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Highly Enantioselective Conjugate Addition of Thiols Using Mild Scandium Triflate Catalysis

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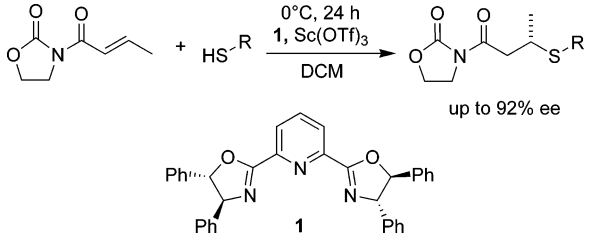


A Sc complex of (4*S*,5*S*)-diphenyl PYBOX **1** was found to serve as a catalyst for the asymmetric conjugate addition reactions between various thiols and 3-crotonoyl-2-oxazolidinone, affording the corresponding adducts in good yields and high enantioselectivies (up to 92% ee). A new improved method for making (4*S*,5*S*)-diphenyl PYBOX is presented.

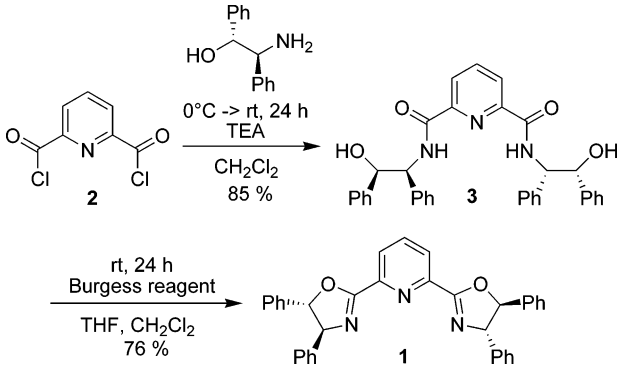
The Michael addition is widely recognized as one of the most important carbon−carbon bond-forming reactions in organic synthesis.[1] Several reagent systems for this type of transformation have been developed that rely on chiral catalysts. However, the asymmetric conjugate addition of thiols to acyclic α,*β*-unsaturated carbonyl systems has proved to be very challenging.

For thiols, different types of catalysts have been utilized, such as cinchona alkaloids,[2] chiral proline derivatives,[3] salens,[4] *N*-oxides,[5] a chiral amino ether−lithium thiolate complex,[6] and lanthanoid tris(binaphthoxide).[7] The most effective chiral catalyst so far has been the nickel(II) aqua complex of 4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) (DBFOX/Ph),[8] which gives enantioselectivities up to 97% ee with additions of arylthiols to 3-crotonoyl-2-oxazolidinone. Unfortunately, the catalyst easily degrades under the reaction conditions, as is also reported in the literature, so an improved catalyst system is in demand.

Previous studies in our group have shown that the 2,6-bis-(4′-phenyloxazolin-2′-yl)pyridine (Ph−PYBOX) ligand can be used in the asymmetric conjugate addition of thiols, for which asymmetric inductions of up to 67% ee were obtained.[9] Desimoni et al. have used (4*S*,5*S*)-diphenyl PYBOX for Mukaiyama−Michael[10] and exo-Diels−Alder[11] reactions with good results. We decided to investigate the activity in the thio-Michael addition.

The (4*S*,5*S*)-diphenyl PYBOX was initially prepared by the method of Desimoni et al.,[10] but the yields in our attempts were low. An improved cyclization with the Burgess reagent is presented in Scheme 1. Ligand **1** was applied in the thiol conjugate addition with $Sc(OTf)_3$.

SCHEME 1. Preparation of (4S,5S)-Diphenyl PYBOX



First, the effects of temperature, solvent, and catalyst amount were studied. Reactions were stirred for 24 h. The results obtained are shown in Table 1. Enantioselectivity was improved 7% when going from room temperature to 0 °C (Table 1, entries 3 and 5). There was no change in enantioselectivity when going from 0 to −12 °C (Table 1, entries 5 and 6). Apparently, the solubility of the catalyst becomes an issue. Among the tested solvents, the best enantioselectivities were obtained with dichloromethane. Enantioselectivity and yield were improved when 10 mol % of catalyst was used instead of 5 mol % (Table 1, entries 2 and 3). The unselective background reaction was also monitored. At room temperature, the effect of the background reaction was significant (Table 1, entry 11). When cooled to 0 °C, less than 2% conversion was observed (Table 1, entry 10).

Having optimized the reaction conditions, we tested the ligand with a variety of thiols and 3-crotonoyl-2-oxazolidinone.[12] The chiral complex was prepared by reacting $Sc(OTf)_3$ (10 mol %) and (4*S*,5*S*)-diphenyl PYBOX **1** (10 mol %) in dichloromethane. 3-Crotonoyl-2-oxazolidinone **4** (100 mol %) was added at the same time. After 1 h of stirring at room temperature, the solution was cooled to 0 °C. Thiols (150 mol %) were added. After 20 h of stirring at 0 °C, the conjugate addition products **5a**−**f** were

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(12) Other substrates were also tested but with poor results. 3-Cinnamoyloxazolidin-2-one and (*E*)-3-hept-2-enoyloxazolidin-2-one with various thiols yielded only traces or no product.

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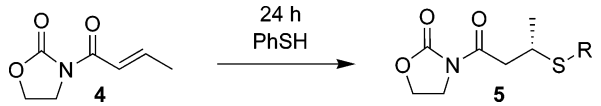
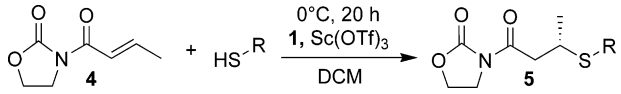
TABLE 1. Evaluation of Effects of Catalyst Amount, Solvent, and Temperature



entry	cat. mol %	solvent	temp	yield %	% ee
1	10	THF	rt	75	66
2	5	CH_2Cl_2	rt	77	81
3	10	CH_2Cl_2	rt	97	85
4	10	CH_2Cl_2	rt	83	70[a]
5	10	CH_2Cl_2	0	95	92
6	10	CH_2Cl_2	−12	93	92
7	10	$CHCl_3$	0	88	89
8	10	MTBE/CH_2Cl_2	0	95	89
9	10	MeCN	0	82	70
10	0	CH_2Cl_2	0	2[b]	0
11	0	CH_2Cl_2	rt	17[b]	0

[a] Proton sponge (10 mol %) was used. [b] Conversion calculated by integrating the ^{1}H NMR spectrum.

TABLE 2. (4*S*,5*S*)-Diphenyl PYBOX (1)-Catalyzed Conjugate Addition



entry	thiol	yield %	% ee[a]
1	thiophenol	95	92
2	thiophene thiol	91	85
3	*p*-toluenethiol	96	86
4	*p*-chlorothiophenol	92	86
5	1-butanethiol	23[b]	68
6	mercaptoethanol	81[b]	91

[a] Absolute stereochemistries were established for entries 1 and 3 (ref 8) and 2 (ref 9), others by analogy. [b] No complete conversion.

then obtained by workup with column chromatography. The Sc(III) triflate complex of (4*S*,5*S*)-diphenyl pybox gives products **5a** and **5b** with an absolute configuration (*S*). With aryl thiols, yields and enantiomeric excesses were high. 1-Butanethiol reacted more slowly than its aromatic counterparts. Erosion in enantioselectivity was also witnessed. The results are summarized in Table 2.

In conclusion, we have demonstrated the effectiveness of the Sc complex of (4*S*,5*S*)-diphenyl PYBOX for the enantioselective conjugate addition of thiols to 3-crotonoyl-2-oxazolidinone. Further studies on the scope of PYBOX-derived catalysts in asymmetric Michael addition of thiols are currently underway.

Experimental Section

***N*^{2},*N*^{6}-Bis((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)pyridine-2,6-dicarboxamide (3).** (1*R*,2*S*)-2-Amino-1,2-diphenylethanol (2.1 g, 10.0 mmol, 200 mol %) and triethylamine (3.4 mL, 24.5 mmol, 490 mol %) were dissolved in CH_2Cl_2 (35 mL), and the mixture was cooled to 0 °C. 2,6-Pyridinedicarbonylchloride (1.0 g, 5.0 mmol, 100 mol %) was dissolved in CH_2Cl_2 (15 mL) and added to the reaction mixture via cannula. The cooling bath was removed, and the solution was stirred for 20 h at room temperature. The reaction mixture was filtered, and the solid was washed with water 4 times. The product was collected to yield **3** (2.6 g, 92%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, 2H, J = 8.8 Hz), 8.12−8.04 (m, 3H), 7.42−7.14 (m, 20H), 5.84 (d, 2H, J = 4.8 Hz), 5.25−5.14 (m, 4H).[10]

2,6-Bis((4*S*,5*S*)-4,5-diphenyl-4,5-dihydrooxazol-2-yl)pyridine (1). Amidoalcohol **3** (1.44 g, 2.6 mmol, 100 mol %) was suspended in THF (80 mL) and CH_2Cl_2 (25 mL). Burgess reagent (1.8 g, 7.6 mmol, 290 mol %) was added. The solid dissolved in 20 min. The reaction mixture was stirred for 17 h at room temperature, after which time the solvents were evaporated. The crude product was crystallized from ethyl acetate. The product was collected to yield **1** (1.02 g, 76%) as colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, 2H, J = 7.9 Hz), 7.98 (t, 1H, J = 7.9 Hz), 7.33−7.26 (m, 20H), 5.53 (d, 2H, J = 8.4 Hz), 5.33 (d, 2H, J = 8.4 Hz).[10]

General Procedure for the Asymmetric Conjugate Addition: (*S*)-3-(3-(Phenylthio)butanoyl)oxazolidin-2-one (5a). 2,6-Bis((4*S*,5*S*)-4,5-diphenyl-4,5-dihydrooxazol-2-yl)pyridine (16 mg, 0.03 mmol, 10 mol %), $Sc(OTf)_3$ (15 mg, 0.03 mmol, 10 mol %), and crotonoyl-oxazolidinone (47 mg, 0.3 mmol, 100 mol %) were dissolved in CH_2Cl_2 (1.2 mL). The solution was stirred for 1 h at room temperature. The mixture was then cooled to 0 °C, and thiophenol (48 μL, 0.45 mmol, 150 mol %) was added. After stirring for 20 h at 0 °C, the products were isolated by adding the cold reaction mixture directly to a silica gel column and eluting with a CH_2Cl_2/MeOH solvent mixture. The product was collected to yield **5a** (75 mg, 95%) as a colorless oil; R_f = 0.72 in 1:30 MeOH/CH_2Cl_2; HPLC[13] R_t^{major} = 40.6 min, R_t^{minor} = 34.2 min, ee = 92%; $[\alpha]_D^{20}$ = −28 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, 2H, J = 7.0 Hz), 7.32−7.22 (m, 3H), 4.36 (t, 2H, J = 8.0 Hz), 3.94 (t, 2H, J = 8.0 Hz), 3.77 (ddq, 1H, J = 6.8 Hz, 6.8 Hz, 6.8 Hz), 3.26 (dd, 1H, J = 7.0 Hz, 17.0 Hz), 3.13 (dd, 1H, J = 7.0 Hz, 17.0 Hz), 1.36 (d, 3H, J = 6.8 Hz).[9]

(*S*)-3-(3-(Thiophen-2-ylthio)butanoyl)-oxazolidin-2-one (5b). Yield 91% (slightly yellow oil); R_f = 0.78 in 1:30 MeOH/CH_2Cl_2; HPLC[14] R_t^{major} = 59.4 min, R_t^{minor} = 42.2 min, ee = 85%; $[\alpha]_D^{20}$ = −7 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, 1H, J = 1.2 Hz, 5.4 Hz), 7.18 (dd, 1H, J = 1.2 Hz, 3.5 Hz), 7.01 (dd, 1H, J = 3.5 Hz, 5.4 Hz), 4.41 (t, 2H, J = 7.9 Hz), 4.01 (t, 2H, J = 7.9 Hz), 3.53 (ddq, 1H, J = 6.8 Hz, 6.8 Hz, 6.8 Hz), 3.33 (dd, 1H, J = 6.8 Hz, 17.3 Hz), 3.07 (dd, 1H, J = 6.8 Hz, 17.3 Hz), 1.34.(d, 3H, J = 6.8 Hz).[9]

(*S*)-3-(3-(*p*-Tolylthio)butanoyl)-oxazolidin-2-one (5c). Yield 96% (colorless oil); R_f = 0.76 in 1:30 MeOH/CH_2Cl_2; HPLC[13] R_t^{major} = 35.2 min, R_t^{minor} = 29.1 min, ee = 86%; $[\alpha]_D^{20}$ = −22 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, 2H, J = 8.0 Hz), 7.12 (d, 2H, J = 8.0 Hz), 4.37 (t, 2H, J = 8.0 Hz), 3.96 (t, 2H, J = 8.0 Hz), 3.69 (ddq, 1H, J = 6.8 Hz, 6.8 Hz, 6.8 Hz), 3.25 (dd, 1H, J = 6.8 Hz, 17.0 Hz), 3.10 (dd, 1H, J = 6.8 Hz, 17.0 Hz), 2.33 (s, 3H), 1.33.(d, 3H, J = 6.8 Hz).[10]

(*S*)-3-(3-(4-Chlorophenylthio)butanoyl)oxazolidin-2-one (5d). Yield 92% (colorless oil); R_f = 0.74 in 1:30 MeOH/CH_2Cl_2; HPLC[13] R_t^{major} = 38.9 min, R_t^{minor} = 35.4 min, ee = 86%; $[\alpha]_D^{20}$ = −21 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}): 3064, 2970, 2927, 2871, 1783, 1702, 1477, 1387. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, 2H, J = 8.5 Hz), 7.28 (d, 2H, J = 8.5 Hz), 4.39 (t, 2H, J = 8.1 Hz), 3.97 (t, 2H, J = 8.1 Hz), 3.73 (ddq, 1H, J = 6.8 Hz, 6.8 Hz, 6.8 Hz), 3.26 (dd, 1H, J = 6.8 Hz, 17.1 Hz), 3.11 (dd, 1H, J = 6.8 Hz, 17.1 Hz), 1.35.(d, 3H, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 153.3, 134.2, 133.6, 132.5, 129.0, 62.1, 42.4, 42.2, 39.2, 21.2. HRMS (ESI) calcd for $C_{13}H_{14}NO_3NaSCl$ $[M + Na]^+$ 322.0269, found 322.0281.

(*S*)-3-(3-(Butylthio)butanoyl)-oxazolidin-2-one (5e). Yield 66% (colorless foam); R_f = 0.63 in 1:30 MeOH/CH_2Cl_2; HPLC[13] R_t^{major} = 24.9 min, R_t^{minor} = 22.6 min, ee = 68%; $[\alpha]_D^{20}$ = −1 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}): 3062, 2962, 2929, 2874, 1782, 1702, 1386. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, 2H, J = 8.1 Hz), 4.34 (t, 2H, J = 8.1 Hz), 3.97 (t, 2H, J = 8.1 Hz), 3.25 (m, 1H), 2.97 (m, 1H), 2.51 (t, 2H, J = 7.3 Hz), 1.5 (tt, 2H, J = 7.3 Hz, 7.3

(13) HPLC analysis was performed on a Daicel OD column eluting with 10% 2-propanol/hexanes.

Hz), 1.34 (tq, 2H, $J = 7.3$ Hz, 7.3 Hz), 1.29 (d, 3H, $J = 6.8$ Hz), 0.84 (t, 3H, $J = 7.3$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 153.4, 62.0, 42.6, 42.5, 35.5, 31.8, 30.22, 22.1, 21.7, 13.7. HRMS (ESI) calcd for $C_{11}H_{19}NO_3NaS$ $[M + Na]^+$ 268.0983, found 268.0986.

(*S*)-(3-(2-Hydroxyethylthio)butanoyl)-oxazolidin-2-one (5f). Yield 81% (colorless oil); $R_f = 0.56$ in 1:30 $MeOH/CH_2Cl_2$; HPLC[13] $R_t^{major} = 32.2$ min, $R_t^{minor} = 26.3$ min, ee = 91%; $[\alpha]_D^{20} = -4$ (*c* 0.3, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}): 3609, 3463, 3056, 2966, 2926, 2874, 1782, 1701, 1387. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44 (t, 1H, $J = 8.1$ Hz), 4.05 (dt, 2H, $J = 2.1$ Hz, 7.9 Hz), 3.77 (m, 2H), 3.34 (dd, 2H, $J = 6.6$ Hz, 14.0 Hz), 3.03 (q, 1H, $J = 8.9$ Hz), 2.79 (dt, 2H, $J = 1.3$ Hz, 6.0 Hz), 1.39 (d, 3H, $J = 6.7$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 153.4, 62.1, 61.1, 42.5, 42.4, 35.3, 33.8, 22.0. HRMS (ESI) calcd for $C_9H_{15}NO_4NaS$ $[M + Na]^+$ 256.0619, found 256.0608.

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Supporting Information Available: Characterization for compounds **1** and **5a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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