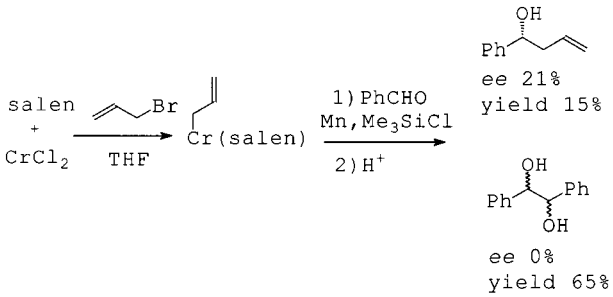
The First Catalytic Enantioselective Nozaki–Hiyama Reaction**

Marco Bandini, Pier Giorgio Cozzi,* Paolo Melchiorre, and Achille Umani-Ronchi*

In recent years, catalytic redox reactions have become more important in organic synthesis since they represent environmentally friendly processes. Titanium,[1a] samarium,[1b] vanadium,[1c] and chromium[1d,2] catalytic redox processes have been recently applied to C–C bond-forming reactions. Among them, the Nozaki–Hiyama reaction[2] performed by Fürstner with catalytic amounts in chromium is of high importance.[3] The crucial points of this catalytic redox cycle are the use of commercial Mn as the stoichiometric reducing agent and Me_3SiCl as the scavenger. Herein we describe the first effective catalytic enantioselective allylation reaction (Nozaki–Hiyama reaction)[4] performed using a catalytic amount (10 mol%) of chiral chromium complex.

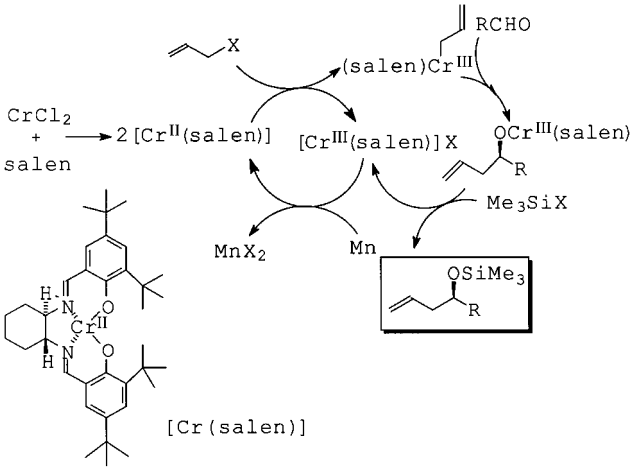
Catalytic asymmetric allylation methodologies have been recognized as important synthetic tools for the stereoselective preparation of homoallylic alcohols and amines.[5] In all the previous reactions described allylstannanes or allylsilanes were used as nucleophiles; however, our enantioselective redox process utilizes allyl halides and the inexpensive and commercially available (*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (salen, **1**) as the chiral ligand (Scheme 1).[6]

In the course of our work, several types of chiral ligands were tested in the reaction of allylchromium complexes with benzaldehyde.[7] However, a promising level of enantioselectivity (21% *ee*) was only obtained by using **1**. The chiral organometallic allyl-Cr(salen) complex was prepared "in situ" by adding anhydrous $CrCl_2$ to a solution of **1** in THF followed by treatment with allyl bromide. Nevertheless, the subsequent addition of Mn, Me_3SiCl, and benzaldehyde at room temperature gave the silylated homoallylic alcohol in low yield (15%); the main product was the pinacol (Scheme 2). We found that this side reaction can be minimized by using CH_3CN as solvent. Optimal reaction conditions require the preparation of the [Cr(salen)] complex in



Scheme 2. Allylation of benzaldehyde mediated by [Cr(salen)] complex, prepared by using $CrCl_2$.

CH_3CN and in the presence of a base (20 mol%, that is 1 equiv base per HCl formed) capable of deprotonating the salen ligand. In fact the *ee* of the homoallylic alcohol significantly increased by adding both inorganic and organic bases such as K_2CO_3, (2,6-di-*tert*-butyl)pyridine, and Et_3N (Table 1).[8]



Scheme 1. A tentative mechanism for the catalytic enantioselective Nozaki–Hiyama reaction.

Table 1. Influence of bases on the enantioselective addition of allyl bromide to PhCHO catalyzed by [Cr(salen)] complex.

Entry	Base[a]	Yield [%][b]	*ee* [%][c]
1	–	56	21
2	K_2CO_3	51	47
3	K_2CO_3[d]	52	25
4	Et_3N	65	65
5	Et_3N[e]	50	50
6	(tBu)$_2$Py	20	58

[a] All the bases were added to a suspension of salen and $CrCl_2$ in CH_3CN. All the reactions, except for that in entry 1, were carried out with 20 mol% of base. [b] Yield of isolated product after desilylation (HCl/THF) and flash chromatography. [c] The *ee* value was evaluated with a cyclodextrin Megadex 5.25 mt chiral column. The absolute configuration of the isolated homoallylic alcohol was assigned by comparison of the GC analysis trace with that of the known product.[5a] [d] The reaction was carried out at 40 °C. [e] 10 equivalents of Et_3N were employed.

The procedure was further improved by avoiding the manipulation of highly air-sensitive $CrCl_2$; instead the reduction of anhydrous $CrCl_3$ with an excess of Mn was employed. The Cr^{II} species was complexed to the salen ligand in the presence of Et_3N (20 mol%) to afford the chiral [Cr(salen)] complex in situ.[9] The resulting chiral catalyst was employed in 10 mol% with allyl halide, Me_3SiCl, and PhCHO (Scheme 3).

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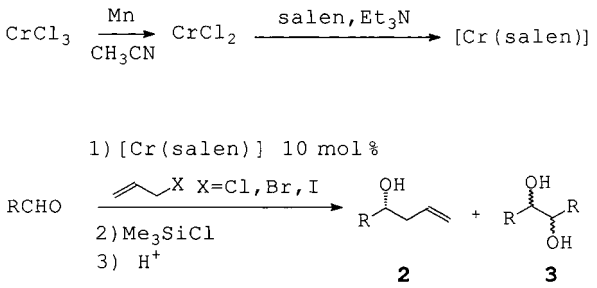
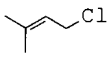


Scheme 3. Enantioselective allylation of aldehydes mediated by [Cr(salen)] complex, prepared by the in situ reduction of $CrCl_3$.

Using the above-mentioned procedure, we screened several allyl halides and the results are summarized in Table 2. Up to 84% *ee* was obtained in the reaction of benzaldehyde with allyl chloride (Table 2, entry 1), while a racemic product was isolated by using the allyl iodide, probably due to its direct reaction with Mn affording an achiral allylating species (Table 2, entry 3). Other substituted allyl halides were successfully employed (entries 4–6). Different silylating agents did not have any significant influence on the asymmetric induction of the process.[10] The optimal conditions (Scheme 3) were employed for a variety of aliphatic and aromatic aldehydes showing the generality of our method (Table 3).

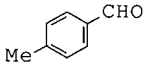
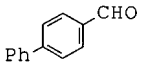
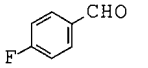
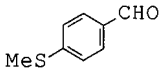
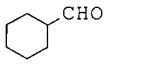
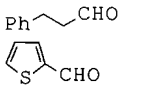
Table 2. Enantioselective addition of various allyl halides to PhCHO catalyzed by [Cr(salen)] complex.

Entry	RX	Yield [%][a]	*ee* [%][b]
1		67	84 (*R*)
2		65	65 (*R*)
3		70	0
4		62	42 (*R*)[c]
5		60	43 (*R*)[c]
6		85	70 (nd)[d]

[a] Yield of isolated product after desilylation (HCl/THF) and flash chromatography. [b] Determined with a cyclodextrin Megadex 5.25 mt chiral column. The absolute configuration of the isolated homoallylic alcohol was assigned by comparison of the GC analysis trace with that of the known product.[5a] [c] Determined with a cyclodextrin Megadex 5.25 mt chiral column on the corresponding O-methyl ether. The absolute configuration was assigned by comparing the optical rotation with that of the known product: $[\alpha]_D = +6.3$ ($c = 0.51$ in C_6H_6); literature value: *R* isomer, $[\alpha]_D = +50.2$ ($c = 1.16$ in C_6H_6).[11a]

The high enantioselectivity (89% *ee*) obtained with the cyclohexanecarbaldehyde is also remarkable (Table 3, entry 5). Higher yields were achieved with aromatic aldehydes substituted in the *para* position with weak electron-releasing groups, while substitution with electron-withdrawing groups gave lower yields with comparable enantioselectivity (Table 3, entry 3). In all cases by-products derived from the pinacol coupling or reduction of the aldehydes were observed. In summary, the reported chromium(salen) allylation represents the first example of an effective enantioselective reaction controlled by the catalytic amount of chromium and the chiral ligand. This reaction allows one to obtain homoallylic alcohols in moderate yields and with good to high enantioselectivity starting from aliphatic and aromatic aldehydes.[12] The synthetic utility of this C–C bond-forming reaction is obvious because the features of the chromium(II) salen complex make the preparation of a large variety of chiral chromium(III) reagents possible.

Table 3. Enantioselective addition of allyl chloride to aldehydes catalyzed by [Cr(salen)] complex.

Entry	R′CHO	Yield of **2** [%][a]	Yield of **3** [%][b]	*ee* of **2** [%][d]
1		67	16	78 (*R*)[e]
2		54	35	82 (*R*)[e]
3		41	40	77 (*R*)[e]
4		46	40	78 (*R*)[e]
5		42[c]	0[h]	89 (*R*)[f]
6		45[c]	13	77 (*S*)[g]
7		40	40	65 (*R*)[e]

[a] Yield of isolated product after desilylation (HCl/THF) and flash chromatography. [b] The products **3** were obtained in racemic form. [c] Refers to the product obtained after desilylation (Bu_4NF/THF) and flash chromatography. [d] Determined with a cyclodextrin Megadex 5.25 mt chiral column. [e] The absolute configuration of the isolated homoallylic alcohol was assigned by analogy to the results obtained with PhCHO. [f] The absolute configuration of 1-cyclohexyl-3-buten-1-ol was determined by comparison of the chiral GC analysis trace with that of the known product.[5a] [g] The absolute configuration was assigned by comparison of the optical rotation with that of the known product $[\alpha]_D = -14.8$ ($c = 0.68$ in $CHCl_3$); literature value: *R* isomer, $[\alpha]_D = +12.2$ ($c = 1.00$ in $CHCl_3$).[11b] The *ee* value was determined by HPLC analysis, column: Chiracel OD, eluent: hexane/isopropyl alcohol (95:5), flow rate: 0.5 mL min^{-1}, retention time: 16.6 min (*R*) and 25.0 min (*S*). [h] In this case 40% yield of (hydroxymethyl)cyclohexane was detected by GC analysis.

Experimental Section

Typical experimental procedure: $CrCl_3$ (8 mg, 0.05 mmol) and Mn (83 mg, 1.5 mmol) were added to anhydrous CH_3CN (2 mL), and the mixture was left to stand for about 5–8 min. Then it was stirred until a green-white precipitate was observed. The ligand **1** (27 mg, 0.05 mmol) was introduced followed by dry triethylamine (14 μL, 0.1 mmol), and the resulting brown solution was stirred at room temperature for 1 h. The solution was treated with allyl chloride (58 μL, 0.75 mmol) and the resulting red solution was stirred for 1 h at room temperature. Finally, PhCHO (51 μL, 0.5 mmol) and Me_3SiCl (95 μL, 0.75 mmol) were added, and the mixture was stirred until consumption of the aldehyde was complete. After quenching with a saturated solution of $NaHCO_3$, the reaction mixture was filtered through celite, and the CH_3CN was evaporated under reduced pressure. The residue was extracted with Et_2O, the organic phases were collected, and the solvent was evaporated under reduced pressure. The resulting oil was dissolved in THF (2 mL) and treated with 1N HCl (0.5 mL). The mixture was stirred to complete desilylation (monitored by TLC). After evaporation of the THF, the residue was extracted with Et_2O. The organic phases were collected, dried over Na_2SO_4, and concentrated in vacuo to give a brown residue, which was purified by flash chromatography (silica gel, cyclohexane/Et_2O

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(4/1), $R_f = 0.3$). The (*R*)-1-phenyl-3-buten-1-ol was isolated as a light yellow oil (50 mg, 67 % yield) in 84 % *ee*.

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[7] Chiral ligands such as bishydrooxazoles, 2,2′-dihydroxy-1,1′-biphenyl (BINOL), $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL), sulfonamides, amino alcohols, and phosphanes afforded the homoallylic alcohol in racemic form.

[8] Bases such as pyridine and *N*-methyl imidazole were screened as well, but in these cases the homoallylic alcohol was isolated in very low yields, probably due to a complexation of the Cr species by the bases.

[9] The use of [Cr(salen)] complex following Jacobsen's protocol in the addition of allyl bromide to benzaldehyde afforded the desired homoallylic alcohol in 52 % yield and 38 % *ee*.

[10] By replacing Me_3SiCl with $ClMe_2Si(CH_2)_3CN$ or $ClMe_2SiCH_2CH_2SiMe_2Cl$ in the allylation of the benzaldehyde we obtained 76 % *ee* and 78 % *ee*, respectively.

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[12] Crystal structures of [Cr^{III}(salen)] complexes and related mechanistic studies were reported by Jacobsen et al. At the present, we are not able to suggest any intermediate for our reaction. However, the observed configuration of the homoallylic alcohol might derive from a mechanism involving cooperative intramolecular dimetallic catalysis: see K. B. Hansen, J. L. Leighton, E. N. Jacobsen, *J. Am. Chem. Soc.* **1996**, *118*, 10924 – 10925; R. G. Konsler, J. Karl, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 10780 – 10781.

N-Confused Calix[4]pyrroles**

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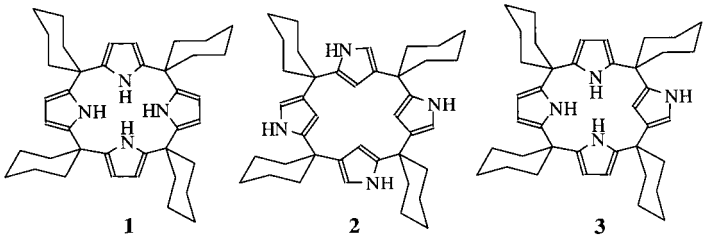
In recent years, calix[4]pyrroles[1] have attracted a lot of attention because of their properties as binders of anions,[2] transition metals,[3] and neutral substrates.[4] However, these compounds have been known for over a century.[5] Their synthesis is straightforward and amounts to a [4+4] cyclocondensation of pyrrole and a ketone, analoguous to the first steps of the Rothemund porphyrin synthesis. In the synthesis of porphyrins, the N-confused isomers (isomers in which one or more of the pyrrole units has the nitrogen atom at the exterior of the macrocycle) can be observed in low yields under certain conditions, as shown recently by a number of authors.[6]

There is one report in the literature[7] where the condensation of cyclohexanone and pyrrole, catalyzed by *p*-toluenesulfonic acid in benzene, was claimed to yield a mixture of the expected calix[4]pyrrole **1** and an isomer which was assigned the structure **2**. Because of the limited solubility of **2**, no NMR spectra were taken, so this assignment should be regarded as



1 **2** **3**

tentative. On the other hand, **1** was the only product claimed when hydrochloric acid was used as the catalyst in ethanol. We decided to reinvestigate this reaction in a systematic manner in order to find out the best conditions to obtain N-confused calix[4]pyrroles, which may be of importance as novel host systems.

Mixtures of equimolar pyrrole and cyclohexanone were heated for 4 h in several solvents at reflux temperature with different acid catalysts. For each reaction the mixture was evaporated to dryness, taken up in chloroform, filtered, and purified by chromatography to yield two different calix[4]pyrroles **1** and **3**. A third, chloroform-insoluble calix[4]pyrrole isomer **4** (see Figure 1) was present in some cases. The results are summarized in Table 1.

In most cases the major product is the expected isomer **1** (up to 80 % yield, m.p. 271 – 272 °C, *m*/*z* 588). The D_4 symmetry is apparent from the ^{1}H NMR spectrum ($CDCl_3$), which is identical with that reported.[8] In all cases a significant amount (6 – 22 %) of an isomer **3**, having much lower

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