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

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A highly enantioselective ene reaction of readily available tosyl α -imino esters with alkenes catalysed by only 0.1 mol% of chiral CuPF₆-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).



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 silanes⁷ and alkylation⁸ of α imino esters **2** have been developed and a recent paper⁹ 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 CuPF₆– 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(1) 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



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(1) 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 CuClO₄. Changing the catalyst to (S)-BINAP-CuClO₄ 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; CH₂Cl₂ 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

Ph +	EtO ₂ C	Catalyst (10 mol%)	Ph HN Ts CO ₂ Et
1a	2a		3a
Entry	Ligand–metal salt	Yield of $3a^{a}$ (%)	Ee ^{<i>b</i>} (%)
1	4a–CuClO₄	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-RuArSbF6	8	5
13	4c–CuPF ₆	3	< 5
14	4d-CuPF ₆	25	< 5
a Isolated vield	b Determined by c	hiral HPI C	

Table 2 The results for the reaction of various alkenes $1\mathbf{a}-\mathbf{e}$ with the tosyl α -imino ester $2\mathbf{a}$ catalysed by (*R*)-Tol-BINAP $4\mathbf{b}$ -CuX (X = PF₆, ClO₄)^{α}

R	R ¹	+	I EtO₂C	Ts Catalyst		HN T	rs CO₂Et
1a R ¹ b R ¹ c R ¹ d R ¹ e R ¹	= Ph, $R^2 = H$ = p-MeOC ₆ H ₄ , = $R^2 = (CH_2)_3$ = $R^2 = (CH_2)_4$ = Me, $R^2 = H$	R ² =	н 2	a 3a b c d	$R^{1} = Ph$ $R^{1} = p-I$ $R^{1} = R^{2}$ $R^{1} = R^{2}$ $R^{1} = Me$, R ² = H MeOC ₆ H ₂ = (CH ₂) ₃ = (CH ₂) ₄ e, R ² = H	4, R ² = H
Entry	Catalyst	1	Load (%)	<i>T</i> /°C	t/h	Yield ^b (%)	Ee ^c (%)
$\frac{1^d}{2}$	4b -CuClO ₄ 4b -CuClO ₄ 4b -CuPF ₆ 4b -CuPF	1a 1a 1a	10 10 1	room temp. room temp. -20	. 18 . 18 . 38 . 22	75 85 80 82	95 95 99
5 6 7	$4b-CuPF_6$ $4b-CuClO_4$ $4b-CuClO_4$ $4b-CuClO_4$	1a 1b 1b	0.3 0.1 1 0.1 0.5		24 15 36	71 81 80 74	95 91 91 92
8 9 10 11 ^e	$4\mathbf{b} - CuPF_6$ $4\mathbf{b} - CuPF_6$ $4\mathbf{b} - CuPF_6$ $4\mathbf{b} - CuPF_6$	1d 1e 1e	0.3 1 2 1	-20 0 0 0	60 17 60	74 72 49 62	92 84 82 78

^{*a*} All reactions were run in CH₂Cl₂ 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.



(*R*)-Tol-BINAP **4b**–CuX (X = PF_6 , ClO₄) as the catalyst. For alkene **1a** it appears that the reaction proceeds well using both THF and CH₂Cl₂ 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**–CuPF₆ 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-CuPF₆ 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**-CuPF₆ (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 CuPF₆-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 CuPF₆–BINAP catalyst. Work is in progress to develop the reaction further and to understand the mechanism.

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