine formation in N-alkylation

4 | CONCLUSIONS

Phosphine-functionalized carbene ligands L1 and L2 were used to examine imine formation in Ru-catalyzed N-alkylation of alcohols with amines. Electron-rich alkylamines produced imines as main products due to decomposition of imine–$RuLH_2$ species. When arylamines and benzylamines were used as substrates, competitive transfer hydrogenation of imines and decomposition of imine–$RuLH_2$ intermediate determined the formation ratio of imines to *sec*-amines. With an increase of electron-donating ability of ligands and substrates, the selectivity to imines was improved.

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SUPPORTING INFORMATION

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