Highly Enantioselective Conjugate Addition of Thiols Using Mild Scandium Triflate Catalysis

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The Michael addition is widely recognized as one of the most important carbon–carbon bond-forming reactions in organic synthesis. 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, chiral proline derivatives, salens, N-oxides, a chiral amino ether–lithium thiolate complex, and lanthanoid tris(binaphthoxide). The most effective chiral catalyst so far has been the nickel(II) aqua complex of 4,6-dibenzo-furandiyld-2,2′-bis(4-phenyloxazoline) (DBFOX/Ph), 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.

Using optimized reaction conditions, we tested the ligand with a variety of thiols and 3-crotonoyl-2-oxazolidinone. The chiral complex was prepared by reacting Sc(OTf)₃ (10 mol %) and (4S,5S)-diphenyl PYBOX 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 formed.

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. Desimoni et al. have used (4S,5S)-diphenyl PYBOX for Mukaiyama–Michael and exo-Diels–Alder reactions with good results. We decided to investigate the activity in the thio-Michael addition.

The (4S,5S)-diphenyl PYBOX was initially prepared by the method of Desimoni et al., 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 5 and 6). 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. The chiral complex was prepared by reacting Sc(OTf)₃ (10 mol %) and (4S,5S)-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 formed.

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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.
then obtained by workup with column chromatography. The Sc(III) trflate complex of (4S,5S)-diphenyl pybox gives products 5a and 5b with an absolute configuration (S). With aryl thiols, yields and enantioemic 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 (4S,5S)-diphenyl PYBOX for the enantioselective conjugate addition of thiols to 3-crotonyl-2-oxazolidinone. Further studies on the scope of PYBOX-derived catalysts in asymmetric Michael addition of thiols are currently underway.

Experimental Section

2,6-Bis(4S,5S)-4,5-diphenyl-4,5-dihydrooxazol-2-ylpyridine (1). Amidoxaloid 3 (1.44 g, 2.6 mmol, 100 mol %) was suspended in THF (80 mL) and CHCl3 (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. 1H NMR (400 MHz, CDCl3) 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(4S,5S)-4,5-diphenyl-4,5-dihydrooxazol-2-ylpyridine (16 mg, 0.03 mmol, 10 mol %), Sc(OTf3) (15 mg, 0.03 mmol, 10 mol %), and crotonoylo-oxazolidine (47 mg, 0.3 mmol, 100 mol %) were dissolved in CHCl3 (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 CH2Cl2/MeOH solvent mixture. The product was collected to yield 5a (75 mg, 95%) as a colorless oil; Rf = 0.72 in 1.33 MeOH/CH2Cl2; HPLC13 Rtaur = 40.6 min, Rtaur = 34.2 min, ee = 92%; [α]D20 = −28 (c 1.0, CHCl3); 1H NMR (400 MHz, CDCl3) 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).

(S)-3-(3-(Thiophen-2-ylthio)butanoyl)oxazolidin-2-one (5b). Yield 91% (slightly yellow oil); Rf = 0.78 in 1.33 MeOH/CH2Cl2; HPLC Rtaur = 59.4 min, Rtaur = 42.2 min, ee = 85%; [α]D20 = −7 (c 0.3, CHCl3); 1H NMR (400 MHz, CDCl3) 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).

(S)-3-(3-(p-Tolylthio)butanoyl)oxazolidin-2-one (5c). Yield 96% (colorless oil); Rf = 0.76 in 1.33 MeOH/CH2Cl2; HPLC Rtaur = 35.2 min, Rtaur = 29.1 min, ee = 86%; [α]D20 = −22 (c 1.0, CHCl3); 1H NMR (400 MHz, CDCl3) 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); Rf = 0.74 in 1.33 MeOH/CH2Cl2; HPLC Rtaur = 38.9 min, Rtaur = 35.4 min, ee = 86%; [α]D20 = −21 (c 1.0, CHCl3); IR (CHCl3, cm−1): 3064, 2970, 2927, 2871, 1783, 1702, 1477, 1387; 1H NMR (400 MHz, CDCl3) 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, CDCl3) 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 C16H14NO2NaSCl [M + Na]+ 322.0269, found 322.0281.

(S)-3-(3-(Butylthio)butanoyl)oxazolidin-2-one (5e). Yield 66% (colorless foam); Rf = 0.63 in 1.33 MeOH/CH2Cl2; HPLC Rtaur = 24.9 min, Rtaur = 22.6 min, ee = 68%; [α]D20 = −1 (c 1.0, CHCl3); IR (CHCl3, cm−1): 3062, 2962, 2929, 2874, 1782, 1702, 1386; 1H NMR (400 MHz, CDCl3) 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), 1.55 (t, 2H, J = 7.3 Hz, 7.3 Hz)

10 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). $^1$H NMR (100 MHz, CDCl$_3$) $\delta$ 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$_3$NaS [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$_2$Cl$_2$; HPLC$^{13} R_{\text{major}}^t = 32.2$ min, $R_{\text{minor}}^t = 26.3$ min, ee = 91%; [α]$_D$$^{20}$ = -4 (c 0.3, CH$_2$Cl$_2$); IR (CH$_2$Cl$_2$, cm$^{-1}$): 3609, 3463, 3056, 2966, 2926, 2874, 1782, 1701, 1387. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 171.2, 153.4, 62.1, 61.1, 42.5, 42.4, 35.3, 33.8, 22.0. HRMS (ESI) calcd for C$_9$H$_{15}$NO$_4$NaS [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.