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Enantioselective henry reactions catalyzed by chiral N-metal complexes containing *R*(+)/*S*(−)-α-ethylphenyl amines

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ABSTRACT

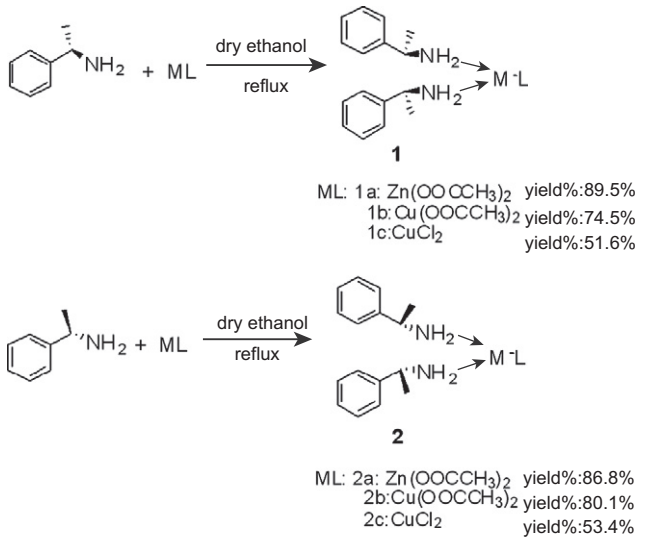
A series of novel N-metal complexes containing chiral α-ethylphenyl amines was synthesized and they catalyzed asymmetric Henry reactions affording products with high enantioselectivity.

Organometallic complexes have been widely used in catalyzing organic and polymer synthesis.[1–17] Recently, it has been reported that zinc and copper complexes can also catalyze Henry reaction,[18–28] as we all know, Henry reaction is a powerful synthetic tool for the construction of complex molecules, and good results have been reported in the literature.[24,29–32] For example, Shibasaki reported the first efficient method by making use of the two-center catalysis[29] and Trost revealed a novel family of dinuclear zinc complexes[30] catalyzing the reaction between nitromethane and aldehydes. Subsequently, Evans's copper acetate–bis(oxazoline) catalyst[31] and Palomo's zinc triflate–amino alcohol complex[32] were both found to effectively catalyze the Henry reaction by concurrent activation. However, some of the catalysts still showed limitations such as moisture or air sensitivity,[33] requirement for high catalyst loading,[33] low temperature to −45 °C,[34–36] uncertain structure of the catalysts[24,29,30,32] or multi-step procedures.[26] These studies inspired us to develop novel chiral ligands and evaluate the catalytic utility of our catalysts–organometallic complexes containing chiral α-phenylethylamine in Henry reaction and the high enantioselectivity of Henry reaction products were achieved.

First, we synthesized novel complexes **1a**, **2a** or **1b**, **2b** (Scheme 1) by reacting *R*(+)/*S*(−)-α-ethylphenyl amine with zinc acetate dihydrate or copper acetate hydrate. The crystal structures of complexes were determined after they were recrystallized from hexane. Similarly, complexes **1c** and **2c** were synthesized by reacting *R*(+)/*S*(−)-α-ethylphenyl amine with cupric chloride in absolute ethanol. Their crystal structures were determined after sitting at room temperature for several days. In summary, we obtained **1a–c** and **2a–c** in moderate to high yields and determined their crystal structure. Then we compared their catalytic activities in asymmetric Henry reactions (Table 1).

Using 15 mol % of catalysts **1a–c** and **2a–c** products **3** and **4** were produced in moderate conversion and excellent enantioselectivity (Table 1) in product **3**. In this reaction, the overall conversion rate was high, but **3** was prone to dehydration and formed **4**. Products **3** and **4** were all characterized by ^{1}H NMR. The configuration of **4a–l** was identified as E-type by ^{1}H NMR experiments. The results were confirmed by X-ray crystallography study of **4i**.

In order to get the optimized conditions, we reduced the amount of catalysts to 15 mol %, the scope of the reaction was further explored at room temperature. Products generally showed high conversion (>99%) and enantioselectivity (82–99%). Notably, 2- and 4-substituted benzaldehydes bearing electron-withdrawing



Scheme 1. N-Metal complexes with chiral α-ethylphenyl amine

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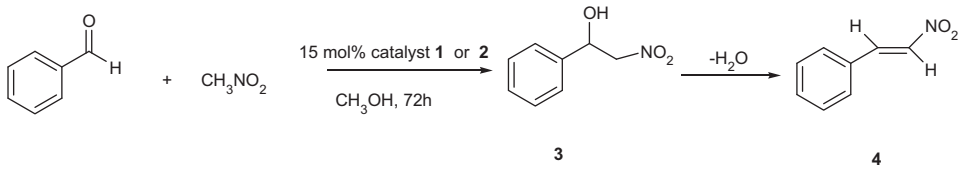
Table 1
Catalysis of asymmetric Henry reactions[a]

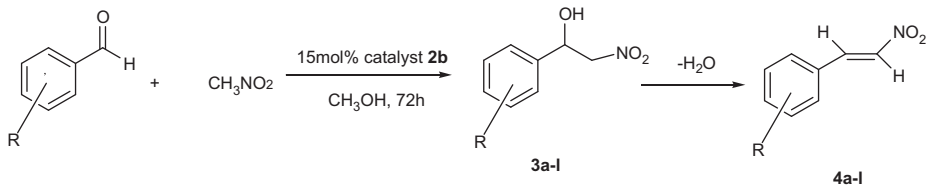


3 4

Complex	Conv.%[b] (**3**)	Yield%[b] (**4**)	ee[c] (%)	$[\alpha]_D^{25}$	Config.[d]
1a	99	32	85	+38.8	*S*
1b	99	39	70	+34.2	*S*
1c	99	46	96	+43.8	*S*
2a	99	35	90	+41.0	*S*
2b	99	30	83	−36.40	*R*
2c	99	43	67	+31.0	*S*

[a] Reactions were carried out with 1 mmol PhCHO and 0.5 mL CH_3NO_2 in 5 mL CH_3OH using 15 mol % of catalyst **1** or **2** at room temperature for 72 h.
[b] Isolated yields after flash chromatography.
[c] Determined by HPLC analysis using a Chiralcel OD-H column with a mobile phase of hexane/isopropanol 9:1.
[d] The absolute configuration of the major product was assigned by comparing with the literature values.[19,24–37,28a]

Table 2
Catalysis of asymmetric Henry reactions[a,31,33–37]



3a-l 4a-l

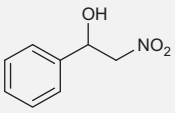
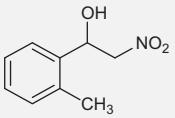
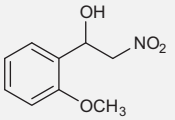
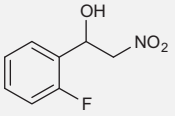
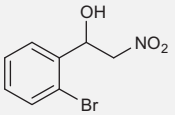
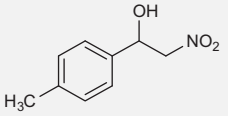
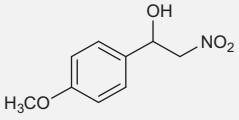
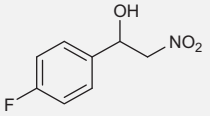
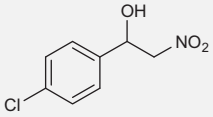
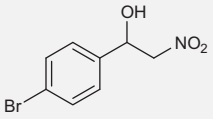
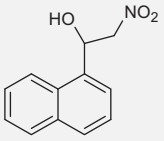
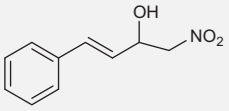
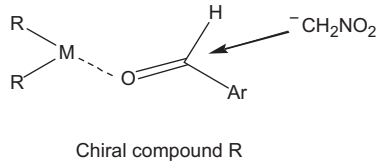
Entry	Products	Conv.%	Yield%[b] (**4**)	ee%[c] (**3**)	Config.[d]
3a		>99	40	83	*R*
3b		>99	47	98	*S*
3c		>99	28	82	*S*
3d		>99	30	88	—[e]
3e		>99	29	97	*S*
3f		>99	29	>99	*S*
3g		>99	34	>99	*S*

Table 2 (*continued*)

Entry	Products	Conv.%	Yield%[b] (**4**)	ee%[c] (**3**)	Config.[d]
3h		>99	40	88	*S*
3i		>99	55	82	*S*
3j		>99	40	86	—[e]
3k		>99	30	>99	*S*
3l		>99	27	60	*R*

[a] Reactions were carried out with 1 mmol PhCHO and 0.5 mL CH_3NO_2 in 5 mL CH_3OH using 15 mol % of catalyst **2b** at room temperature for 72 h.
[b] Isolated yields after flash column.
[c] Determined by HPLC analysis using a Chiralcel OD-H column with a mobile phase of hexane/isopropanol 9:1.
[d] The absolute configuration of the major product was *S*/*R*, as assigned by comparing HPLC with the literature.[26–37,28a]
[e] The absolute configuration of the major product was not determined.



Scheme 2. The proposed mechanism for the enantioselective catalysis.[32]

or electron-donating groups all afforded the products with high yields and high enantioselectivity (Table 2).

We propose a mechanism (Scheme 2) in which the benzaldehyde coordinates to either a copper or zinc atom, followed by nucleophilic attack of $^{-}CH_2NO_2$ onto the less sterically hindered face of the carbonyl group, affording products with high enantioselectivity.[32]

In conclusion, we have synthesized a series of novel catalysts by easy preparation procedures for asymmetric Henry reactions. The catalysts afforded products with high enantioselectivity and produced two kinds of important organic intermediates, β-nitroalcohol and E-nitrostyrenes, in one pot.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.055.

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