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Journal Name

ARTICLE

Modular Construction of Multifunctional Ligands for Enantioselective Ruthenium-Catalyzed Carbenoid N-H Insertion Reaction: An Enzyme-like and Substrate-sensitive Catalyst System

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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It was found firstly that the cinchonine and BINOL -derived multifunctional ligands bearing silicon-based bulky group exhibited promising enantioselective induction in the ruthenium-catalysed carbenoid N-H insertion reaction, in which the Ru-L26 system with multiple stereogenic centers was proved to be an enzyme-like catalyst because it exhibited narr substrate scope and size-sensitive discrimination in this reaction.

Introduction

Chiral ligands generally play critical role in numerous stereoselective or chemoselective transformations in asymmetric organometallic catalysis. Thus in the past decades, the catalytic asymmetric synthesis of chiral molecules with organometallic complex focused on extending the reach of chiral ligands to better control enantioselective induction in this field.[1] Over the past years, our group has been interested in the design and preparation of multifunctional ligands with multiple stereogenic centers because of their powerful potentials in catalytic asymmetric application in organic transformations.[2] For example, our group recently reported a novel multifunctional *N*,*O*,*P*-ligand (HZNU-Phos) with multiple stereogenic centers that prepared from chiral binaphthol (BINOL) -derived aldehyde and primary amine bearing phosphine moiety for copper-catalyzed conjugate addition and palladium-catalyzed allylic alkylation,[2a,b] in which the novel ligand has been demonstrated as highly effective in these reactions. Inspired by previous work on catalytic carbenoid N-H insertion reactions, we hypothesized that the concept of modular synthesis of multistereogenic ligands by combining axial chiral BINOL derivatives with sp^3-carbon stereogenic amines would be applicable for the development of novel ruthenium catalyst system and corresponding enantioselective carbenoid N-H insertion reactions.

Carbenoid N-H insertion reactions, one of the most attractive carbon-nitrogen bond-forming transformations, have recently attracted considerable interest because they allow for synthesis of biologically active nitrogen-containing molecules, including α-amino acids and its derivatives.[3] In particular, the versati products of N-H insertion reactions have been found for wide utility both as precursors in the synthesis of complex natural products, and the building blocks of proteins and peptides.[4] Therefore, the development of highly efficient and enantioselective methods for the construction of α-amino acid or its derivatives by carbon-nitrogen bond-forming insertion reaction is a valuable and fundamental goal in organic synthesis.[5] Since the early work of copper bronze catalyzed N-H insertion reaction was reported in 1952 by Yates,[6] transitio metal-catalyzed carbenoid N-H insertion reactions by means of amines and diazocarbonys have proved to be an extremely simple approach for the synthesis of α-amino esters in an efficient and atom-economical way.[7] Especially since 1996, the investigation of catalytic asymmetric versions of the carbenoid N-H insertion reaction has attracted considerable attention.[8] However, whereas catalytic carbenoid insertion have been evolved into an extremely powerful tool in organic synthesis,[9] the enantioselective insertion of an α-diazocarbonyl compounds into N-H bond is still in its infancy in comparison to catalytic asymmetric hydrogenation. For example, as two representative and seminal advances, chiral rhodium (II) carboxylates reported by McKervey[8a] and Chiral copper- and silver-based catalysts reported by Jørgensen[8c] only gave low to moderate enantioselectivities (up to 48% *ee*).

Recently, other copper complexes have been found by Zhou and other groups to be highly enantioselective catalyst systems in this reaction,[10,11] in which the catalytic enantioselective insertion of α-diazoesters into N-H bonds by using the copp complexes of chiral spirobisoxazoline ligands as catalysts, particularly impressive advances in this context. This work also further supported the highly important role of chiral ligands in the enantioselective metal-catalyzed transformations. In view of the synthetically useful N-H insertion reactions, furth

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† Footnotes relating to the title and/or authors should appear here. Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

investigation and breakthrough was made by the groups of Fu[11], Feng[12], and Zhou[13] respectively in the past years, in which several interesting copper and rhodium complexes have been achieved successfully for such carbenoid N-H insertion reactions. Despite previous achievements in this field,[14] there is no report on the ruthenium-catalyzed asymmetric carbenoid N-H insertion reactions because of possibly different mechanistic procedure with chiral ruthenium chemistry. In addition, the effort to exploration of alternative approach with easily achieving ligands as well as the development of novel catalyst system and concept with high catalytic activity and perfect stereochemistry is also highly desirable.

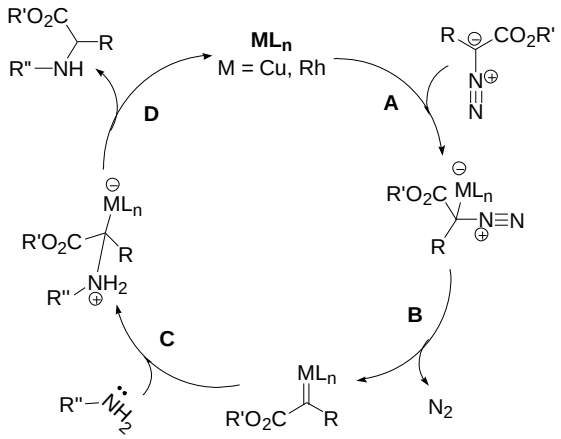


Figure 1. General mechanism for metal-catalyzed carbenoid N-H insertion reactions: Steps A, B, and D were crucial for copper catalysis and Step B is the rate-determining step (RDS) for rhodium catalyst system.[3c]

Meanwhile, previous studies on the general mechanism of metal-catalyzed carbenoid insertion reactions revealed that the rate-determining step (RDS) of copper catalysis was different from that of rhodium (II), according to theoretical calculations and experimental results steps A, B, and D were crucial for copper(I) catalysis (Figure 1).[3c,15] And the mechanism of ruthenium catalysis in this N-H insertion reaction is unclear, therefore further experimental investigation are need to be carried out to clarify the mechanistic pathway. In addition, in comparison to copper and rhodium-based catalyst system, ruthenium catalyst, such as $[RuCl_2(p\text{-cymene})]_2$, has also been found to highly reactive catalyst for carbenoid N-H insertion reactions.[16] For example, Che and Xu[16a] has found that only 1 mol% of $[RuCl_2(p\text{-cymene})]_2$ was enough effective for the intermolecular carbenoid N-H insertion reaction of aniline within 30 mins. Unfortunately, to our knowledge, there is no successful report on the design and synthesis of chiral ligands for enantioselective ruthenium-catalyzed N-H insertion reaction to date.

Herein, we want to report the first example of enantioselective ruthenium-catalyzed N-H insertion reaction of α-diazoesters into N-H of aromatic amines in the presence of multifunctional *N,N,O*-ligand bearing silicon-based bulky group that obtained from chiral BINOL- and cinchona alkaloid-coupled backbone, providing the widely prospect of the concept of modular construction of novel multifunctional ligands with multiple stereogenic centers to mimic the catalytic model of artificial metalloenzymes. However, there are no general methods or concepts for the design and preparation of chiral ligands for ruthenium-catalyzed carbenoid N-H insertion reactions. We hypothesized that multifunctional *N,N,O*-ligands with different coordination points as well as tuneable cavity would be beneficial to the enantioselective activity of ruthenium-based chiral catalyst (Figure 2). In brief, we considered two design criteria on the basis of possible mechanism of ruthenium-catalyzed carbenoid N-H insertion reactions proposed in previous work[16] as well as that of copper and rhodium catalysis.[15] One requirement was that the ligand should contain a Lewis basic nitrogen center (Schiff base or secondary amine) that, through ligand association, can increase the nucleophilicity of aromatic amine reagents. The other criterion, used previously in BINOL-based ligand development, involves the use of Brønsted acidic phenol moiety to form Ru-O bond, which would be an enough stable Ru-complex linked with chiral backbone during the carbenoid N-H insertion reaction.

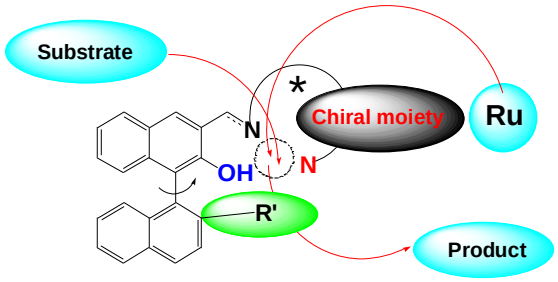
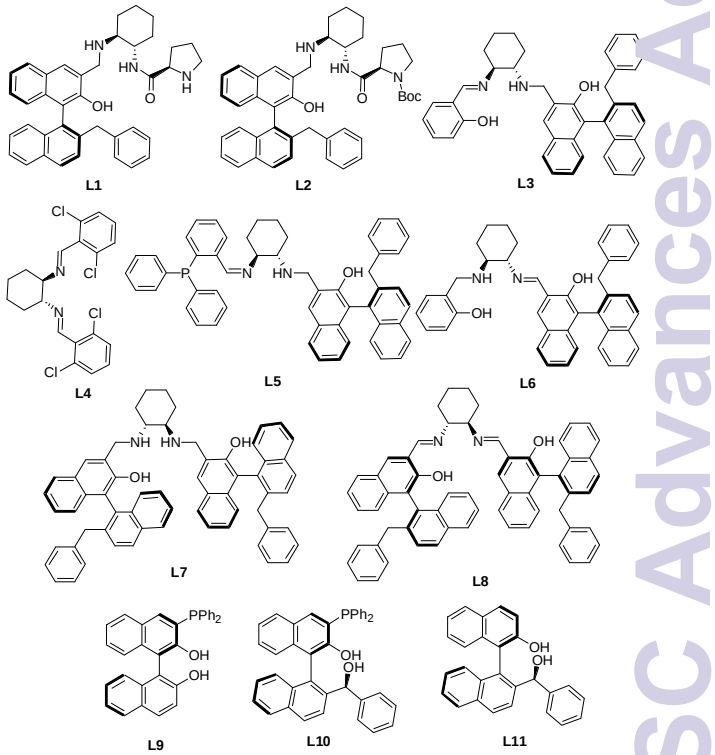
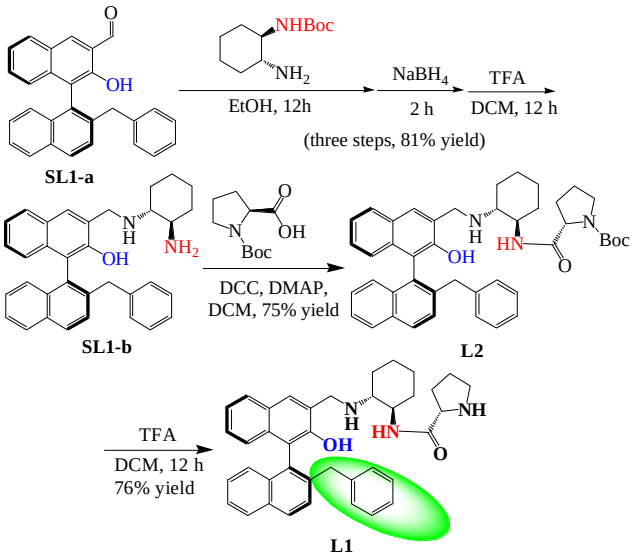


Figure 2. The design of *N,N,O*-groups-containing multifunctional ligands for ruthenium-catalyzed N-H insertion reaction



Scheme 1. BINOL-derived chiral ligands **L1-L11** used in this work

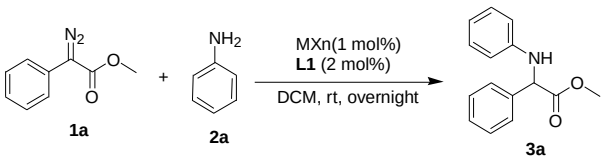
Results and discussion



Scheme 2. The synthesis of multifunctional N,N,O-ligands based on Ar-BINMOL-derived backbone

Initially, on the basis of our hypothesis, a series of BINOL-derived multifunctional ligands or phosphine ligands have been designed (Scheme 1 and Scheme 2, see Supporting Information).[17,18] These multifunctional ligands were prepared easily from chiral BINOL-derived aldehyde. As shown in Scheme 2, for the synthesis of the ligand **L1** and **L2**, we developed an efficient approach to prepare Ar-BINMOL-derived aldehyde (**SL-a**) through the key step of neighbouring lithium-assisted [1,2]-Wittig rearrangement (NLAWR).[17] And after the subsequent transformations of **SL-a** with classic condensation, reduction, and deprotection, we then furnished the introduction of *trans*-1,2-diaminocyclohexane and proline-derived motifs to the molecule **SL-a** that led to the formation of multifunctional *N,N,O*-ligand **L1** and **L2**.

Table 1. The effect of various metal salts on the catalytic asymmetric N-H insertion reaction in the presence of multifunctional ligands **L1**.



Entry	Metal Catalyst[a]	Yield (%)[b]	Ee (%)[c]
1	$AgSbF_6$	<20	8
2	$Pd(dba)_2$	NR	-
3	$Cu(CH_3CN)_4PF_6$	50	8
4	$Ru(NO)Cl_3$	<20	-
5	$[RuCl_2(p\text{-cymene})]_2$	>90	17
6	$Pd(OAc)_2$	<20	0

Note: [a] Reaction conditions: 1 mol% metal catalyst, 2 mol% ligand (**L1**), substrate **1a** (0.3 mmol), and substrate **2a** (0.3 mmol), in THF, at room temperature. [b] Isolated yields. [c]The *ee* value was determined by chiral HPLC.

With the multifunctional ligand **L1** in hand, we firstly investigated the catalytic activity of various transition metal catalysts in this reaction. In this study, the insertion of α-diazo-α-phenylacetate (**1a**) into N-H bond of aniline (**2a**) was initially performed in dichloromethane at room temperature. As shown in Table 1, comparison of these metal catalysts, including $Cu(CH_3CN)_4PF_6$ and $Pd(OAc)_2$, clearly revealed that the multifunctional ligand **L1** has a matched combination of activity with $[RuCl_2(p\text{-cymene})]_2$ in term of enantioselectivity and conversion.

To investigate the enantioselective induction of BINOL-derived multistereogenic ligands showed in Scheme 1, we then take the N-H insertion reaction of α-diazo-α-phenylacetate (**1a**) with aniline (**2a**) as a model Ru-catalyzed carbenoid insertion reaction under the established reaction conditions (Table 1). As shown in Figure 3, when these multifunctional ligands **L1-L11** were used in this reaction, the corresponding *ee* value was varied largely from 0 to 33% *ee*. The examples in Figure 3 illustrated that Schiff base and phenol moiety on BINOL backbone were useful building block used to guarantee promising enantioselectivity. Notably, the presence of phosphine moiety on the multifunctional ligand leads to almost no reaction (**L5**, **L9**, and **L10**).[17] And interestingly, the position of Schiff base moiety on the multifunctional ligand is also important for achieving enantioselective induction in this reaction. For example, the difference of **L3** and **L6** relayed on modulation of Schiff base, secondary amine, and Ar-BINMOL-based building block. As a result, **L6** gave better enantioselectivity in comparison to that of **L3** in this reaction. Although Ar-BINMOL-derived salan **L7** and salen **L8** exhibited excellent enantioselectivity in copper-catalyzed fluorination or cobalt-catalyzed Henry reaction respectively,[18] these ligands were not effective in the enantioselective ruthenium-catalyzed carbenoid N-H insertion reaction. Then the solvent effects on Ru-catalyzed carbenoid N-H insertion was evaluated in the presence of ligand **L6** (**Table 2**). Most of solvents, such as toluene, methanol, hexanes, and etc., exhibited negative effects on the catalytic asymmetric ruthenium-catalyzed insertion reaction. Thus it was found that higher enantioselectivity (57% *ee*) but with low yield (30%) could be obtained in THF. We hypothesized that the further modification of multifunctional ligand **L6** would lead to the establishment of suitable ligand for the ruthenium-catalyzed N-H insertion reaction.

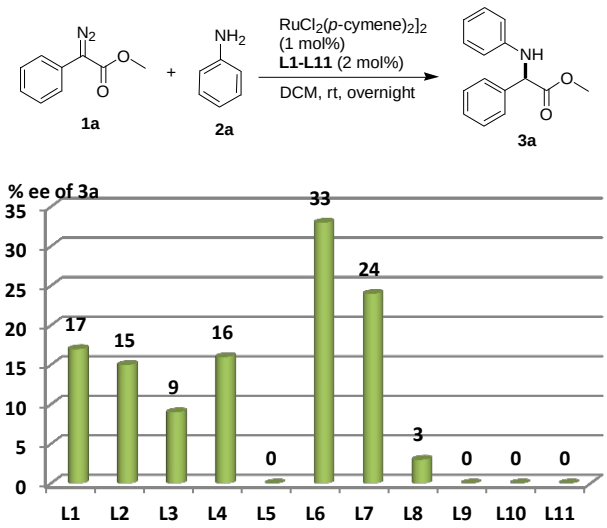
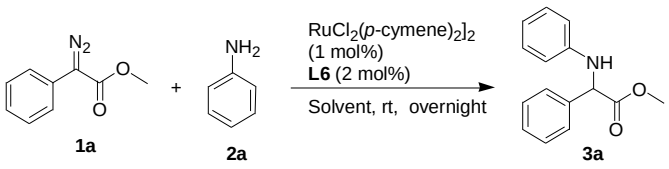
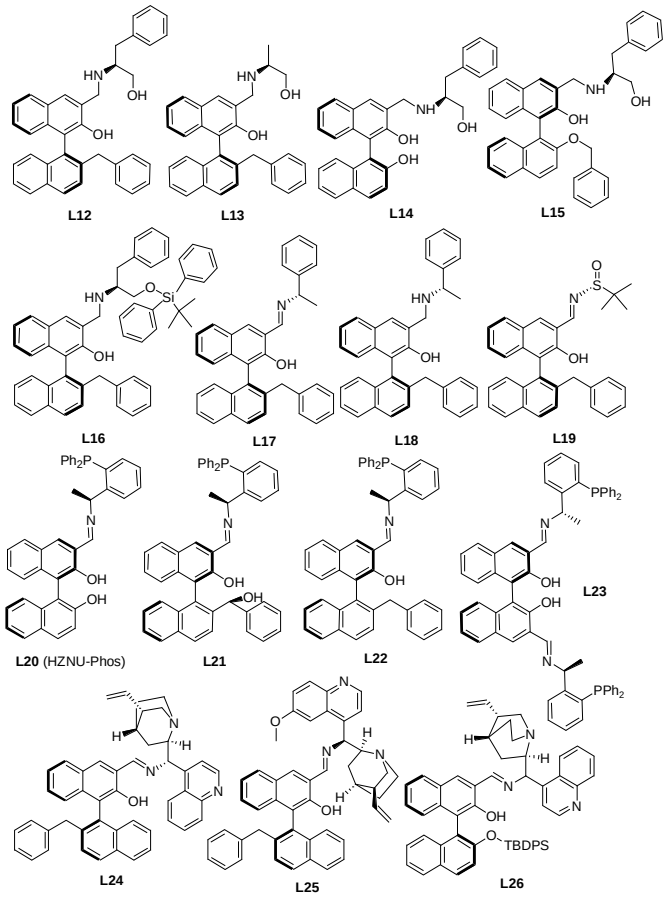


Figure 3. The enantioselective activity of ligands **L1-L11** for the Ru-catalyzed carbenoid N-H insertion reaction in DCM. The yields of the product **3a** with **L1-L11** used in this reaction respectively are: 90% (**L1**), 5[illegible] (**L2**), 91% (**L3**), 70% (**L4**), 0% (**L5**), 92% (**L6**), 80% (**L7**), 35% (**L8**), 0% (**L9**), 0% (**L10**), 93% (**L11**).

Table 2. The effect of solvents on the ruthenium-catalyzed N-H insertion in the presence of multifunctional ligand **L6**.



Entry	Solvent	Isolated yield (%)	Ee (%)
1	Toluene	36	0
2	THF	30	57
3	MeOH	NR	-
4	DCE	73	34
5	DMF	NR	0
6	*n*-Hexane	NR	-
7	TMSOTMS	NR	-
8	PhOMe	48	0
9	Et_2O	52	32
10	*t*-BuOMe	45	40



Scheme 3. BINOL- and chiral amine-derived multifunctional ligands **L12-L26**.

Encouraged by these results, we continued to modify and synthesize novel multifunctional ligands containing chiral BINOL-derived backbone and amine-based group (See Supporting Information). As shown in Scheme 3 and Figure 4, ligands **L12-L26** played different catalytic activity in the enantioselective Ru-catalyzed carbenoid N-H insertion reaction, providing 0-59% *ee*. The best result was achieved by ligand **L26** that prepared from BINOL-derived aldehyde and cinchonine-derived primary amine. Next, modularity of multifunctional ligand structures was exploited through the combinational linkage of cinchonine-derived primary amine with various aldehydes (Scheme 4). These studies indicated that it is very difficult to give excellent enantioselectivity in the Ru-catalyzed carbenoid N-H insertion reactions. Besides, the phenomena of chirality matching or mismatching in this work has found to be very important for the ligand-assisted asymmetric Ru-catalyzed N-H insertion reaction. For example, the ligand **L25** achieved from quinidine-derived primary amine almost resulted in no reaction. It may be arisen from the instability of such ruthenium complex. Further studies summarized in Figure 5 established that **L26** bearing silicon-based bulky group was best multifunctional ligand in the enantioselective carbenoid N-H insertion reaction in term of enantioselectivity (59% *ee*) and yield (98%). Notably, the direct use of all the commercial available cinchona alkaloids and its primary amine derivatives gave no enantioselectivity in this reaction.

With **L26** as the optimal multifunctional ligand, a broad range of substituted anilines were examined with α-diazo-ε phenylacetate under the standard reaction conditions. As shown in Table 3, all of the N-H insertion reactions took place smoothly and afforded the desired products in good yields (up to 98%). Although varied enantioselectivities (up to 82.5:17.5 *er*) were obtained for most of substrates (Table 3), the multifunctional ligand **L26** still exhibited promising activity during the generation of ruthenium carbine intermediate. Moreover, two α-diazoesters with Me- or Et-ester were also examined under the same reaction conditions. The desired α-amino esters were also obtained in high yields. Although present ruthenium-catalyzed N-H insertion reaction resulted in only moderate enantioselectivities in the presence of multifunctional *N,N,O*-ligand, to our knowledge, these are the best results for asymmetric ruthenium-catalyzed carbenoid N-H insertion in term of enantioselectivity.

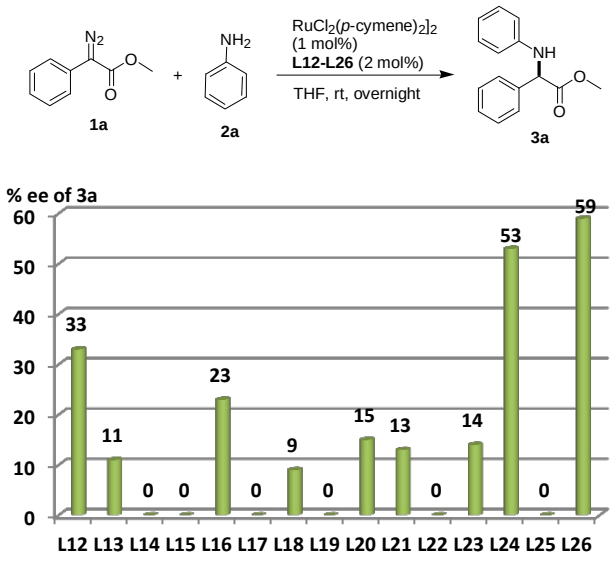
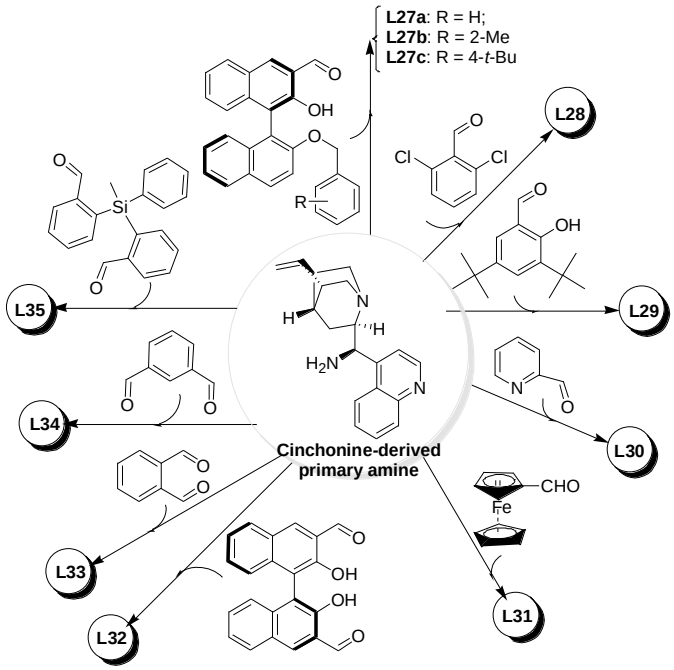
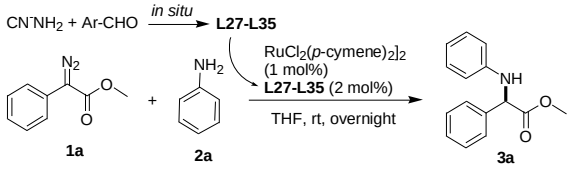


Figure 4. The enantioselective activity of ligands **L12-L26** for the Ru-catalyzed carbenoid N-H insertion reaction in THF. The yields of the product **3a** with **L12-L26** used in this reaction respectively are: 93% (**L12**), 93% (**L13**), 93% (**L14**), 93% (**L15**), 93% (**L16**), 92% (**L17**), 92% (**L18**), 90% (**L19**), 90% (**L20**), 70% (**L21**), 63% (**L22**), 80% (**L23**), 30% (**L24**), <10% (**L25**), 95% (**L26**).



Scheme 4. The combination of aromatic aldehydes with cinchonine-derived primary amine to *in-situ* form Schiff base ligands **L27**-**L35**.



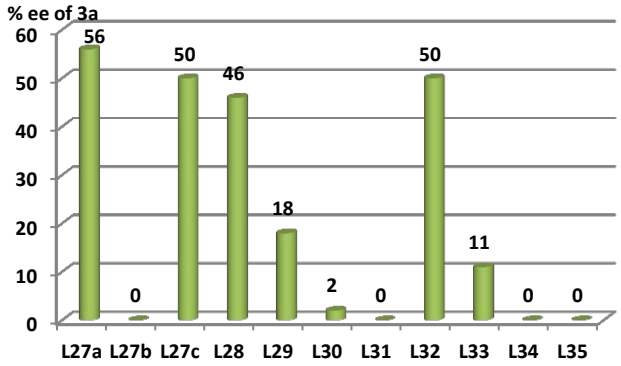
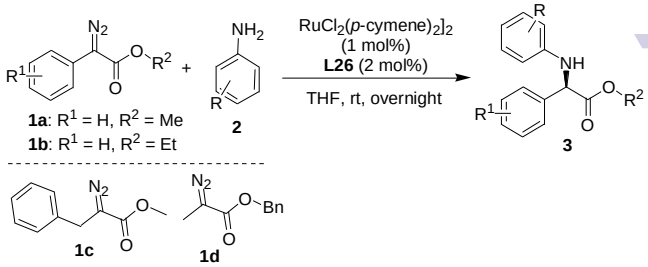


Figure 5. The enantioselective activity of ligands **L27**-**L35** for the Ru-catalyzed carbenoid N-H insertion reaction in THF. The yields of the product **3a** with **L27**-**L35** used in this reaction respectively are: <10% (**L27a**), <10% (**L27b**), 25% (**L27c**), 90% (**L28**), 90% (**L29**), 90% (**L30**), <10% (**L31**), 80% (**L32**), 93% (**L33**), <10% (**L34**), <10% (**L35**)

It is well known that previously reported chiral copper complex or other transition metal catalysts (Rh or Ag) controlled by various chiral ligands were successfully used for various α-diazoesters in catalytic asymmetric N-H insertion reaction,[8-13] in which no obvious differences in reactivity of aromatic or aliphatic diazo-substrate in the presence of certain catalyst system. Especially for aromatic diazoesters, no obvious differences in reactivity and enantioselectivity between α-diazo-α-phenylacetate and other substituted diazoesters was observed. Unfortunately and unexpectedly, we found that the utilization of the ligand **L26** in the N-H insertion reaction of substituted diazoesters led to almost no reaction. Thus differe… from copper or rhodium catalysis, the nature of substituent on benzene ring of diazoesters significantly influenced the conversion and enantioselectivity of ruthenium-catalyzed N-H insertion reaction. As shown in Table 3, methoxy-, methyl-, and halide-substituted diazoesters resulted in poor or no conversion. These outcomes indicated that aromatic diazoesters bearing substituted groups at any position are unsuitable substrates. In addition, the catalytic N-H insertion reaction of aliphatic diazoesters was very sluggish, exhibited poor reactivity with almost no conversion after 24 hrs. This pronounced effect indicated that the ruthenium-**L26** complex is substrate-sensitive because of narrow substrate scope, and it might be responsible for preferential activation and interaction of α-diazo-α-phenylacetate in this reaction. Also at that time, we believed that **L26**-Ru complex might form a cage-shaped metal comple… for size-sensitive discrimination of α-diazo-α-phenylaceta… from various substituted diazoesters.

Table 3. The Ru-catalyzed carbenoid N-H insertion reaction of various aromatic amines with α-diazoesters in the presence of multifunctional ligand **L26**



Entry	R/R[1]	Yield (%)[b]	e.r.[c]	*ee* (%)[c]
1	H/H	**3a**: 95	79.5:20.5	59
2	2-Me/H	**3b**: 85	66.5:33.5	33
3	3-Me/H	**3c**: 87	75.5:24.5	51
4	4-Me/H	**3d**: 80	70.5:29.5	41
5	2-F/H	**3e**: 83	59.5:40.5	19
6	3-F/H	**3f**: 82	82.5:17.5	65
7	2-Cl/H	**3g**: 79	56:44	12
8	3-Cl/H	**3h**: 85	76.5:23.5	53
9	4-Cl/H	**3i**: 87	79:21	58
10	2-Br/H	**3j**: 79	56.5:43.5	13
11	3-Br/H	**3k**: 88	72.5:27.5	45
12	4-Br/H	**3l**: 82	77:23	54
13	3-I/H	**3m**: 84	79.5:20.5	59
14	4-I/H	**3n**: 60	64.5:35.5	29
15	2-OMe/H	**3o**: 65	70:30	40
16	3-OMe/H	**3p**: 78	77:23	54
17[d]	H/**1b**	**3q**: 87	76.5:23.5	53
18	H/3-Br	**3r**: 21	64.5:35.5	29
19	H/2-Br	**3s**: <5	-	-
20	H/4-Me	**3t**: <5	-	-
21	H/2-Me	**3u**: <5	-	-
22	H/2-OMe	**3v**: <5	-	-
23	H/**1c**	**3w**: <5	-	-
24	H/**1d**	**3x**: <5	-	-
25[e]	H/3-Br	**3r**: 37	62:38	24

Note: [a] Reaction conditions: 1 mol% [$RuCl_2$(*p*-cymene)]$_2$, 2 mol% ligand (**L26**), substrate **1** (0.3 mmol), and substrate **2** (0.3 mmol), in THF, at room temperature. [b] Isolated yields. The *ee* value or *e.r.* was determined by chiral HPLC. [d] The R' is ethyl (**1b**). [e] The addition of 20 mol% of **1a** as additive in this reaction.

Inspired by previous results on additive-accelerated organic reactions[19] and the concept of springboard chemistry that high-reactive substrate act as a "tractor" or "reactive springboard" to drive the catalytic reaction of low-reactive substrate (HDL catalysis),[20] we hypothesized that high-reactive substrate might accelerate the ruthenium-catalyzed N-H insertion reaction of aromatic or aliphatic diazoesters with various substituents. Unfortunately, the enhancement of low-reactive diazoesters with HDL catalysis was not satisfied in yields and enantioselectivity (Table 3, entry 25).[21]

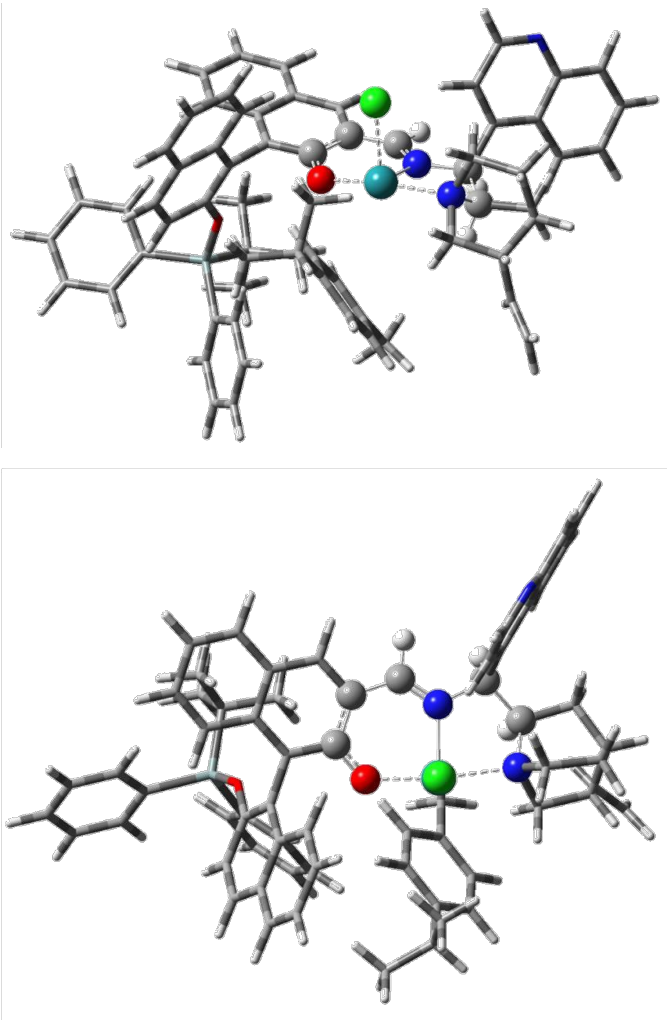
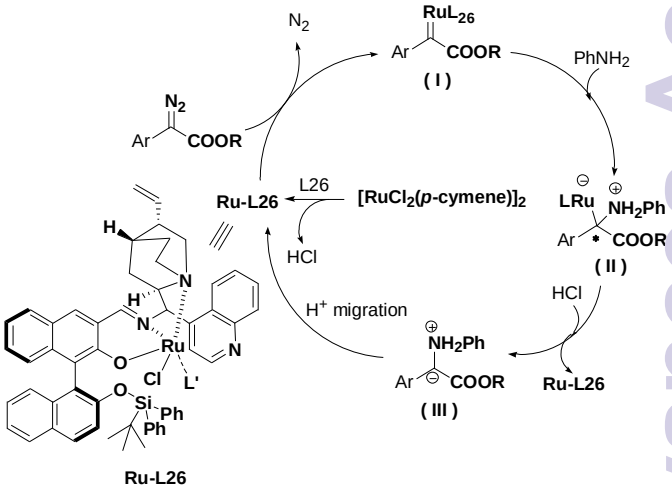


Figure 6. Views of the optimized structure of Ru-**L26** complex (up, top view; down, side view): Geometry of Ru catalyst optimized at HF/LANL2DZ (Ru), 3-21G (C, H, O, N, Si) level of theory.[25] r(Ru…O)= 2.040 Å; r(Ru…N_{sp2})= 2.048 Å; r(Ru…N_{sp3})= 2.215 Å.

On the basis of the aforementioned experiments and precious reports[22-24], we proposed a preliminary carbenoid N-H insertion reaction mechanism shown in Scheme 5. In the initial step, the reaction of $[RuCl_2(p\text{-cymene})]_2$ with multifunctional ligand **L26** resulted in the formation of a Ru-**L26** complex that determined by ESI-MS analysis (See Figure S1 of Supporting Information). And then the treatment with α-diazoester led to the generation of a chiral Ru-carbene intermediate (I),[22] which reacted quickly with aniline to give a possible chiral metal ylide (II) similarly to Cu or Rh catalyst system.[13,23] In the key step, the trace HCl generated from the catalyst system would possibly assist proton transfer and hydrogen transfer to form the desired N-H insertion product, in which the Ru-**L26** complex and the Brønsted acid are simultaneously regenerated for the next catalytic cycle. Notably, as shown in the schematic drawing of Figure 6,[25] the Ru-**L26** complex could have an unexpected cage structure that could discriminate different aromatic α-diazoesters if these bear bulky and branched groups on aromatic rings. Accordingly, the outcomes of enantioselective transformations of aromatic or aliphatic α-diazoesters provide direct evidence and information involving the possible molecular interaction between substrates and Ru-**L26** complex. According to this proposed mechanism, the addition of Lewis base or Brønsted base could inhibit the formation of the desired product. As expected, we have found that almost no N-H insertion product was obtained in the presence of base additive (See Table S2 of Supporting Information). And in addition, the use of catalytic amount of Brønsted acid, such as PhCOOH and CF_3COOH, the carbenoid N-H insertion reaction was carried out smoothly with the same level of enantioselectivity. Similarly to the copper catalysis, we found that the most of multifunctional ligands evaluated in this work could slow or even halt ruthenium catalysis.[16,26] Although more detailed investigations were needed to be carried out to get direct evidence for the elucidation of precise reaction mechanism, the new model established with multifunctional ligand for ruthenium catalysis will help the further design and synthesis of novel and powerful ligands for enantioselective Ru-catalyzed organic reactions.



Scheme 5. The proposed mechanism for asymmetric ruthenium-**L26** complex catalysed carbenoid N-H insertion reaction.

Experimental

Typical procedure for the ruthenium-catalyzed N-H insertion reaction:

$RuCl_2(p\text{-cymene})_2]_2$ (1.8 mg, 0.003 mmol, 1 mol%), **L26** (50 mg, 0.06 mmol, 2 mol%) were introduced into an oven-dried Schlenk tube in argon-filled glove box. After fresh THF (1 mL) was injected into the Schlenk tube, the solution was stirred at

room temperature under the argon atmosphere for 1 h. A solution of aniline **2a** (27 mg, 0.3 mmol) and methyl 2-diazo-2-phenylacetate **1a** (52.8 mg, 0.3 mmol) in 2 mL THF was injected into the reaction mixture at room temperature. The resulting mixture was stirred at room temperature for overnight. After filtrating and removing solvent in vacuum, the product was isolated by flash chromatography (petroleum ether/ethyl acetate = 50:1, v/v) as a colorless solid. All the products are known and confirmed by GC-MS, NMR, IR, HRMS (see Supporting Information). For example, **3a**: R_f = 0.30 (PE/EA = 10:1, v/v, PE = petroleum ether, EA = ethyl acetate), 89% yield; HPLC analysis with Chiralcel AD-H column (hexane/*i*-PrOH = 95:5 v/v, 1 mL/min, 254nm); t_R = 10.6 min, t_R = 11.8. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49 (d, *J* = 7.7 Hz, 2H), 7.11 (t, *J* = 7.5 Hz, 2H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.55 (d, *J* = 7.9 Hz, 2H), 7.31 (td, *J* = 13.8, 7.3 Hz, 3H), 5.06 (d, *J* = 12.8 Hz, 1H), 3.72 (d, *J* = 11.4 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.3 , 145.9, 137.6, 129.3, 128.9, 128.4, 127.3, 118.3, 113.5, 60.8, 52.8 ppm. HRMS (ESI) Calcd for $[C_{15}H_{16}NO_2, M+H]^+$: 242.1176; Found: 242.1177.

Conclusions

In summary, it can be seen from this work and previous efforts that the development of ruthenium-catalyzed carbenoid N-H insertion reaction is not an easy task at present. On the basis of this high-throughput screening of multifunctional ligands that combined with BINOL-derived aldehydes and chiral primary amines, we have tried to demonstrate firstly that the catalyst system of $[RuCl_2(p\text{-cymene})]_2$ with multifunctional ligand **L26** bearing silicon-based bulky group could be worked as an efficient catalyst in the catalytic asymmetric carbenoid N-H insertion reaction. The major findings in this work including: a) The single phenol group of the chiral BINOL-based backbone was important to the enantioselective induction of Ru-**L26** complex. b) The cinchonine-derived primary amine that was used to form Schiff base moiety was proved to be crucial building block in the construction of the multifunctional ligands with promising enantioselectivity in this reaction. The experimental results supported that the chirality matching of (*S*)-BINOL-derived aldehyde and cinchonine-derived primary amine would be beneficial to the formation of stable ruthenium complex from $[RuCl_2(p\text{-cymene})]_2$. Although the final results achieved in this work are not perfect, to our knowledge, it is a first example of ruthenium-catalyzed carbenoid N-H insertion reaction with the aid of multifunctional *N,N,O*-ligands, which is a complementary to copper- or rhodium-catalyzed synthesis of amino esters through intermolecular carbon-nitrogen bond-forming reaction of α-diazoesters with amines. The new chemistry on the asymmetric ruthenium-catalyzed N-H insertion reaction will possibly inspire researcher to explore more effective ligand in this field.

Acknowledgements

Financial support by the National Natural Science Foundation of China (NSFC Grant No. 21173064, 51203037, and 21472031), Fundamental Research Funds for the Central Universities (GK201501005), and Zhejiang Provincial Natural Science Foundation of China (LR14B030001) is appreciated.

Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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