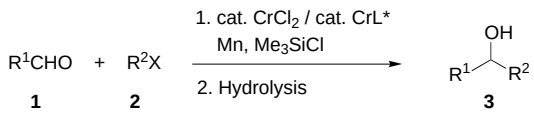

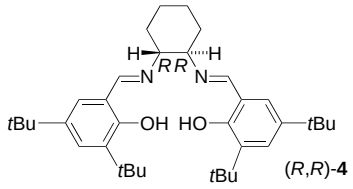

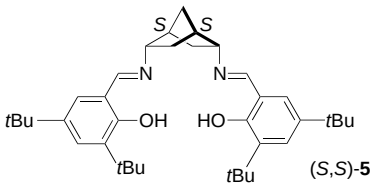

Scheme 1. Ligands for the catalytic asymmetric Nozaki–Hiyama–Kishi reaction; diaminocyclohexane-derived salen **4** and the novel ligand **5**, based on *endo,endo*-2,5-diaminonorbornane (DIANANE).

Highly Enantioselective Catalysts

A Highly Enantioselective Catalyst for the Asymmetric Nozaki–Hiyama–Kishi Reaction of Allylic and Vinylic Halides**

Albrecht Berkessel, Dirk Menche, Christoph A. Sklorz, Michael Schröder, and Ian Paterson*

Dedicated to Professor Emanuel Vogel on the occasion of his 75th birthday

The nucleophilic addition of organochromium reagents to aldehydes (Scheme 1) is a versatile carbon–carbon bond-forming reaction that is compatible with a wide range of functionality in both components.[1] A large number of applications, particularly in the synthesis of structurally diverse natural products, have resulted. The organochromium reagents are easily prepared in situ by the oxidative addition of chromium(II) species to allyl, propargyl, aryl, and vinyl halides or triflates **2** (requiring catalytic amounts of a Ni^{II} salt for sp^2 carbon centers), and efficiently add to aldehydes **1** to give the corresponding alcohols **3** in good yields (Scheme 1).[1] While the original procedure for the Nozaki–Hiyama–Kishi (NHK) reaction relies on the use of stoichiometric quantities of chromium(II) chloride, Fürstner et al. have developed a method requiring only catalytic amounts of the active Cr^{II} species; cheap and toxicologically benign manganese is used as the reducing agent, and a trialkylchlorosilane effects the perpetuation of the catalytic cycle.[2] This important finding triggered numerous efforts to develop a catalytic and enantioselective version of this reaction.[2–5] Nevertheless, only one such example appears to have been reported, namely by the research group of Umani-Ronchi, which uses the salen ligand **4**, derived from *trans*-1,2-diaminocyclohexane (Scheme 1).[5] Whereas the enantioselectivities observed for allyl chorides were high (for example, up to 84% *ee* in the addition to benzaldehyde), the use of the ligand **4** does not yet provide a broadly applicable synthetic method. In particular, the substrate spectrum is still fairly narrow; other halides such as allyl bromide and iodide were found to add with only moderate (52% *ee*) or no selectivity to benzaldehyde. As an asymmetric NHK process for generating enantiomerically enriched allylic alcohols would be extremely valuable, the omission of vinyl halides as substrates for this reaction is significant.[5a–e] We now report our preliminary results using the novel salen ligand (*S,S*)-**5** in NHK reactions, which surpasses the current limitations of **4** by promoting the catalytic addition of allylic and vinylic halides (and triflates) to aromatic and aliphatic aldehydes with synthetically useful levels of asymmetric induction.

Salen ligands used in asymmetric catalysis are mainly based on commercially available chiral 1,2-diamines and various salicylic aldehyde components. Comparatively little attention has been paid to significantly modifying the diamine backbone, for example, by attenuating the separation of the nitrogen atoms. We imagined that this parameter might play a particularly important role in further improving the catalytic properties and, thus, we devised a novel chiral diamine that exhibits a larger nitrogen-atom separation.[6,7] We envisaged *endo,endo*-2,5-diamino-norbornane (**9**, DIANANE, Scheme 2) to be a promising candidate. This novel building block has the advantages of possessing C_2 symmetry and having a rigid hydrocarbon backbone. In our synthesis of **9**, the diketone **6** is converted to a bis(*endo* diamine) by

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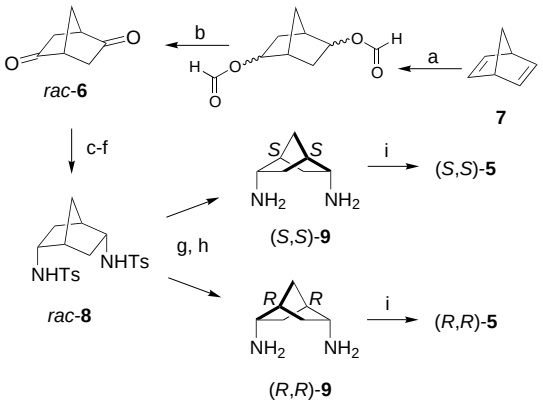
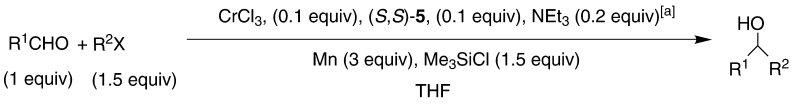


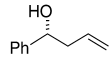
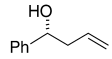
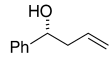
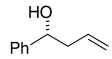
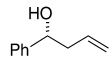
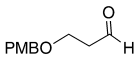
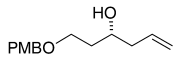
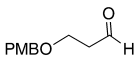
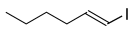
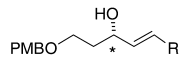
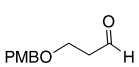
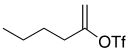
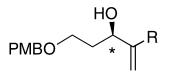
Scheme 2. Enantiodivergent synthesis of (*S,S*)-**5** and (*R,R*)-**5**. a) HCO_2H, reflux, 84%;[9] b) Jones reagent, 44%;[9] c) $NH_2OH{\cdot}HCl$, EtOH, reflux, 1 h; d) $NiCl_2$, $NaBH_4$, MeOH, −35 °C to −20 °C, 1 h, 70–75% (over two steps); e) TsCl, NEt_3, CH_2Cl_2, −78 °C to RT; f) crystallization from MeOH, 35% (over two steps); g) preparative HPLC, Chiralpak AD, 50 cm, 5 cm diameter, flow: 80 mL min^{-1}, eluent: hexane/isopropanol 60:40, retention times: 24–33 min for (*R,R*)-**8** and 46.5–62.5 min for (*S,S*)-**8**; h) Li, NH_3, −33 °C, 80 min, 85%; i) 3,5-di-*tert*-butyl salicylic aldehyde, MeOH, RT, 30 min, 76–81%.

treatment of the corresponding dioxime with $NaBH_4/NiCl_2$ (Scheme 2). Consequently, the pure enantiomers of DIANANE **9** (that is, (*S,S*)-**9** and (*R,R*)-**9**) can be prepared from the enantiomerically pure diketone **6** and *ent*-**6**, respectively. However, instead of relying on the known enantioselective, but multistep approach to **6**/*ent*-**6** from norbornadiene (**7**),[8] we employed the readily available racemic form of the diketone (*rac*-**6**),[9] and resolved the racemic mixture of DIANANE at a later stage. As summarized in Scheme 2, the *N,N′*-bistosylates of DIANANE (**8** and *ent*-**8**) were efficiently separated by preparative HPLC on a chiral stationary phase. Absolute configurations of the crystalline sulfonamides **8** and *ent*-**8** were determined by X-ray crystallography.[10] Reductive *N*-detosylation followed by condensation with 3,5-di-*tert*-butyl salicylic aldehyde afforded the desired salen ligands (*S,S*)-**5** and (*R,R*)-**5**, respectively.

An evaluation of the catalytic performance of the (*S,S*)-**5** and (*R,R*)-**5** ligands was performed. Typical reaction conditions[2,5] comprised 10 mol% of $CrCl_3$, an excess of Mn and Me_3SiCl, and in situ preparation of the Cr^{II} complex, in the presence of NEt_3 and MeCN as solvent (Table 1). The addition of allyl bromide to benzaldehyde proceeded asymmetrically (46% *ee*, room temperature). After optimization of the reaction parameters (solvent, concentration, and temperature), the corresponding homoallylic alcohol was obtained with high enantioselelectivity (90% *ee*) and good yield (72%; Table 1, entry 1). THF proved to be the best solvent among those tested (DMF, DME, CH_3CN), while a catalyst concentration of 0.025 M gave the best results. Optimal enantioselectivity was observed for the allyl bromide/benzaldehyde system at 5 °C (90% *ee*). A variety of different substrates was screened under these conditions. In

Table 1: Catalytic, enantioselective Nozaki–Hiyama–Kishi-type additions in the presence of ligand (*S,S*)-**5**.



Entry	Aldehyde	Halide	Product	*ee* [%]	Yield [%][b]	Reaction temperature[c]
1				90[d,e]	72	5 °C
2				31[d,f]	[g]	RT
3				79[d,e]	76	RT
4				54[e,h]	78	RT
5				64[f,h]	[g]	RT
6				92[e,h]	69[i]	10 °C
7				75[h,j]	59[i]	15 °C
8				61[h,k,l]	54[i]	20 °C

[a] For entries 7 and 8, the reaction was run in the presence of 0.02 equiv of $NiCl_2$. [b] Yield after flash chromatography. [c] Reaction temperature was optimized for entries 1, 2, 5, 6, 7, and 8. [d] Enantiomeric excess was determined by gas chromatography (GC) of the corresponding TMS ethers on a chiral stationary phase (Macherey–Nagel: Lipodex A, 95 °C). [e] Absolute configurations were assigned by comparison of optical rotations with literature data.[5d,11,12] [f] Absolute configuration based on GC/HPLC data (that is, comparison of the products of entries 2 and 1 and of the products of entries 3 and 5 on an analytical scale). [g] Not determined. [h] Enantiomeric excess determined by HPLC on a chiral phase (Daicel: Chiralcel OD-H). [i] Some debenzylation occured as a side reaction. [j] Absolute configuration determined by 1) oxidative cleavage (ozonolysis), 2) reduction to 1,2,4-butanetriol, 3) GC co-injection with a sample of known absolute configuration.[13] [k] Reaction was performed with (*R,R*)-**5**. [l] Assignment of absolute configuration in analogy to entry 7.

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contrast to the salen ligand **4**, ligand **5** was also able to effect, for the first time, an enantioselective addition of allyl iodide (Table 1, entry 2). Allyl chloride added with similar selectivity (84% *ee* using **4**,[5] versus 79% *ee* using DIANANE-based **5**; Table 1, entry 3). Of the three allyl halides tested, the bromide thus afforded the best enantioselectivity. The related β-methylallyl halides (Table 1, entries 4 and 5) reacted just as smoothly as the allyl halides. However, the observed enantioselectivities for these compounds (54% and 64% *ee* for the chloride and bromide, respectively) were not as high as for allyl bromide (90% *ee*). As a model for projected applications in polyketide natural-product synthesis, we tested PMB-protected 3-hydroxypropanal (PMB = *para*-methoxybenzyl), shown in entry 6 of Table 1.[12,14,15] Again, after optimizing the reaction temperature, coupling with allyl bromide occurred with high enantioselectivity (92% *ee*).[16]

The encouraging results achieved with allylic halides prompted us to examine the use of our catalytic NHK process with vinyl iodides and triflates for the enantioselective synthesis of allylic alcohols. As expected, 2 mol% of Ni^{II} (in the form of $NiCl_2$) was required for the coupling reaction to occur efficiently.[2] Under these reaction conditions, the addition of *E*-1-iodohex-1-ene[17] to the PMB-protected 3-hydroxypropanal test system afforded the corresponding *E*-allylic alcohol adduct in an unoptimized 59% yield with 75% *ee* (Table 1, entry 7). Likewise, the vinyl triflate[18] (entry 8, Table 1) added to this same aldehyde to produce the isomeric allylic alcohol with 61% *ee*. Notably, these last two addition reactions represent the first examples of synthetically useful levels of asymmetric induction being realized for catalytic, enantioselective NHK reactions of vinylic halide and triflate substrates.

In summary, we have demonstrated that our DIANANE-based salen ligands, (*S,S*)-**5** and (*R,R*)-**5**, promote efficient and highly enantioselective catalytic Nozaki–Hiyama–Kishi reactions. With this novel ligand modification, the addition of various organochromium intermediates to aromatic and aliphatic aldehydes proceeded under catalytic conditions with good levels of stereoinduction (up to 92% *ee*). Notably, the asymmetric additions of allyl iodide and, in particular, vinyl halides and triflates to aldehydes were achieved with useful levels of enantioselectivity. We are currently exploring the generality and functional-group compatibility of this catalytic carbon–carbon bond-forming process, together with examining its utility with chiral substrates, in the context of projected applications to the stereocontrolled synthesis of more complex structures, such as those that occur in polyketide natural products.

Experimental Section

Typical Procedure: Anhydrous THF (1 mL) was added to $CrCl_3$ (4.0 mg, 25.0 μmol) and Mn (42 mg, 750 μmol) in a dried Schlenk tube under argon, and the mixture was stirred for 1 h at room temperature. After addition of the ligand (*S,S*)-**5** (14.0 mg, 25.0 μmol) and anhydrous NEt_3 (7 μL, 5.0 mg, 50 μmol), the suspension was stirred for another hour at room temperature.[19] Finally, allyl bromide was added (32 μL, 45.4 mg, 375 μmol). After 1 h, the mixture was cooled to 5 °C, PhCHO (25 μL, 26.2 mg, 250 μmol) and Me_3SiCl (48 μL, 41.2 mg, 380 μmol) were added, and the suspension was stirred at that temperature. When the aldehyde was completely consumed (as confirmed by thin-layer chromatography (TLC)), saturated aqueous $NaHCO_3$ was added. After filtration and evaporation, the aqueous phase was extracted with Et_2O. After evaporation of the combined organic phases, the residue was dissolved in THF (1 mL). Aqueous 1M HCl (0.5 mL) was added and the mixture was stirred until desilylation was complete (confirmed by TLC). The solvent was removed, the residue extracted with Et_2O, and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent and flash chromatography (hexane/Et_2O 4:1) gave (*R*)-1-phenyl-3-buten-1-ol as a pale-yellow oil (26.7 mg, 180 μmol, 72% yield, 90% *ee*).

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[19] For entries 7 and 8, 0.02 equiv of $NiCl_2$ were added prior to the halide.

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