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Catalytic enantioselective addition of aromatic amines to enones: synthesis of optically active β-amino acid derivatives

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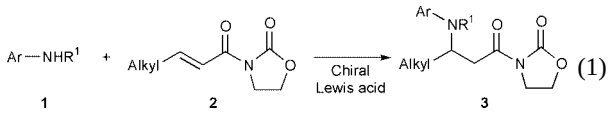
A catalytic enantioselective addition of aromatic amines to enones has been developed; the potential of the reaction is shown for aromatic amines reacting with alkyl oxazolidinones in good yield and with moderate to excellent enantiomeric excess, and the transformation of the products to β-amino acid amides.

Optically active β-amino acids are important molecules[1] which show biological activity in their free from, or as present in many different types of molecules, *e.g.* peptides and depsipeptides.[2a] Furthermore, β-amino acid derivatives can easily be converted into important molecules such as β-lactams.[2b]

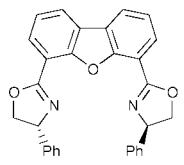
Optically active β-amino acids are traditionally prepared by a diastereoselective approach,[1b,3] while only very few methods are available for the direct formation of these compounds by the addition of nitrogen compounds to α,β-unsaturated carbonyl compounds catalysed by chiral Lewis acids as the catalysts.[4] In these investigations *O*-benzylhydroxylamine, hydrazoic acid or imines were used as the nitrogen source in the presence of different chiral Lewis acids.

In the following we will present the first enantioselective addition of secondary aromatic amines **1** to alkyl oxazolidinones **2** catalyzed by chiral Lewis acids [eqn. (1)].[5] This reaction gives the Michael adduct **3**, which leads to a simple synthetic approach of optically active β-amino acids.

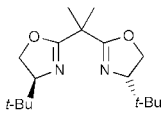


1 2 3 (1)

The reaction of *N*-methylaniline **1a** with 3-[(*E*)-2-butenoyl]-1,3-oxazolidin-2-one **2a** proceeds well in the presence of chiral Lewis acids. The results for the use of DBFOX-Ph[6] (*R*)-**4** and *t*-Bu-BOX[7] (*S*)-**5** as ligands in combination with different Lewis acids are presented in Table 1.



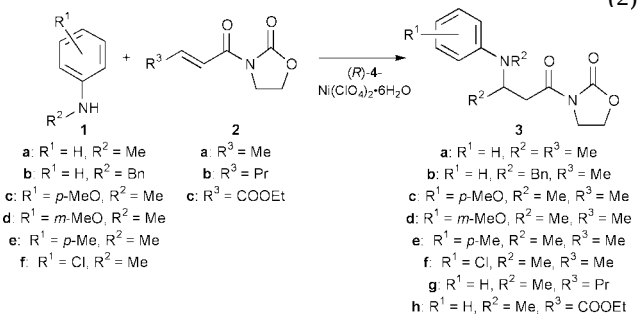
(*R*)-**4**



(*S*)-**5**

The reaction of **1a** with **2a** proceeds with high conversion and **3a** is obtained in up to 90% ee using (*R*)-**4**-Ni$(ClO_4)_2 \cdot 6H_2O$ (5 mol%) as the catalyst (Table 1, entries 1,2).† The solvent effect is notable for the reaction as only 19% conversion is found in THF (entry 3), while much higher conversion is obtained in CH_2Cl_2 (entries 1,2). Other metal salts can also be used in combination with (*R*)-**4** as the chiral ligand with various degree of success (entries 4,5). Surprisingly, the *t*-Bu-BOX (*S*)-**5** ligand in combination with copper salts, which has been found to be an excellent chiral catalyst for reactions of *e.g.* **2**,[7a,c] gave no conversion in the present reaction (entry 6), while the corresponding *t*-Bu-BOX-Zn$(OTf)_2$ catalyst gave moderate conversion and low enantioselectivity (entry 7).

A selection of aromatic amines **1a–f** has been reacted with the oxazolidinones **2a–c** in the presence of (*R*)-**4**-Ni$(ClO_4)_2 \cdot 6H_2O$ (5 mol %) as the catalyst [eqn. (2)] and the results are shown in Table 2.



(2)

The N-substituent is important for the conversion as an exchange of *N*-methyl to *N*-benzyl gives a significant reduction in yield and enantioselectivity (Table 2, entries 1,2). The reaction of *N*-methylanilines, having electron-donating substituents (**1c–e**) with **2a** proceeds in high yield and with up to 89% ee (entries 3–5). It should be noted that applying Ni$(ClO_4)_2 \cdot 6H_2O$ (5 mol%) and varying the equivalents of (*R*)-**4** from 2 to 0.6 relative to the Lewis acid does not alter the yield

Table 1 Screening of chiral ligands, Lewis acids and reaction conditions for the reaction of *N*-methylaniline **1a** with 3-[(*E*)-2-butenoyl]-1,3-oxazolidin-2-one **2a** at room temperature

Entry	Catalyst	Loading (%)	Solvent	Conv.[a] (%)	Ee[b] (%)
1	(*R*)-**4**-Ni$(ClO_4)_2 \cdot 6H_2O$	10	CH_2Cl_2	76	88
2	(*R*)-**4**-Ni$(ClO_4)_2 \cdot 6H_2O$	5	CH_2Cl_2	62	90
3	(*R*)-**4**-Ni$(ClO_4)_2 \cdot 6H_2O$	5	THF	19	84
4	(*R*)-**4**-Mg$(ClO_4)_2 \cdot 6H_2O$	5	CH_2Cl_2	63	39
5	(*R*)-**4**-Zn$(ClO_4)_2 \cdot 6H_2O$	5	CH_2Cl_2	15	64
6	(*S*)-**5**-Cu$(OTf)_2$	10	CH_2Cl_2	—	—
7	(*S*)-**5**-Zn$(OTf)_2$	10	CH_2Cl_2	50	14

[a] Determined by 1H-NMR spectroscopy. [b] Determined by chiral HPLC.

Table 2 Reaction of aromatic amines **1a–f** with the oxazolidonones **2a–c** in the presence of (*R*)-**4**-Ni$(ClO_4)_2 \cdot 6H_2O$ (5 mol%) as the catalyst in CH_2Cl_2 at room temperature

Entry	Amine	Oxazolidinone	Yield[a] %	Ee[b] %
1	**1a**	**2a**	**3a**–62	90
2	**1b**	**2a**	**3b**–6	34
3	**1c**	**2a**	**3c**–75	76
4	**1d**	**2a**	**3d**–73	89
5	**1e**	**2a**	**3**–87	48
6	**1f**	**2a**	**3f**–23	96
7	**1a**	**2b**	**3g**–25	95
8	**1a**	**2c**	**3h**–93	0

[a] Isolated yield after column chromatography. [b] Determined by chiral HPLC.

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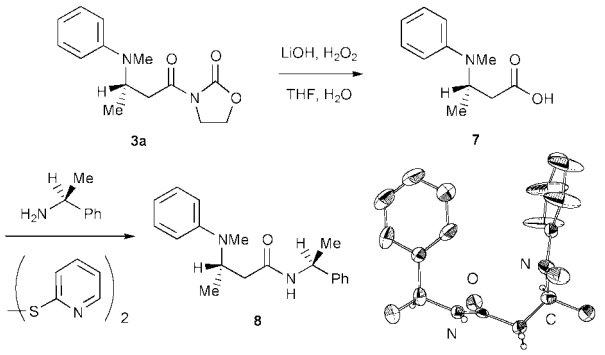

Scheme 1

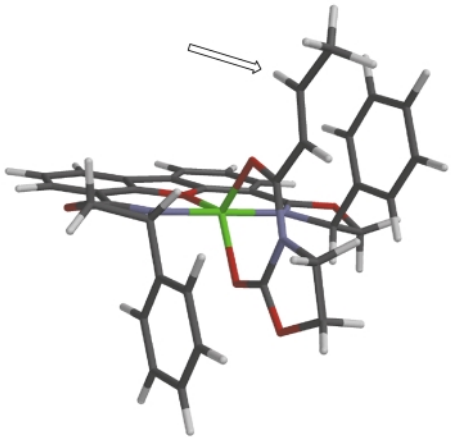

Fig. 1 Proposed intermediate for the catalytic enantioselective addition of secondary aromatic amines to enones catalyzed by (*R*)-DBFOX-Ph-Ni(II).

and enantioselectivity of the reaction of **1c** with **2a**. The reaction of *N*-methyl-*p*-chloroaniline **1f** with **2a** proceeds also with an excellent enantioselectivity, 96% ee of **3f**, however the yield at rt was moderate (entry 6); increasing the reaction temperature to 40 °C improves the yield to 53% and a reduction in enantioselectivity to 60% ee. The reaction of **1a** with **2b** proceeds with an excellent enantioselectivity, 95% ee of **3g** being obtained at rt (entry 7). The yield of **3g** was improved to 52% by performing the reaction in dichloroethane at 60 °C where 69% ee was obtained.

An important aspect of the present chemistry is that the products can be converted easily into various types of β-amino acid ester derivatives. The N-protecting group such as the *p*-methoxyphenyl group can be removed by standard chemistry.[8] In the following we will show that the oxazolidinone in **3** can be removed and exchanged with *e.g.* a chiral amine, which has been used to assign the absolute configuration of the product (Scheme 1). The adduct **3a** was first hydrolyzed with LiOH–H_2O_2 in a THF–H_2O solution giving the carboxylic acid **7**. Condensation with (*S*)-phenylethylamine gave the crystalline diastereomer **8**. The stereochemistry of **8** was assigned by X-ray analysis to be (*S*,*S*) (Scheme 1), *i.e.* the absolute configuration of the stereocenter formed in the addition reaction is (*S*).‡

Based on the absolute configuration of **8** we have proposed the intermediate in Fig. 1. The intermediate has a trigonal bipyrimidal coordination[6] at the metal center with the DBFOX-Ph (*R*)-**4** ligand occupying three sites and the oxazolidinone the remaining two. This intermediate has the β-*Si* face of the alkene shielded by the phenyl substituent of the chiral ligand, while the β-*Re* face is available for approach of the secondary aromatic amine leading to the addition adduct having an absolute configuration consistent with the experimental results.

In summary, a new catalytic enantioselective addition reaction of secondary aromatic amines to enones has been developed. This reaction proceeds in good yields and with moderate to excellent enantioselectivity in the presence of a chiral nickel complex. It was demonstrated that one of the products could be converted into an optically active amide which was used for the assignment of the absolute configuration of the addition adduct. Based on the absolute configuration, a chiral trigonal bipyrimidal nickel complex was proposed as the intermediate.

We are indebted to The Danish National Research Foundation for financial support.

Notes and references

† *Representative experimental procedure*: to a flame dried Schlenk tube was added $Ni(ClO_4)_2 \cdot 6H_2O$ (4.6 mg, 0.0125 mmol) and (*R*)-**4** (6.4 mg, 1.1 eq.). The mixture was dried under vacuum for 1 h and freshly distilled anhydrous CH_2CI_2 (1.0 ml) was added and the solution was stirred for 0.5 h. Subsequently, **2a** (38.8 mg, 0.25 mmol) and **1a** (135 μl, 1.25 mmol) were added and reacted for 40 h. The product **3a** was obtained by FC (50% Et_2O in pentane) as a pale yellow oil in 62% yield with 90% ee detected by HPLC using a Daicel Chiralpak AS column (hexane : *i*-PrOH 95 : 5; t_r(min) = 18.9 min, t_r(major) = 21.6 min.), $[\alpha]^{rt}D = -19.2°$ (c = 14.1 mg ml^{-1} in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 2H; Ar), 6.85 (d, J = 9.2 Hz, 2H; Ar), 6.71 (td, J = 7.2, 0.8 Hz, 1H; Ar), 4.66 (m, 1H; NHC*H*CH_3), 4.24 (m, 2H; $OCOCH_2$), 3.86 (ddd, J = 16.4, 10.8, 7.2 Hz, 1H; NCH_2), 3.70 (ddd, J = 16.0, 10.8, 7.2 Hz, 1H, NCH_2), 3.27 (dd, J = 15.2, 8.4 Hz, 1H; $CHCH_2$), 3.08 (dd, J = 15.2, 6.0 Hz, 1H; $CHCH_2$), 2.76 (s, 3H; $CHCH_3$), 1.25 (d, J = 6.8 Hz, 3H; $CHCH_3$); ^{13}C NMR δ 171.8, 153.8, 150.4, 129.3, 117.5, 114.3, 62.3, 51.9, 42.7, 39.7, 30.6, 18.2; HRMS [M$^+$] Calcd $C_{14}H_{18}N_2O_3$, 262.1317; found 262.1315.

‡ *Crystallographic data* for **8**: $C_{19}H_{24}N_2O$; MW: 296.42; hexagonal, space group *P*65, a = 10.329(1), b = 10.329(1), c = 28.108(4) Å, V = 2597(1) Å^3, Z = 6. 5067 independent reflections measured at 120 K on a Siemens SMART CCD diffractometer. Mo-Kα. 1824 reflections with $I > 3\sigma(I)$ and 199 variables yields R = 0.049, R_w = 0.052. CCDC 1626611. See http://www.rsc.org/suppdata/cc/b1/b103334b/ for crystallographic data in .cif or other format.

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