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Highly enantioselective phenylacetylene addition to aldehydes catalyzed by a chiral *N,O*-ferrocene ligand

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Abstract—Ferrocenyl oxazoline alcohols are found to be effective in catalyzing the addition reaction of an alkynylzinc reagent to aromatic and aliphatic aldehydes with up to 93% ee of the thus produced chiral propargyl alcohols.

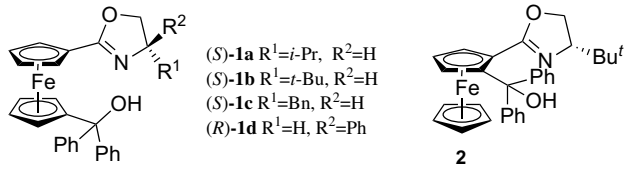
1. Introduction

Chiral propargylic alcohols are useful building blocks for the enantioselective synthesis of complex molecules.[1] In recent years, significant progress has been made in the catalytic enantioselective addition reaction of acetylenes to aldehydes.[2] Many chiral ligands, such as *N*-methylephedrine,[3] BINOL and its derivatives,[4] and other amino alcohol compounds,[5] have successfully been used in this reaction. Usually, a titanium complex or $Zn(OTf)_2$ was required in these catalytic systems. Some procedures have also been developed by Chan and co-workers[6] and Pu and Xu[7] independently, using different ligands to catalyze the addition of phenylacetylene to aromatic aldehydes in the absence of other metal reagent except dialkylzinc. Recently, we have reported the synthesis of chiral 1,1′-*N,O*-ferrocenyl ligands **1** and their application in the addition of diethylzinc reagents to aldehydes, with up to 90.9% ee of the corresponding alcohols being observed.[8] Further studies have shown that these ligands are also effective in the reaction of phenylacetylene with aldehydes in the presence of diethylzinc. Both aromatic and aliphatic aldehydes are suitable substrates. Herein, we report our results for the enantioselective addition of alkynylzinc to aldehydes without the use of a titanium complex.

2. Results and discussions

Chiral 1,1′-*N,O*-ferrocenyl ligands **1** and **2** were synthesized by known procedures (Scheme 1).[8,9a] To show the effect of the hydroxymethyl substituent of the ferrocene ligand **1** in the reaction, ligands **3** and **4** with dimethylhydroxymethyl and hydroxymethyl as substituents were also synthesized using the same procedures as illustrated in Scheme 2.

All of these ligands were tested in the addition reaction of phenylacetylene with benzaldehyde using 10 mol% of ligands and 220 mol% of diethylzinc (Eq. 1). The results showed that the framework and the substituent on the oxazoline ring of the ligands had a great impact on the outcome of the reaction (Table 1). When the substituent on the oxazoline ring was *tert*-butyl, 1,1′-ferrocenyl oxazoline alcohol **1b** showed higher stereoselectivity than 1,2-ferrocene **2**[9] (entries 1 and 2). The results showed that the hindrance of the hydroxymethyl moiety on the other Cp ring affected the reaction's outcome greatly. With dimethylhydroxymethyl and hydroxymethyl groups as substituents, a dramatic drop in enantioselectivity of the reaction was observed, even



Scheme 1.

Keywords: Ferrocene ligand; Alkynylation; Aldehyde; Organozinc reagent; Asymmetric addition.
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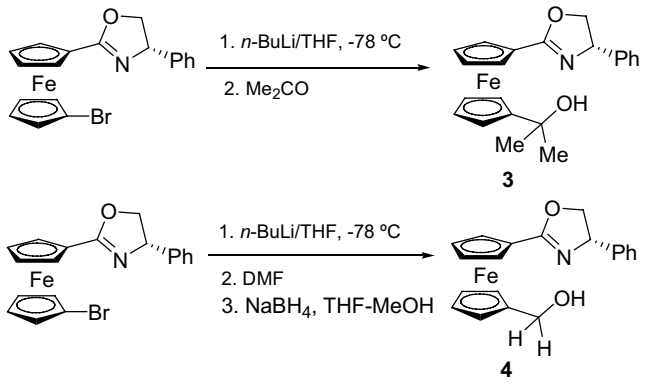
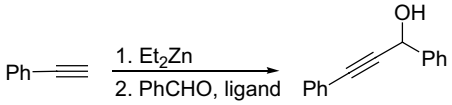


Scheme 2.

when 20 mol% of the ligand was used (entries 9 and 10). In pursuit of a good catalytic system with high enantioselectivity and yield, other 1,1′-ferrocene ligands as well as the effects of solvent and temperature on the reaction were examined. Among the ligands and solvents tested, ligand **1d**, with Ph as the substituent on the oxazoline ring in CH_2Cl_2, gave the best result (Table 1, entry 8 vs entries 2–7). The temperature effect was also significant, with a lower enantioselectivity being given at either lower or higher than 0 °C. However, the yield was higher if the reaction proceeded at higher temperatures (entries 11 and 12).



(1)

Under the optimized condition, other aldehydes were tested with the results shown in Table 2. It can be seen that not only aromatic but also aliphatic aldehydes are suitable substrates. In all cases, ligand **1d** proved to be

Table 1. The effect of reaction conditions on the enantioselectivity of the alkynylation of benzaldehyde[a]

Entry	Ligand	Solvent	Yield (%)[b]	Ee (%)[c]	Configuration[d]
1	(S,R_p)-**2**	Toluene	74	23	(+)-(R)
2	(S)-**1b**	Toluene	82	63	(+)-(R)
3	(S)-**1a**	Toluene	78	70	(+)-(R)
4	(S)-**1c**	Toluene	87	60	(+)-(R)
5	(R)-**1d**	Toluene	84	85	(−)-(S)
6	(R)-**1d**	THF	68	90	(−)-(S)
7	(R)-**1d**	Hexane	88	86	(−)-(S)
8	(R)-**1d**	CH_2Cl_2	90	87	(−)-(S)
9[e]	(S)-**3**	CH_2Cl_2	93	32	(+)-(R)
10[e]	(S)-**4**	CH_2Cl_2	95	40	(+)-(R)
11[f]	(R)-**1d**	CH_2Cl_2	85	63	(−)-(S)
12[g]	(R)-**1d**	CH_2Cl_2	99	49	(−)-(S)

[a] All reactions were carried out at 0 °C with the ratio of ligand/phenylacetylene/Et_2Zn/benzaldehyde = 0.1:2.4:2.2:1.
[b] Isolated yield based on aldehyde.
[c] Determined by HPLC.
[d] Configurations were assigned by comparison with the sign of the specific rotation of known compounds.
[e] 20 mol% of ligand was used.
[f] The reaction was carried out at −20 °C.
[g] The reaction was carried out at rt.

Table 2. Enantioselective alkynylation of aldehydes with ligand **1d**[a]

Entry	Aldehyde	Yield (%)[b]	Ee (%)[c]	Configuration[d]
1	p-BrC_6H_4CHO	86	86	(−)
2	o-ClC_6H_4CHO	72	67	(−)
3[e]	o-ClC_6H_4CHO	82	89	(−)
4	m-$O_2NC_6H_4CHO$	87	82	(−)
5	p-$MeOC_6H_4CHO$	82	90	(−)
6	1-Naphthaldehyde	84	88	(−)
7[e]	1-Naphthaldehyde	86	93	(−)
8[e]	α-Furan-CHO	85	82	(−)
9[e]	c-$C_6H_{11}CHO$	74	81	(−)-(R)
10[e]	$PhCH_2CHO$	72	65	(−)
11[e]	Me_2CHCHO	88	83	(−)
12[e]	Me_3CCHO	88	75	(−)
13	PhCH=CHCHO	88	54	(−)
14[e]	MeCH=CHCHO	82	59	(−)

[a] Run in 2 mL of CH_2Cl_2 at 0 °C with ratio of ligand **1d**/phenylacetylene/Et_2Zn/aldehyde = 0.1:2.4:2.2:1.
[b] Isolated yield based on aldehyde.
[c] Determined by HPLC.
[d] Configurations were assigned by comparison with the sign of specific rotation of known compounds.
[e] 20 mol% ligand was used.

effective and the propargylic alcohols were produced with good chemical yields and enantioselectivity. Usually good enantioselectivity was provided for most of the aromatic aldehydes when 10 mol% of the ligand was used while a significant increase of ee value was observed when 20 mol% of the ligand was used (Table 2, see entry 2 vs entry 3 and entry 6 vs entry 7). When 20 mol% of the ligand was used as a catalyst, aliphatic aldehydes reacted with the alkynylzinc reagent smoothly, with good enantioselectivity (entries 9–12) and 93% ee being obtained in the alkynylation of 1-naphthaldehyde, catalyzed by 20 mol% of **1d** (entry 7).

3. Conclusion

In conclusion, we have demonstrated that 1,1′-ferrocene oxazoline alcohol **1d** is an effective catalyst for the reaction of phenylacetylene with various aromatic and aliphatic aldehydes under mild conditions. Good ees and yields of products were obtained and the use of other kinds of metal species is not required in the reaction.

4. Experimental

4.1. General

All reactions were performed under a dry argon atmosphere. Toluene, hexane, and THF were freshly distilled from sodium. Dichloromethane was freshly distilled from calcium hydride. Reagents were used as received without further purification, except for the aldehydes, which were redistilled before use. Ligands **1a**–**d** were synthesized according to the literature.[8] Ligand **2** was synthesized according to the literature.[9a] Melting points are uncorrected. NMR spectra were recorded on a Varian AMX-300 spectrometer in $CDCl_3$ at room temperature. Chemical shifts are given in parts per million downfield from tetramethylsilane. Optical rotations were measured on a Perkin–Elmer 341MC polarimeter with a thermally jacketed 10 cm cell at 20 °C (concentration *c* given as g/100 mL). IR spectra were recorded in KBr and measured in cm^{-1}, using a Shimadzu IR-440 infrared spectrophotometer. Mass spectra were taken using HP 5989A mass spectrometers. Elemental analyses were performed on a Foss-Heraeus Vario EL instrument. Enantiomeric excesses were determined by chiral HPLC on a Chiralcel OD column.

4.2. 1-[(*S*)-4-Phenyl-2,5-oxazolinyl]-1′-(α-dimethylhydroxymethyl)-ferrocene 3

A solution of 1-[(*S*)-4-Phenyl-2,5-oxazolinyl]-1′-bromoferrocene[10] (328 mg, 0.8 mmol) in THF (10 mL) was cooled to −78 °C and treated with *n*-butyllithium (1.6 M in hexane, 0.5 mL, 0.8 mmol). The reaction mixture was stirred for an additional 30 min, acetone (70 mg, 1.2 mmol) then added and the resulting mixture stirred at 0 °C for 20 min. Water (10 mL) was added to the reaction solution and the mixture extracted with ethyl ether (20 mL × 3) The organic layer was washed with brine (20 mL × 2) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel, ethyl acetate/petroleum 1:5) to afford **3** (177 mg, 57%). Mp, 66–68 °C; $[\alpha]_D^{20} = -117$ (*c* 0.62, $CHCl_3$); ^1H NMR: δ 1.46 (s, 3H), 1.53 (s, 3H), 4.12–4.22 (m, 4H), 4.27–4.29 (m, 1H), 4.42–4.45 (m, 2H), 4.72 (dd, $J = 8.7$, 9.9 Hz, 1H), 4.81–4.83 (m, 1H), 4.92–4.93 (m, 2H), 5.26 (dd, $J = 8.4$, 9.9 Hz, 1H), 7.26–7.38 (m, 5H); ^{13}C NMR: δ 167.3, 142.0, 128.6, 127.5, 126.6, 101.7, 74.6, 70.6, 70.5, 69.9, 69.8, 69.2, 68.9, 68.7, 68.6, 67.5, 67.0, 31.4, 31.1; MS: *m*/*z* 389 (M^+, 1), 390 (71), 388 (6), 372 (100), 283 (20), 193 (99), 163 (34); IR (KBr): 3369, 2970, 2926, 1643, 1605, 1480, 1378, 1120, 1026, 491 cm^{-1}; Anal. Calcd for $C_{22}H_{23}FeNO_2$: C, 67.88; H, 5.96; N, 3.60. Found: C, 67.63; H, 5.93; N, 3.36.

4.3. 1-[(*S*)-4-Phenyl-2,5-oxazolinyl]-1′-(α-hydroxymethyl)-ferrocene 4

A solution of 1-[(*S*)-4-Phenyl-2,5-oxazolinyl]-1′-bromoferrocene[10] (328 mg, 0.8 mmol) in THF (10 mL) was cooled to −78 °C and treated with *n*-butyllithium (1.6 M in hexane, 0.5 mL, 0.8 mmol). The reaction mixture was stirred for an additional 30 min after which DMF (285 mg, 3.9 mmol) was added and the resulting mixture stirred at 0 °C for 20 min. H_2O (10 mL) was added to the reaction solution and the mixture then extracted with ethyl ether (20 mL × 3). The organic layer was washed with brine (20 mL × 2) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel, ethyl acetate/petroleum 1:2) to afford formyl ferrocene. The formyl ferrocene was dissolved in THF (6 mL) and added to a solution of $NaBH_4$ (66 mg, 1.7 mmol) in THF (4 mL) and MeOH (2 mL). The reaction mixture was stirred at rt for 5 h. Water (10 mL) was then added and the resulting mixture extracted with ethyl ether (20 mL × 3). The organic layer was washed with brine (20 mL × 2) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel, ethyl acetate/petroleum 1:3) to afford **4** (191 mg, 66%). Mp, 127–128 °C; $[\alpha]_D^{20} = -160$ (*c* 0.32, $CHCl_3$); ^1H NMR: δ 3.45 (br, 1H), 4.19–4.27 (m, 4H), 4.30–4.31 (m, 1H), 4.35–4.36 (m, 2H), 4.40–4.44 (m, 2H), 4.73–4.79 (m, 2H), 4.87–4.89 (m, 1H), 5.28 (dd, $J = 8.2$, 9.9 Hz, 1H), 7.26–7.40 (m, 5H); ^{13}C NMR: δ 168.1, 141.9, 128.7, 127.6, 126.7, 91.1, 74.7, 70.9, 70.7, 69.7, 69.6, 69.4, 69.1, 68.9, 68.6, 68.2, 60.0; MS: *m*/*z* 361 (M^+, 4), 362 (100), 346 (5), 193 (91), 180 (25), 163 (43); IR (KBr): 3204, 2908, 1638, 1484, 1381, 1237, 1010, 493 cm^{-1}; Anal. Calcd for $C_{20}H_{19}FeNO_2$: C, 66.50; H, 5.30; N, 3.88. Found: C, 66.50; H, 5.15; N, 3.64.

4.4. General procedure for the catalytic asymmetric addition of alkynylzinc to aldehydes

To a solution of phenylacetylene (123 mg, 1.2 mmol) in CH_2Cl_2 (2 mL) was added Et_2Zn (1.1 M in hexane,

1.1 mL, 1.2 mmol) at room temperature. The resulting mixture was stirred for 2 h after which ferrocene **1d** (26 mg, 0.05 mmol) was added and the reaction mixture stirred for an additional 30 min. The reaction system was cooled to 0 °C at which point the aldehyde (0.5 mmol) was added under an argon atmosphere. After complete consumption of the substrate (monitored by TLC), the reaction was quenched with saturated aqueous NH_4Cl. The mixture was then extracted with diethyl ether (10 mL × 3). The organic layer was washed with brine (10 mL × 2), dried over Na_2SO_4, and evaporated under reduced pressure to give an oily residue. Purification of the residue by column chromatography gave the corresponding optically active alcohol. The enantiomeric excess was determined by HPLC analysis using a Chiralcel column. The configuration was assigned by comparison with the sign of the specific rotation of the known compounds.

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