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Enantioselective Michael additions on α,β-unsaturated *N*-acylated oxazolidin-2-ones using mild scandium triflate catalysis

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Abstract—The asymmetric conjugate addition of thiophenol to (*E*)-3-crotonoyloxazolidin-2-one catalysed by the scandium(III) triflate complex of Ph-PYBOX gave the corresponding adduct in 66% ee. Lanthanoid triflates gave lower enantioselectivities (⩽28% ee).

The asymmetric conjugate addition of thiols to acyclic α,β-unsaturated systems remains a challenge. Different catalysts have been employed, such as cinchona alkaloids,[1] chiral proline derivatives,[2] salenes,[3] *N*-oxides,[4] a chiral amino ether–lithium thiolate complex[5] and a lanthanoid tris(binaphthoxide),[6] but a general method is yet to be found. The most interesting catalyst to us was the nickel(II) aqua complex of 4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) (DBFOX/Ph),[7] which gives enantioselectivities up to 97% ee in additions of arylthiols to (*E*)-3-crotonoyloxazolidin-2-one. Unfortunately, the catalyst easily degrades under the reaction conditions, as also reported in the literature, so an improved catalyst system is in demand.

The commercially available ligand 2,6-bis(4′-phenyloxazolin-2′-yl)pyridine (Ph-PYBOX) complexed with scandium(III) triflate has proven effective in many types of reactions,[8] but has not been employed in conjugate additions with thiols, so we decided to investigate it in this work.

We investigated the synthesis[9] of compound (*S*)-**3**[10] (Scheme 1) through an asymmetric conjugate addition of (*E*)-3-crotonoyloxazolidin-2-one (**1**) and thiophene-2-thiol (**2**), an intermediate for the anti-glaucoma drug dorzolamide (**4**).[11] In addition to Sc(III) triflate, we also employed the La(III), Ce(IV) and Yb(III) triflate complexes of (*R*,*R*)-Ph-PYBOX (**5**), as well as the Sc(III) triflate complex of (*R*,*R*)-DBFOX/Ph (**6**). The Sc(III) triflate used was anhydrous, the lanthanoid triflates were hydrates. The results are shown in Table 1.

All reactions proceeded to completion as judged by TLC. Addition of a proton sponge (*N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine) did not improve the enantioselectivity as with the DBFOX/Ph–Ni-complex.[7] DBFOX/Ph produced only racemic **3**, as scandium does not seem to 'fit' inside the centre of DBFOX/Ph (Sc-Ph-PYBOX has N–Sc distances of 2.33 Å, Ni-DBFOX/Ph has N–Ni and O–Ni distances of 2.05 and 2.12 Å).[12] Cerium(IV) triflate did not readily dissolve in the reaction media and thus the formation of the catalyst complex was not complete.

The Ph-PYBOX–triflate complexes were also used in the Michael addition with thiophenol (**7**, Scheme 2 and Table 2).[13] The ligand **9**, designated inda-PYBOX, also successfully applied in enantioselective synthesis,[8a,14] was prepared[15] and tested. Molecular sieves were employed in the reactions to see if the water of crystallisation of the lanthanoid triflates had any effect on the enantioselectivity.

The molecular sieves had no marked effect on the Sc(III)-catalysed reactions, and the enantioselectivies in the reactions catalysed by lanthanoids still remained low. Ce(IV) triflate continued having solubility problems,

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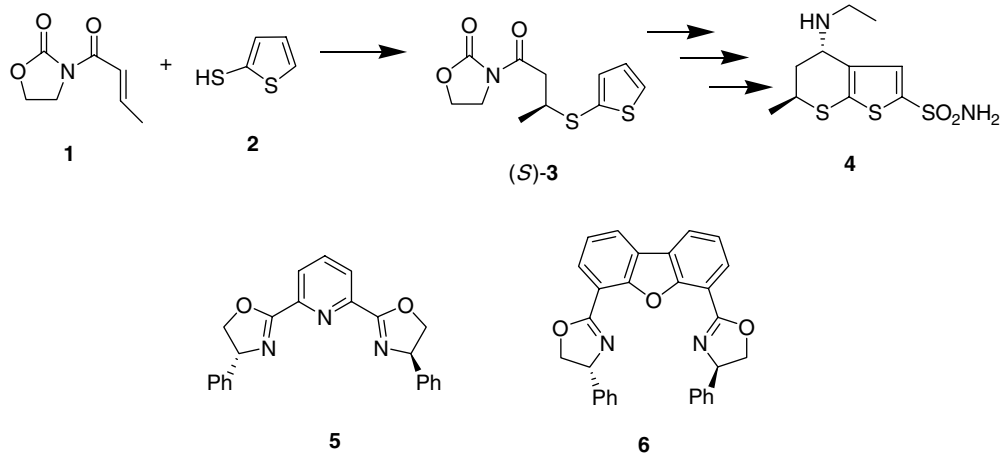
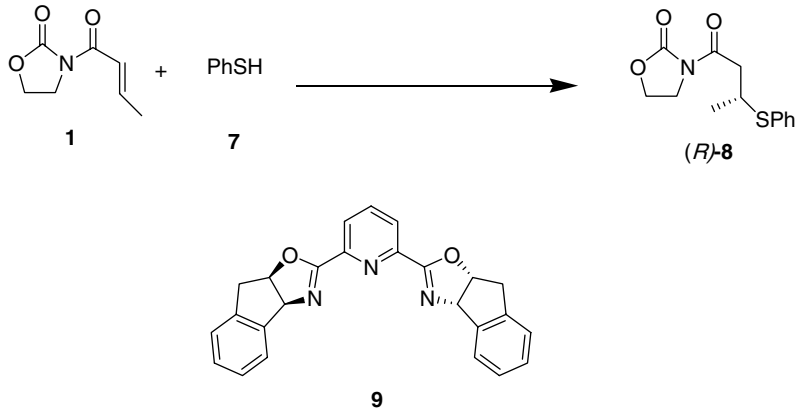


Scheme 1. Synthetic path and the ligands Ph-PYBOX **5** and DBFOX/Ph **6**.

Table 1. Michael addition of thiophene-2-thiol with 5 mol % of catalyst

Ligand	Triflate	%ee	Configuration	Notes
Ph-PYBOX	Sc(III)	59	*R*	
Ph-PYBOX	Sc(III)	45	*R*	Proton sponge (5 mol %)
Ph-PYBOX	Sc(III)	67	*R*	−20 °C
DBFOX/Ph	Sc(III)	0		
Ph-PYBOX	La(III) (hydrate)	13	*R*	
Ph-PYBOX	Ce(IV) (hydrate)	6	*R*	Solubility problems
Ph-PYBOX	Yb(III) (hydrate)	22	*R*	



Scheme 2. Michael addition with thiophenol and inda-PYBOX **9**.

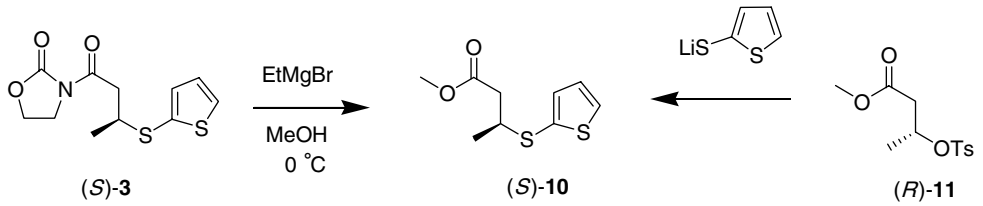
Table 2. Michael addition with thiophenol and 5 mol % of catalyst

Ligand	Triflate	%ee	Configuration	Yield (%)	Notes
Ph-PYBOX	Sc(III)	66	*R*	[a]	
Ph-PYBOX	Sc(III)	62	*R*	86	Molecular sieves
inda-PYBOX	Sc(III)	57	*S*	86	Molecular sieves
Ph-PYBOX	La(III) (hydrate)	29	*R*	99	Molecular sieves
Ph-PYBOX	Ce(IV) (hydrate)	14	*S*	24[b]	Molecular sieves
Ph-PYBOX	Yb(III) (hydrate)	28	*R*	99	Molecular sieves

[a] Yield not measured.
[b] Incomplete conversion.

and gave the opposite enantiomer. Inda-PYBOX proved to be less selective than Ph-PYBOX.

The absolute configuration of **3** was determined by transforming it to the corresponding methyl ester **10**



Scheme 3. Determination of the absolute configuration of (*S*)-**3**.

(Scheme 3) with EtMgBr in methanol at 0 °C. A sample of (*S*)-**10**[16] was prepared from tosylate (*R*)-**11**[17] via the method of Blacklock et al.[11] Comparison of the HPLC data and optical rotation confirmed the absolute configuration of **3**.

The asymmetric Michael addition of thiophene-2-thiol and thiophenol to (*E*)-3-crotonoyloxazolidin-2-one catalysed by metal triflate–Ph-PYBOX complexes produced low to moderate enantioselectivities. Scandium(III) triflate performed markedly better (59–66% ee) compared to La(III), Ce(IV) and Yb(III) triflates (6–29% ee). The enantioselectivity with inda-PYBOX was slightly lower than with Ph-PYBOX, whilst DBFOX/Ph gave only racemic product.

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9. General procedure for the Michael addition: (*E*)-3-crotonoyloxazolidin-2-one (**1**, 0.039 g, 0.25 mmol, 100 mol %), ligand (5 mol %) and triflate (5 mol %) were stirred in dichloromethane (0.5 ml) for 45 min with molecular sieves (if used). Thiophene-2-thiol (120 mol %, ~0.55 M in dichloromethane) or thiophenol (120 mol %) was added, and the mixture stirred overnight. The crude product was evaporated and purified by flash chromatography (30% EtOAc/hexanes).
10. 3-((*S*)-3-(Thiophen-2-ylthio)butanoyl)oxazolidin-2-one (**3**): Yellow oil; $[\alpha]_D^{20}$ −10.3 (*c* 0.590, $CHCl_3$, 75% ee of (*S*) measured with HPLC: Daicel Chiralcel OD, 10% isopropanol/hexanes, 1.0 ml/min, $t(R) = 39.31$ min, $t(S) = 46.50$ min); IR (NaCl window) 1779, 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.40 (dd, 1H, ArH, $J = 5.3$ and 1.3 Hz), 7.17 (dd, 1H, ArH, $J = 3.6$ and 1.2 Hz), 7.01 (dd, 1H, ArH, $J = 5.4$ and 3.6 Hz), 4.40 (t, 2H, O–CH_2, $J = 8.3$ Hz), 4.00 (dd, 2H, N–CH_2, $J = 8.0$ and 2.0 Hz), 3.52 (sext, 1H, CH_2–C*H*Me–S, $J = 6.9$ Hz), 3.32 (dd, 1H, CO–C*H*H–CHMe–S, $J = 17.2$ and 6.8 Hz), 3.07 (dd, 1H, CO–CH*H*–CHMe–S, $J = 17.2$ and 7.1 Hz), 1.34 (d, 3H, CH_3–CH, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 170.8 (C=O), 153.2 (C=O), 136.1 (Ar), 131.2 (S-*C*(=C)–S), 130.6 (Ar), 127.6 (Ar), 62.1 (O-*C*H_2), 42.4 (*C*H_2–N), 42.0 (CO–*C*H_2–CHMe–S), 41.2 (CH_2–*C*HMe–S), 20.9 (CH_3); HRMS calcd for $C_{11}H_{13}NO_3NaS_2$ [M+Na]: 294.0235, found: 294.0225.
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13. (*S*)-3-(3-Phenylthiobutanoyl)oxazolidin-2-one (**8**): Yellow oil; $[\alpha]_D^{20}$ +13.9 (*c* 1.267, $CHCl_3$, 66% ee of (*R*) measured with HPLC: Daicel Chiralcel OD, 10% isopropanol/hexanes, 1.0 ml/min, $t(R) = 33.22$ min, $t(S) = 41.87$ min) (lit.[7] −11.05, *c* 1.23, $CHCl_3$, 52% ee of (*S*)); ^1H NMR (400 MHz, $CDCl_3$) 7.46–7.50 (m, 2H, Ar), 7.25–7.35 (m, 3H, Ar), 4.37–4.42 (m, 2H, O–CH_2), 3.92–4.03 (m, 2H, N–CH_2), 3.75–3.85 (m, 1H, CH_2–C*H*Me–S), 3.29 (dd, 1H, CO–C*H*H–CHMe–S, $J = 6.5$ and 17.0 Hz), 3.16 (dd, 1H, CO–CH*H*–CHMe–S, $J = 7.4$ and 17.0 Hz), 1.38 (d, 3H, CH_3–C–S, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 171.0, 153.3, 134.1, 132.8, 128.9, 127.3, 62.0, 42.4, 42.3, 39.0, 21.3.
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16. Methyl (*S*)-3-(thiophen-2-ylthio)butyrate (**10**): Colourless oil; From **3**: $[\alpha]_D^{20}$ +16.8 (*c* 0.131, $CHCl_3$, 67% ee of (*S*) measured with HPLC: Daicel Chiralcel OD, 0.5% isopropanol/hexanes, 0.5 ml/min, $t(R) = 22.29$ min, $t(S) = 26.37$ min); from **11**:[14] $[\alpha]_D^{20}$ +14.0 (*c* 0.136, $CHCl_3$, 57% ee of (*S*)); IR (NaCl window) 3103, 2952, 1738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.41 (dd, 1H, Ar, $J = 1.2$ and 5.4 Hz), 7.16 (dd, 1H, Ar, $J = 1.2$ and 3.6 Hz), 7.02 (dd, 1H, Ar, $J = 3.6$ and 5.4 Hz), 3.23 (s, 3H, CH_3–O), 3.39 (dquint, 1H, CH_2–C*H*(CH_3)–S, $J = 6.8$ and 8.1 Hz), 2.67 (dd, 1H, ROOC–C*H*H–C, $J = 6.4$ and 15.7 Hz), 2.43 (dd, 1H, ROOC–CH*H*–C, $J = 8.1$ and 15.7 Hz), 1.31 (d, 3H, CH_3–CH–S, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 171.6, 136.2, 130.8, 130.7, 127.6, 51.7, 41.8, 41.4, 20.7.
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