Catalytic enantioselective ene reactions of imines: a simple approach for the formation of optically active α-amino acids

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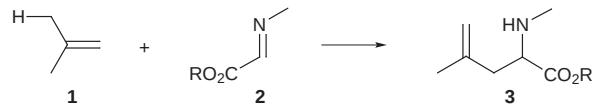
Received (in Cambridge, UK) 15th October 1998, Accepted 21st October 1998

A highly enantioselective ene reaction of readily available tosyl α-imino esters with alkenes catalysed by only 0.1 mol% of chiral $CuPF_6$–BINAP complexes is presented.

The development of asymmetric catalytic reactions has in recent years added a new and very important aspect to chemistry as it allows one to use a small amount of chiral catalysts to form directly optically active compounds.[1]

The ene reaction of alkenes **1** with α-imino esters **2** can give α-amino acids **3** which are among the most fundamental compounds in nature (Scheme 1).



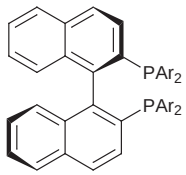
1 **2** **3**

Scheme 1

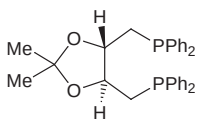
Within the last decade the asymmetric catalytic addition reactions of carbonyl compounds have been developed to a level where they can be performed with a high degree of stereoselectivity.[2–4] Compared with the highly efficient catalytic enantioselective ene reaction of carbonyl compounds, the related ene reaction of imines has only met with very limited success.[5] The catalytic enantioselective ene reaction of imines has, to the best of our knowledge, not yet been achieved regardless of its potential broad application. One of the problems with this reaction compared with the related reaction of carbonyl compounds is that the imine probably competes with the chiral ligand in coordinating to the Lewis acid and therefore suppresses the chiral information from the ligand.

Recently the first catalytic enantioselective hetero-Diels–Alder reaction,[6] addition of enol silanes[7] and alkylation[8] of α-imino esters **2** have been developed and a recent paper[9] dealing with the catalytic ene reaction of **2** with alkenes prompted us to present our results at the present stage of investigations.

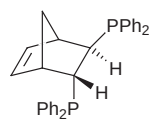
Here we present a highly enantioselective ene reaction of alkenes with tosyl α-imino esters catalysed by chiral $CuPF_6$–BINAP complexes. The strategy behind the catalytic enantioselective ene reaction of α-imino esters is the use of chiral phosphine ligands in combination with copper(I) salts. The chiral phosphine ligands (*R*)-BINAP **4a**, (*R*)-Tol-BINAP **4b**, (*R*,*R*)-DIOP **4c** and (*R*,*R*)-NORPHOS **4d** have been found to be



4a Ar = Ph
4b Ar = Tol



4c



4d

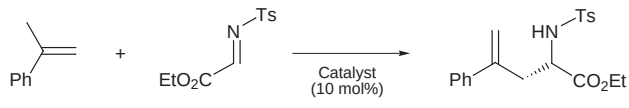
the most promising of the different ligands tested for the ene reaction of α-methylstyrene **1a** with tosyl α-imino ester **2a** in the presence of various Lewis acids. Some representative results are presented in Table 1.

The results for the screening of the various ligands and Lewis acids show that (*R*)-BINAP **4a** and (*R*)-Tol-BINAP **4b** in combination with copper(I) salts catalyse the ene reaction of α-methylstyrene **1a** with tosyl α-imino ester **2a** giving adduct **3a** in good yield and up to 95% ee (Table 1, entries 1–6). The ee of **3a** is counterion-dependent and the highest ees are obtained with PF_6 and ClO_4 as the anions; it is of practical importance that $CuPF_6$ can be used as this Lewis acid is safer, more stable and easier to handle than $CuClO_4$. Changing the catalyst to (*S*)-BINAP–$CuClO_4$ leads to the opposite enantiomer with the same yield and ee. Choosing copper(II) as the Lewis acid in combination with the BINAP ligands leads to a significant reduction in the ee of **3a** (entry 7). The combination of ligand **4b** with other Lewis acids gives only reasonable results in the case of silver(I) (entries 8–12). The application of the chiral ligands (*R*,*R*)-DIOP **4c** and (*R*,*R*)-NORPHOS **4d** leads only to very low yield and ee of **3a** when tested for the ene reaction in combination with $CuPF_6$ as the Lewis acid (entries 13, 14). The results presented in Table 1 are all performed in THF; CH_2Cl_2 can also be used and similarly good results as those presented in entries 1–6 are obtained. The latter solvent has the advantage that the reaction course can easily be monitored by the colour change; the coordination of **2a** to the catalyst complex at the reaction temperature gives a dark purple colour, and when the reaction goes to completion the colour becomes a clear light yellow. We have also tried various chiral bisoxazolines in combination with different Lewis acids but only low to moderate ees were obtained.

The potential and scope of the ene reaction of various alkenes **1a**–**e** with the tosyl α-imino ester **2a** in the presence of (*R*)-Tol-BINAP **4b**–CuX as the catalyst are presented in Table 2.[10]

The results show that both aromatic (**1a**,**b**), cyclic (**1c**,**d**) and simple aliphatic alkenes (**1e**) react with **2a** in the presence of

Table 1 The results for the reaction of α-methylstyrene **1a** with the tosyl α-imino ester **2a** in the presence of the various chiral phosphine ligands **4a**–**d** and Lewis acids (10 mol%) at room temperature in THF

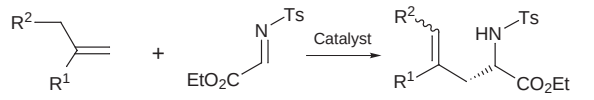


1a **2a** **3a**

Entry	Ligand–metal salt	Yield of **3a**[a] (%)	Ee[b] (%)
1	**4a**–$CuClO_4$	73	93
2	**4b**–$CuClO_4$	75	95
3	**4a**–$CuPF_6$	77	93
4	**4b**–$CuPF_6$	80	95
5	**4a**–CuOTf	58	76
6	**4b**–CuOTf	67	80
7	**4b**–$Cu(OTf)_2$	75	24
8	**4b**–AgOTf	75	73
9	**4b**–$AgClO_4$	72	67
10	**4b**–$AgSbF_6$	63	68
11	**4b**–$Pd(SbF_6)_2$	61	< 5
12	**4b**–$RuArSbF_6$	8	5
13	**4c**–$CuPF_6$	3	< 5
14	**4d**–$CuPF_6$	25	< 5

[a] Isolated yield. [b] Determined by chiral HPLC.

Table 2 The results for the reaction of various alkenes **1a**–**e** with the tosyl α-imino ester **2a** catalysed by (*R*)-Tol-BINAP **4b**–CuX (X = PF_6, ClO_4)[a]



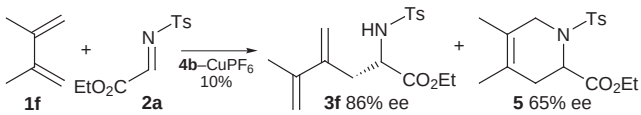
1a R^1 = Ph, R^2 = H
b R^1 = *p*-$MeOC_6H_4$, R^2 = H
c R^1 = R^2 = $(CH_2)_3$
d R^1 = R^2 = $(CH_2)_4$
e R^1 = Me, R^2 = H

2a

3a R^1 = Ph, R^2 = H
b R^1 = *p*-$MeOC_6H_4$, R^2 = H
c R^1 = R^2 = $(CH_2)_3$
d R^1 = R^2 = $(CH_2)_4$
e R^1 = Me, R^2 = H

Entry	Catalyst	1	Load (%)	*T*/°C	*t*/h	Yield[b] (%)	Ee[c] (%)
1[d]	**4b**–$CuClO_4$	**1a**	10	room temp.	18	75	95
2	**4b**–$CuClO_4$	**1a**	10	room temp.	18	85	95
3	**4b**–$CuPF_6$	**1a**	1	−20	38	80	99
4	**4b**–$CuPF_6$	**1a**	0.5	0	22	82	98
5	**4b**–$CuPF_6$	**1a**	0.1	0	24	71	95
6	**4b**–$CuClO_4$	**1b**	1	0	15	81	91
7	**4b**–$CuClO_4$	**1b**	0.1	0	36	80	91
8	**4b**–$CuPF_6$	**1c**	0.5	−20	18	74	92
9	**4b**–$CuPF_6$	**1d**	1	0	60	72	84
10	**4b**–$CuPF_6$	**1e**	2	0	17	49	82
11[e]	**4b**–$CuPF_6$	**1e**	1	0	60	62	78

[a] All reactions were run in CH_2Cl_2 on a 0.4 mmol scale unless otherwise stated. [b] Isolated yield. [c] Determined by chiral HPLC using a Chiralcel OJ or OD column. [d] Solvent THF. [e] The reaction was performed on a 3 mmol scale.



Scheme 2

(*R*)-Tol-BINAP **4b**–CuX (X = PF_6, ClO_4) as the catalyst. For alkene **1a** it appears that the reaction proceeds well using both THF and CH_2Cl_2 as these solvents, giving good yields and high ees of **3a** at room temperature in the presence of 10 mol% of the catalyst (entries 1, 2). Reducing the catalyst loading to 1, 0.5 and even 0.1 mol% causes no significant reduction in the yield of **3a** and even higher enantioselectivities (up to 99%) are obtained (entries 3–5). The *p*-methoxy substituted alkene **1b** reacts in a similar manner with **2a** and an ee of up to 91% is obtained using only 0.1 mol% catalyst loading (entry 7). Methylenecyclopentane **1c** reacts also in a highly enantioselective manner with **2a** with only 0.5 mol% of **4b**–$CuPF_6$ as the catalyst and up to 92% ee is found (entry 8), while methylenecyclohexane **1d** is less reactive and leads to a small reduction in ee compared with **1c** (entry 9). The reaction of isobutylene **1e** with **2a** in the presence of (*R*)-Tol-BINAP **4b**–$CuPF_6$ as the catalyst (entries 10, 11) gives also the corresponding ene product **3e** in reasonable yields and with high ee; the latter reaction can be performed in a gram scale with a catalytic loading of only 1 mol% without affecting the yield and ee. This reaction has been used to assign the absolute stereochemistry of the ene product **3e** as this adduct is easily transformed to the *N*-tosylleucine ethyl ester the stereochemistry of which is found to be *S* by correlation with the same compound prepared from (*S*)-leucine. The absolute stereochemistry of **3e** indicates that the alkene approaches the *si*-face of the tosyl α-imino ester **2a** when coordinated to the catalyst.

2,3-Dimethylbuta-1,3-diene **1f** reacts with the tosyl α-imino ester **2a** in the presence of (*R*)-Tol-BINAP **4b**–$CuPF_6$ (10 mol%) as the catalyst to give both the ene product **3f** and the hetero-Diels–Alder product **5**, with a preference for the latter (**3f**:**5** = 1:9) (Scheme 2). The ee of the ene adduct **3f** was 86% at room temperature, while 65% ee was found for **5**.

We have presented a highly enantioselective ene reaction of alkenes with tosyl α-imino esters catalysed by $CuPF_6$–BINAP complexes. The substrates for this ene reaction are aromatic, cyclic and simple alkenes and the reaction provides a simple method for the preparation of both optically active natural and non-natural α-amino acids; the potential of the ene reaction derives from the fact that it proceeds with only 0.1 mol% of the $CuPF_6$–BINAP catalyst. Work is in progress to develop the reaction further and to understand the mechanism.

Thanks are expressed to the Danish National Science Foundation for financial support.

Notes and references

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10 *Experimental procedure*: A 0.008 M solution of the catalyst was prepared by the addition of $CuPF_6$·4MeCN (15 mg, 0.04 mmol) and (*R*)-Tol-BINAP (30 mg, 0.044 mmol) under N_2 to a flame dried Schlenk tube. The mixture was stirred for 1 h under vacuum, freshly distilled CH_2Cl_2 (5 ml) was added with a syringe under N_2 and the light yellow solution was stirred for 1–3 h until it had become absolute homogeneous. Catalytic reaction (1 mol% catalyst): To a flame dried Schlenk tube was added freshly destilled CH_2Cl_2 (1 ml) and an aliquot of the previously prepared catalyst solution (500 μl) under N_2 and stirred for 5 min; then the tosyl α-imino ester **2a** (0.4 mmol) was added at room temp. The dark purple solution was cooled to the desired reaction temperature before the alkene (0.8 mmol) was added. Then the reaction was kept at that temperature until the dark purple colour had changed into a clear yellow solution (10–65 h). After evaporation of the solvent the crude product was purified by flash chromatography (20% EtOAc–pentane) to give the ene adduct.

Communication 8/08019D

Typeset and printed by Black Bear Press Limited, Cambridge, England