A New Asymmetric Tridentate Carbazole Ligand: Its Preparation and Application to Nozaki–Hiyama Allylation

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Abstract: The manuscript describes our studies on a newly designed tridentate ligand. The new ligand **1** was successfully synthesized, and it was found that the asymmetric catalysis of Nozaki–Hiyama allylation with ligand **1** affords the product with good enantioselectivity in high yield.

Key words: asymmetric catalysis, carbazole, chromium, allylations, Nozaki–Hiyama reaction, tridentate ligand

Cr(II)-mediated C-C bond-forming reactions developed by Nozaki et al.[1] have been known as useful reactions due to their high chemoselectivity and excellent compatibility with various functional groups. Therefore, these reactions have been used frequently in numerous total syntheses of natural products.[2]

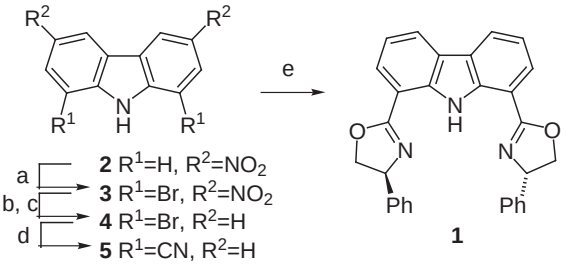
Recently, a catalytic redox system using $CrCl_2$, Mn, and TMSCl was reported by Fürstner et al. which reduces the quantity of chromium salts making these reactions more valuable and environmentally benign.[3]

Asymmetric Cr(II)-mediated C-C bond-forming reactions have been also reported;[4] however, asymmetric catalysis on the reactions was limited to the studies by Cozzi and Umani–Ronchi.[5] They reported the first enantioselective Nozaki–Hiyama allylations using a commercially available salen ligand, but the enantioselectivities and yields were not satisfactory. In addition, the formation of a considerable amount of a side-product, pinacols, was also a problem. In this paper we report the studies on a new chiral ligand effective for the asymmetric catalysis of Nozaki–Hiyama allylation.

We have designed and synthesized a C_2-symmetrical tridentate bis(oxazolinyl)carbazole ligand **1**, because: 1) the allyl-Cr(III)-ligand complex will not undergo significant dissociation due to the stabilization by three bonds, a σ-bond with the carbazole nitrogen and two coordination bonds with the oxazoline nitrogens; 2) ligand **1** leaves a vacant coordination site at which an aldehyde can bind; 3) electronic and/or steric tuning of the catalyst formed with a metal ion and the ligand **1** will be possible when an appropriate substituent is attached on the carbazole ring and/or the oxazole ring.

As shown in Scheme 1, preparation of ligand **1** started from the known compound, 3,6-dinitrocarbazole (**2**).[6] Bromination of **2** in DMF afforded 1,8-dibromide-3,6-dinitrocarbazole (**3**), which was reduced, then diazotized, and *in situ* reduced to afford **4**. Rosenmund–von Braun reaction of **4** gave dinitrile **5**, which was followed by bis-oxazoline formation using (*R*)- or (*S*)-phenylglycinol with $ZnCl_2$ to afford ligand **1**.[7]

With ligand **1** in hand, asymmetric catalysis of Nozaki–Hiyama allylation was investigated. We adopted Fürstner's conditions[3] because metallic Mn was surmised to be a suitable co-reducing reagent for enantioselective allylation due to its low intrinsic reactivity.[3,8]



Scheme 1 Synthesis of Ligand **1**, *Reagents and Conditions:* (a) Br_2 (10.0 equiv), $NaHCO_3$ (5.0 equiv), DMF, r.t., 22 h, quant.; (b) $Na_2S_2O_4$ (10.0 equiv), NaOH (6.0 equiv), EtOH, H_2O, 80 °C, 10 min; (c) $NaNO_2$ (5.0 equiv), 50% H_2PO_3(100 equiv), 0 °C, 20 min, 60% (2 steps); (d) CuCN (3.1 equiv), NMP, reflux, 1 h, 84%; (e) (*S*)-phenylglycinol (2.3 equiv), $ZnCl_2$ (2.8 equiv), C_6H_5Cl, reflux, 3 days, 39%.

First, ligand **1** (10 mol%), $CrCl_2$ (9.7 mol%), and Mn (2.0 equiv) were mixed in THF under an atmosphere of Ar at room temperature. The Cr(II)-ligand **1** complex thus prepared *in situ* was used for the enantioselective allylation. To the reaction mixture was added allylbromide (2.0 equiv), and the mixture was stirred at room temperature for 30 minutes. Then, benzaldehyde (1.0 equiv) and TMSCl (2.0 equiv) were added successively to the reaction mixture at room temperature. After 12 h, isolated crude products were treated with 2 N HCl to afford alcohol **6** in 63% yield (2 steps, 71% ee, 63%, entry 1 in Table 1).

It was surmised that HCl forms in the preparation of the Cr(II)-ligand **1** complex, impeding the catalyst formation. Hence, the effect of the base on the yield and selectivity was next investigated. The yield was increased to 96% when pyridine (py) (entry 2) or triethylamine (TEA)

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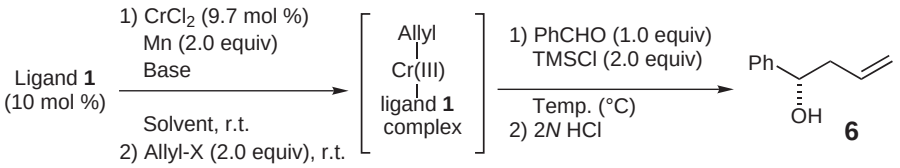
Table 1 Enantioselective Allylation of Benzaldehyde with **1**



Entry	X	Base (equiv)	Solvent	Temp (°C)	Time (h)	Ee (%)[a,b]	Yield (%)[c]
1	Br	-	THF	r.t.	12	*S* (71)	63
2	Br	Py (0.2)	THF	r.t.	12	*S* (69)	96
3	Cl	TEA (0.2)	THF	r.t.	24	*S* (41)	64
4	Br	TEA (0.2)	THF	r.t.	12	*S* (71)	96
5	Br	TEA (0.2)	THF	–10	40	*S* (61)	62
6	Br	TEA (0.2)	Et_2O	r.t.	12	–	0
7	Br	TEA (0.2)	CH_3CN	r.t.	12	*S* (24)	31[d]
8	Br	TEA (0.2)	DMF	r.t.	12	*S* (30)	13[e]
9	I	TEA (0.2)	THF	r.t.	1	*S* (68)	74
10	I	TEA (0.2)	THF	0	9	*S* (22)	95
11	Br	DIPEA (0.2)	THF	r.t.	12	*S* (68)	92
12	Br	$NaHCO_3$ (0.3)	THF	r.t.	12	*S* (73)	74
13	Br	K_2CO_3 (0.1)	THF	r.t.	12	*S* (71)	93
14	Br	NaH (0.1)	THF	r.t.	12	*S* (62)	87
15	Br	*n*-BuLi (0.1)	THF	r.t.	12	*S* (61)	84

[a] Ee determined by HPLC. For HPLC conditions, see General Procedure.[9]
[b] Absolute configuration determined by comparison of optical rotation to known literature value.
[c] Isolated yields.
[d] 1,2-Diphenyl-1,2-ethanediol was also obtained, but not isolated.
[e] 1,2-Diphenyl-1,2-ethanediol (57%) was also obtained.

(entry 4) was used, but the enantioselectivity did not change significantly.

As shown in Table 1, yield and enantioselectivity of the asymmetric catalysis clearly depend on the solvent, and THF was found to be the best one. Actually, the asymmetric catalysis did not proceed in Et_2O (entry 6), and furthermore, the enantioselectivity as well as the yield was considerably diminished in acetonitrile or DMF (entries 7 and 8). The low yield was found to arise chiefly from the formation of side-product, pinacols. Interestingly, no pinacol formation was observed when THF was used as the solvent.

Use of allylbromide was also important to achieve the good enantioselectivity in the reaction with ligand **1**, because as shown in Table 1, use of allylchloride or allyliodide decreased the yield and/or the enantioselectivity (entries 3 and 9). One reason for the low selectivity is found in the formation of racemate by the reaction of the achiral allylmanganese reagent formed in situ.[10]

Surprisingly, when the reaction was carried out using allylbromide at –10 °C (entry 5) or allyliodide at 0 °C (entry 10), the enantioselectivity was diminished. This result is not explained well, but could be surmised that the solubility of the Cr(II)-ligand **1** complex and/or the related allyl complex is reduced at the low temperature,[11] and the selectivity is diminished again by the achiral allylmanganese reagent formed.

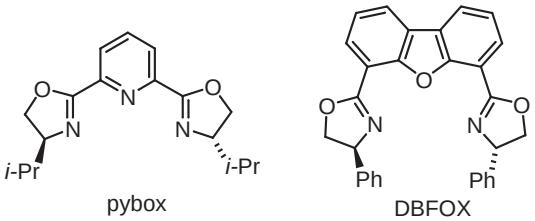


Figure 1 Pybox[12] and DBFOX[13]

Asymmetric catalysis on the allylation with other ligands has also been investigated. However, the enantioselectivity obtained was not satisfactory, that is, 44% ee with pybox[12] and 3.5% ee with DBFOX (Figure 1).[13]

The enantioselectivity of the asymmetric catalysis with ligand **1** is not so high, and indeed lower than the selectivity obtained with the commercially available salen ligand by Umani–Ronchi et al.[5] However, the yield with ligand **1** is high, exceeding the yields obtained with the salen ligand. Hence, modifications of ligand **1** by attaching appropriate substitutents on its carbazole ring or oxazole ring are currently being investigated to achieve high enantioselectivity.

In summary, a newly designed ligand **1** has been synthesized and it was found that the asymmetric catalysis of Nozaki–Hiyama allylation with ligand **1** affords the product in high yield with good enantioselectivity. Studies of the reaction mechanism with ligand **1** and further modifications of the new ligand to improve the enantioselectivity are now under way, and the results will be reported in due course.

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(7) (a) Witte, H.; Seeliger, W. *Liebigs Ann. Chem.* **1974**, 996. (b) Data for **1**: mp 144–145 °C; $[\alpha]_D^{21}$ +757 (*c* 0.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 12.26 (1 H, s), 8.24 (2 H, d, *J* = 7.6 Hz), 7.98 (2 H, d, *J* = 7.6 Hz), 7.37–7.20 (12 H, m), 5.49 (2 H, dd, *J* = 10.0 Hz, 8.8 Hz), 4.86 (2 H, dd, *J* = 10.0 Hz, 8.3 Hz), 4.31 (2 H, dd, *J* = 8.8 Hz, 8.3Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.7, 142.2, 139.0, 128.4, 127.1, 126.5, 125.8, 123.7, 123.4, 118.8, 110.1, 73.7, 69.8; IR (KBr) 3368, 1642, 1618, 1604, 1500, 1428, 1327, 1298, 1286, 1210, 1170, 1138, 1062, 1052, 958, 748, 700 cm^{-1}; FAB-MS $[M + H]^+$ calculated for $C_{30}H_{24}O_2N_3$: 458.1869, found : 458.1837.

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(9) **General Procedure**: A mixture of ligand (*S, S*)-**1** (26.9 mg, 0.059 mmol), $CrCl_2$ (7.0 mg, 0.057 mmol), and Mn (85.3 mg, 1.55 mmol) was azeotroped three times with toluene and dried under high vacuum, and was suspended in THF (2 mL). The color of the suspension immediately turned to brown. To the stirred suspension was added triethylamine (0.016 mL, 0.118 mmol), and after 30 min to the resulting mixture was added allylbromide (0.102 mL, 1.18 mmol). After stirring for 30 min, to the stirred mixture were added benzaldehyde (0.060 mL, 0.59 mmol) and TMSCl (0.149 mL, 1.18 mmol) successively at room temperature. After 12 h the color of the reaction mixture turned to reddish-brown. The reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL), filtered through Celite, and evaporated under vacuum. The crude product was dissolved in THF (5 mL), and the stirred mixture was treated with 2 N HCl (1 mL) for 20 min. The reaction was quenched with adding saturated aqueous $NaHCO_3$ (3 mL), and the aqueous layer was extracted with CH_2Cl_2 (10 ml × 4). The combined organic layer was dried over Mg_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 10:1) to afford the known compound, (*S*)-1-phenyl-3-buten-1-ol (64.7 mg, 71% ee, 96%): ee was determined by HPLC (254 nm); Daicel Chiral Cell OD-H 0.46 cm ϕ × 25 cm; hexane/*iso*-propanol = 19:1; flow rate=0.3 mL/min); retention time: 26.4 min for (*R*)-1-phenyl-3-buten-1-ol, 28.7 min for (*S*)-1-phenyl-3-buten-1-ol.

(10) In the absence of $CrCl_2$ and ligand **1**, the allylated products were obtained in 8% yield under the conditions of entry 1 (Table 1). Aliphatic aldehydes are surmised to be rather inert to the allylmanganase reagent. Cf. ref.[3]

(11) The relationship between the reaction temperature and the solubility of the Cr(II)-ligand **1** complex and/or the related allyl complex was hard to observe under the described reaction condition because insoluble manganese powder was in the flask. Further investigation of the chromium complexes formed in situ is now under investigation.

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