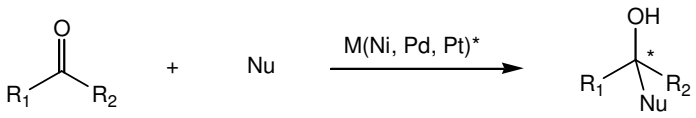
Catalytic asymmetric carbonyl addition reactions catalysed by group 10 metals

The addition of a nucleophilic species to the carbonyl group is one of the most important methodology for carbon-carbon bond construction and various solutions have been offered to achieve an asymmetric version.

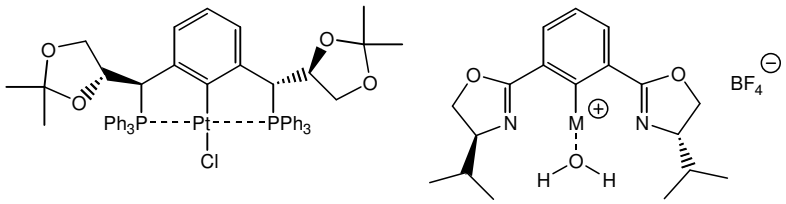


Among those, recourse to group 10 transition elements has received growing attention only in recent years.
This letter briefly highlights the use of chiral Ni-, Pd- and Pt-derived complexes in the transformation portrayed in general terms in the Scheme above.

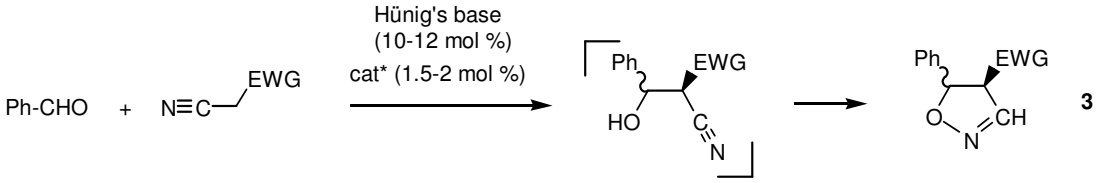
Asymmetric Aldol-type condensation [1-4]

Asymmetric Aldol-type condensation has been realised in the presence of several Pt(II) and Pd(II) complexes with C-2 symmetry.

Thus, the cationic complex prepared in situ by reaction of **1** with AgOTf catalysed the condensation of benzaldehyde with methyl α-isocyanoacetate in CH_2Cl_2 at rt to give a mixture of trans/cis 2-oxazoline **3** (EWG = CO_2Me ; trans/cis : 70/30) in up to 65% ee for the major trans diastereomer. Similarly, cationic aqua complexes **2** catalysed the condensation of benzaldehyde with tosMIC in THF at rt to give the sole trans 2-oxazoline **3** (EWG = Tos) with 57% ee (M = Pd) and 68% ee (M = Pt), respectively .



1 **2** M = Pt, Pd



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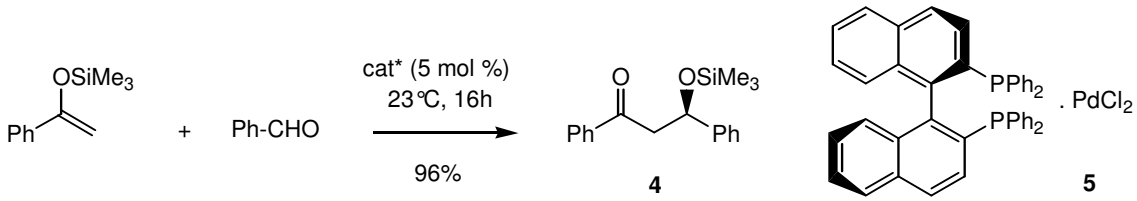
Asymmetric Mukaiyama aldol condensation of acetophenone silyl enol ether with benzaldehyde to give aldol product **4** was achieved in up to 71% ee in the presence of 5 mol% of the cationic complex generated from $PdCl_2$-(*R*)-binap **5** and AgOTf in wet DMF in the presence of 4Å molecular sieves.



4 **5**

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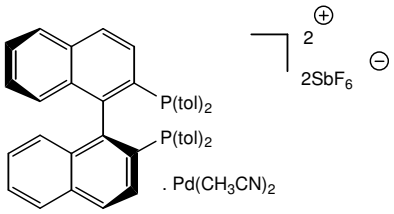
Asymmetric ene-reaction [5-6]

The palladium dicationic complex **6** was shown to catalyse the ene reaction of 1,1-disubstituted and trisubstituted olefins with ethyl glyoxylate to give α-hydroxy-esters (e.g. **8**) in excellent chemical yields and with enantioselectivities ranging from 73 to 88%. The same reaction could also be executed at –50°C in CH_2Cl_2 with equal efficiency (85% ee) in the presence of the complex (2 mol%) prepared in situ by reaction of **7** with AgOTf, and pentafluorophenol as an additive.



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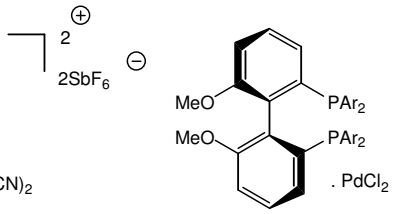
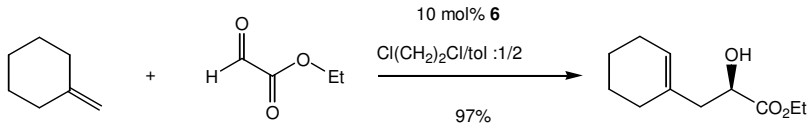


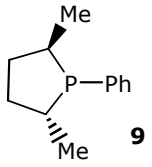
7 Ar = *p-tert*-Bu-Ph



8 88% ee

Asymmetric cyclisation of ω–formyl-1,3-dienes [7]

Nickel-catalysed cyclisation of 1,3-diene and tethered aldehyde groups has been realised in an asymmetric manner by using a catalytic amount of chiral phosphorane **9** in the presence of silanes. For instance, cyclisation of prochiral diene-aldehyde **10** using $Ni(cod)_2$ and ligand **9** in the presence of $(EtO)_3SiH$ in a polar solvent (DMF or CH_3CN) afforded a mixture of cyclisation products **11** (73% ee) and **12** in a ratio of 50 :1. Use of other silanes and non-polar solvents (THF, toluene) gave less satisfying results both in term of chimioselectivity (ratio **11** :**12**) and enantioselectivity.



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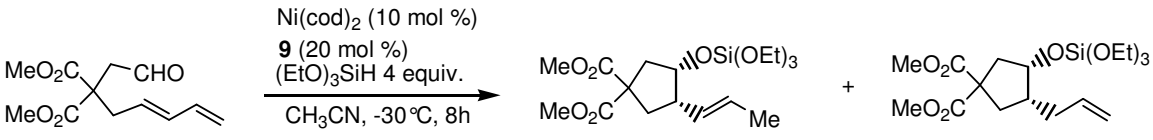
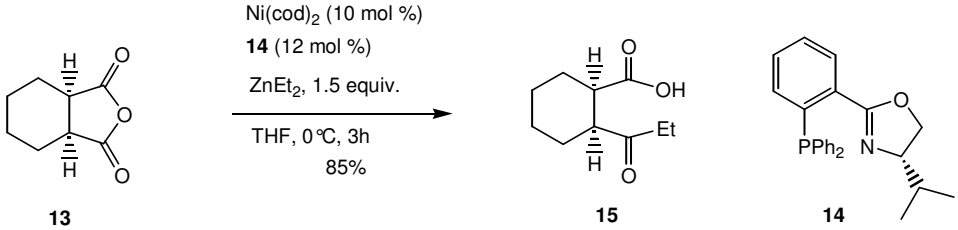


10 **11** **12**

Desymmetrisation of a cyclic anhydride [8]

Desymmetrisation of anhydride **13** conducted in the presence of diethylzinc (1.2-1.5 equiv.), $Ni(cod)_2$ (10 mol %), p-trifluoromethylstyrene (0.2 equiv.) and chiral phosphino-oxazoline ligand **14** (12 mol %) in THF afforded the γ-keto acid **15** in up to 79% ee. Use of CHIRAPHOS as the ligand provided higher ee (88%) but the chemical yield of the transformation did not exceed 10%.



13 **15** **14**

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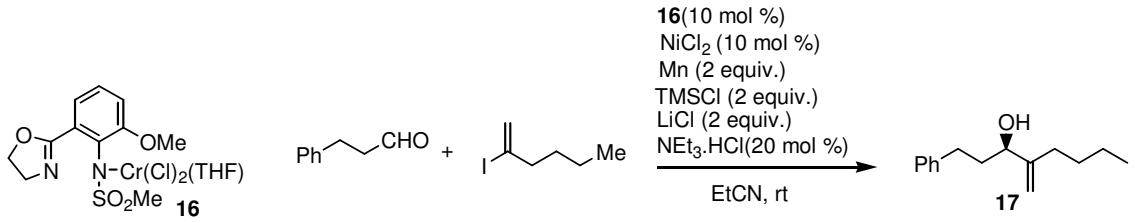
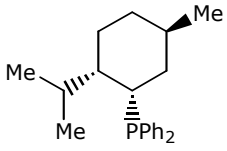
Asymmetric Nozaki-Hiyama-Kishi reaction [9]

The Cr(III) / sulfonamide ligand complex **16**, in the presence of TMSCl and Mn(0), was found to catalyse the Ni/Cr mediated Nozaki-Hiyama-Kishi coupling reaction (e.g. formation of *R*-**17** in c.a. 86 % ee). The same conditions were applied to prepare a fragment of the marine natural product halochondrin B, a new anti-cancer drug candidate.

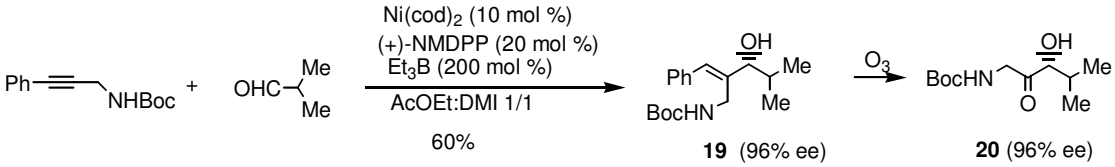


Asymmetric reductive coupling of alkynes and aldehydes [10-12]

Nickel-catalysed intermolecular reductive coupling (exclusive cis-addition) of aryl-C≡C-alkyl alkynes with aldehydes can be accomplished in the presence of a catalytic amount of the commercially available (+)-(neomenthyl)-diphenylphosphine **18** (NMDPP) to give trisubstituted allylic alcohols with excellent regioselectivity and in up to 96% ee. Variation of the alkyne substituents are tolerated and branched aldehydes provide the best results. The tranformation of allylic alcohols to α-hydroxy ketones further enhanced the synthetic utility of the reaction (e.g. **19** →**20**).

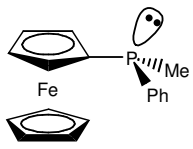


(+)-NMDPP **18**

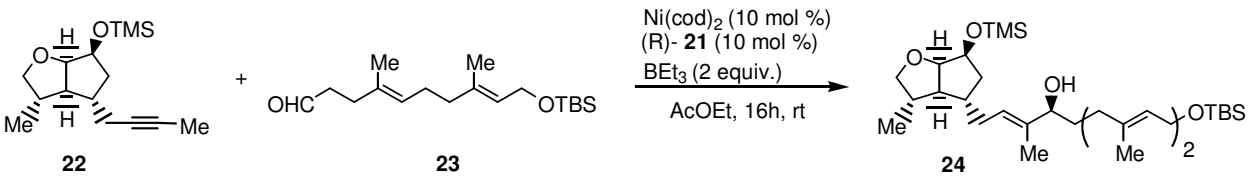


19 (96% ee) **20** (96% ee)

Chiral ligand **18** was less suited to promote the reductive coupling of alkyl-C≡C-alkyl alkynes with aldehydes in good enantioselectivities. In that case, a catalyst incorporating the *P*-ferrocenylphosphine ligand (*R*)-**21** gave encouraging results. As an illustration, nickel-catalysed reaction of alkyne **22** with aldehyde **23** in the presence of ligand (*R*)-**21** afforded mainly adduct **24** (70% combined chemical yield) which was next transformed to (-)-terpestacin, a sesterterpene exhibiting anti-angiogenesis activity.



(*R*)-**21**



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