

Enantioselective Henry Reaction Catalyzed by Optically Active Ketoiminatocobalt Complexes

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In the presence of a catalytic amount of optically active ketoiminatocobalt complexes, the enantioselective Henry reaction proceeded to afford β -nitro alcohols in good-to-high yields with high enantioselectivities.

The Henry reaction¹ is one of the most useful and atom-economical² reactions for carbon–carbon bond formation to afford β -hydroxynitroalkanes, which can be further converted to amines by reduction,³ to carbonyl compounds by the Nef reaction,⁴ and to nitroalkenes by dehydration,⁵ etc.⁶ The catalytic enantioselective version of this reaction was first reported by Shibasaki *et al.*⁷ using heterobimetallic catalysts with lanthanide BINOL systems. Although the copper/bisoxazoline complexes by Jørgensen⁸ and Evans,⁹ the dinuclear zinc complex catalysts by Trost,¹⁰ and the chiral quarternary ammonium bifluoride by Maruoka¹¹ were reported to provide a successful catalytic enantioselective Henry reaction, a reliable catalysis is still expected to be developed for the direct carbon–carbon bond formation¹² without any pretreatment, such as enolization. The optically active 3-oxobutylideneaminatocobalt complexes (Figure 1) were originally developed as effective catalysts for the enantioselective borohydride reductions of carbonyl compounds,¹³ and were found to also work as chiral Lewis acid catalysts for the enantioselective hetero Diels–Alder reaction¹⁴ and carbonyl–ene reaction.¹⁵ Recently, it was reported that these types of cobalt complexes could be successfully used for the enantioselective 1,3-dipolar cycloaddition reactions of nitrones with α,β -unsaturated aldehydes.¹⁶ Therefore, they are expected to activate carbonyl compounds as an effective chiral Lewis acid even in the presence of a strongly electron-donating compound,¹⁷ such as nitrones and amine bases. In this communication, we would like to describe that the enantioselective Henry reaction in the presence of amine bases was catalyzed by the optically active ketoiminatocobalt complexes to afford the corresponding nitro alcohols in good-to-high yields with high enantioselectivity.

Various ketoiminatocobalt complexes were examined for the catalytic enantioselective nitroaldol reaction of 2-naphthaldehyde with nitromethane in the presence of diisopropylethylamine as a base (Entries 1–6 in Table 1). When the complexes

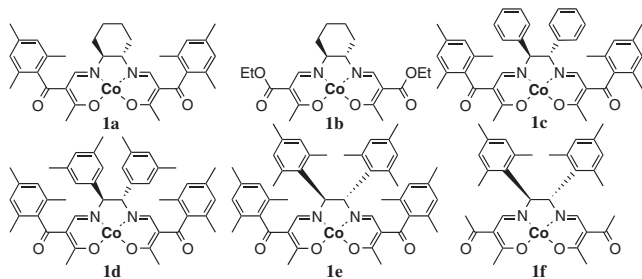


Figure 1. Various cobalt(II) complex catalysts.

Table 1. Various cobalt complex catalysts for enantioselective nitroaldol reaction

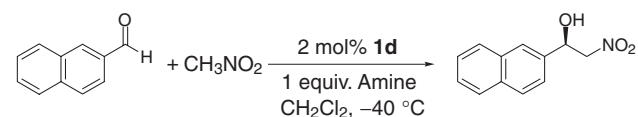
Entry	Aldehyde	Catalyst	Time/h	Yield/%	Ee/% ^a
1	2a	1a	67	64	19
2	2a	1b	67	53	5
3	2a	1c	67	82	55
4	2a	1d	67	quant.	69
5	2a	1e	67	93	12
6	2a	1f	60	90	13
7	2b	1c	64	92	70
8	2b	1d	24	88	84
9	2b	1e	64	97	49
10	2b	1f	64	99	40

Reaction conditions: Cobalt(II) catalyst 0.01 mmol (2.0 mol %), aldehyde 0.5 mmol, nitromethane 18.5 mmol and diisopropylethylamine 0.5 mmol in CH₂Cl₂ 5 mL. Reaction temperature: –60 °C (Entries 1–6), –65 °C (Entries 7–10) ^aDetermined by HPLC analysis using Daicel Chiralpak AD–H or Chiralcel OD–H.

1a and **1b** bearing the chiral 1,2-diaminocyclohexane were employed as catalysts, the corresponding nitro alcohol was obtained in 64 and 53% yield with 19% ee and 5% ee, respectively. The cobalt complex catalysts with the optically active 1,2-diarylethylenediamines **1c** and **1d** afforded the nitro alcohols in good yield with 55% ee and 69% ee, respectively, though the more sterically demanding complex **1e** and **1f** derived from 1,2-bis(2,4,6-trimethylphenyl)ethylenediamine did not improve the enantioselectivity. Similar results were obtained for the reaction of *o*-chlorobenzaldehyde (Entries 7–10). For both aldehydes, the cobalt complex **1d** was found to be the most suitable catalyst for the enantioselective Henry reaction.

For the enantioselective nitroaldol reaction of 2-naphthaldehyde, various amine bases were screened (Table 2). In the presence of DBU (Entry 1), the reaction was completed in 1 h to obtain the product in 94% yield but no enantioselection was observed. The primary and secondary amines afforded the nitro alcohol in 36 and 50% yields with 14 ee and 48% ee (Entries 2 and 3), respectively. In the reaction with tertiary amines, the chemical yields and the enantioselectivities were both improved (Entries 4–10), and among them, it was found that diisopropylethylamine was the most suitable amine for the present Henry reaction (Entry 10). The catalytic enantioselective Henry reaction catalyzed by the cobalt complex was successfully applied to various aldehydes (Table 3).

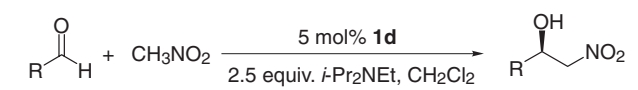
The nitroaldol reaction of benzaldehyde proceeded quantitatively with 81% ee (Entry 1), and *p*-chlorobenzaldehyde afforded the corresponding β -alcohol in quantitative yield with 85% ee

Table 2. Examination of amine bases for enantioselective direct nitroaldol reaction

Entry	Amine	Time/h	Yield/%	Ee/% ^a
1	DBU	1	94	0
2	<i>c</i> -HexNH ₂	44	36	14
3	<i>i</i> -Pr ₂ NH	42	50	48
4	Et ₂ NMe	40	13	34
5	Et ₃ N	27	64	54
6	<i>n</i> -Pr ₃ N	42	44	34
7	<i>c</i> -Hex ₂ NMe	20	72	45
8	<i>c</i> -Hex ₂ NEt	44	73	48
9	<i>t</i> -BuNEt ₂	45	quant.	55
10	<i>i</i> -Pr ₂ NEt	36	93	61

Reaction conditions: Cobalt(II) catalyst 0.01 mmol (2.0 mol%), aldehyde 0.5 mmol, nitromethane 18.5 mmol and amine 0.5 mmol in CH₂Cl₂ 5 mL. ^aDetermined by HPLC analysis using Daicel Chiralpak AD-H.

(Entry 2). It was found that *ortho*-halo substitution improved the enantioselectivity; e.g., the reaction of *o*-chlorobenzaldehyde, *o*-fluorobenzaldehyde, and *o*-trifluoromethylbenzaldehyde were effectively catalyzed to afford the corresponding β -nitro alcohols in high yields and high enantioselectivities up to 92% ee (Entries 3–6). The enantioselectivity for *o*-bromobenzaldehyde (Entry 7) was slightly improved compared with that of benzaldehyde. A similar effect of *ortho*-halo substitution on the reactivity and enantioselectivity was reported for the enantioselective hetero Diels–Alder reaction catalyzed by ketoiminatocobalt com-

Table 3. Catalytic enantioselective Henry reaction of various aldehydes

Entry	R in aldehyde	Temp/°C	Time/h	Yield/%	Ee/% ^a
1 ^b	Ph	-40	144	quant.	81
2	<i>p</i> -ClPh	-78	72	quant.	85
3 ^{b,c}	<i>o</i> -ClPh	-70	65	quant.	91
4	<i>o</i> -FPh	-78	40	98	92
5 ^d		-78	90	90	91
6	<i>o</i> -CF ₃ Ph	-78	62	93	90
7	<i>o</i> -BrPh	-78	70	85	84
8	<i>p</i> -MeOPh	-40	90	11	53
9	<i>o</i> -MeOPh	-60	63	quant.	90
10	2-Naphthyl	-78	136	quant.	84
11 ^c	PhCH=CH-	-65	90	72	79
12	Ph(CH ₂) ₂ -	-78	41	83	81
13	BnOCH ₂ -	-78	40	83	81
14	<i>c</i> -Hex	-78	112	91	73

Reaction conditions: Cobalt(II) catalyst 0.015 mmol (5.0 mol%), aldehyde 0.3 mmol, nitromethane 11.1 mmol and diisopropylethylamine 0.75 mmol in CH₂Cl₂ 3 mL. ^aDetermined by HPLC analysis using Daicel Chiralpak AD-H or Chiralcel OD-H. ^bAcetone was used as the solvent. ^c2.0 mol% catalyst and 1.0 equiv. amine was used. ^dCatalytic amount of amine (0.15 mmol, 0.5 equiv. vs aldehyde) was used.

plexes.¹⁸ The sense of asymmetric induction was the same in both reactions of benzaldehyde and *o*-chlorobenzaldehyde,¹⁹ although the origin of these effects is not clear. 2-Naphthaldehyde and cinnamaldehyde reacted with nitromethane to afford the corresponding β -nitro alcohols in high yields with 84 and 79% ee, respectively (Entries 10 and 11). It is noted that in the presence of a catalytic amount of optically active ketoiminatocobalt complexes, the enantioselective Henry reaction of various aldehydes proceeded to afford the corresponding β -nitro alcohols in good-to-high yields with high enantioselectivities. The detailed study of the intermediates and the scope and limitations of the substrates are now under way.

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- The absolute configurations of the β -nitro alcohols obtained from benzaldehyde and *o*-chlorobenzaldehyde were determined by comparing the optical rotations reported in the literature. (Ref. 9) The enantioselective sense in the reaction of the alkylaldehyde was also the same as that of the arylaldehydes; (*R*)-nitro alcohol was obtained corresponding to the (*S,S*)-cobalt complex catalysts.