

Chiral *N,N'*-Dioxide Ligands: Synthesis, Coordination Chemistry and Asymmetric Catalysis

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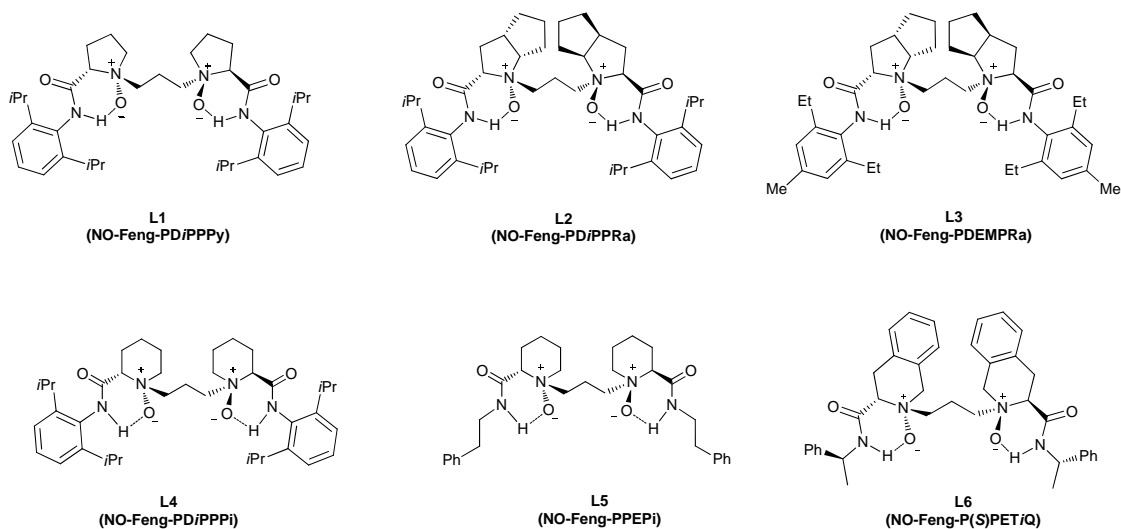
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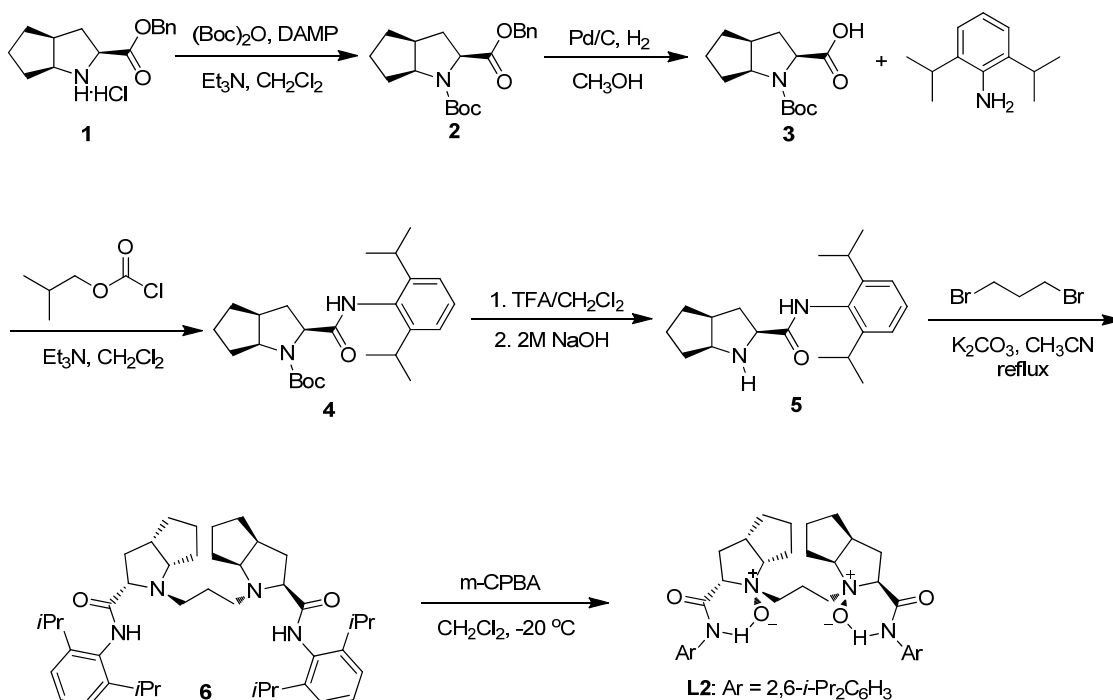
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1. List of the structures of *N,N'*-dioxides mentioned in the text



2. Typical procedure for *N,N'*-dioxide preparation



To a solution of (2*S*,3*aS*,6*aS*)-2-azabicyclo[3,3,0]octane-3-carboxylic acid benzyl ester **1** (4.22 g, 15.0 mmol) in CH₂Cl₂ (25 mL) was added DMAP (1.5 mmol), Et₃N (32.5 mmol) at 0 °C. After stirring for 20 min, (Boc)₂O (16.5 mmol) was added. The reaction was stirred at 30 °C and detected by TLC until the reaction was finished (<12 h). The mixture was then washed with 1 M KHSO₄ solution, saturated NaHCO₃ solution, brine, dried over anhydrous Na₂SO₄, concentrated, and directly used for the next step (100% yield).

To a solution of **2** (15.0 mmol) in CH₃OH (15 mL), 10% Pd/C was added. The mixture was stirred under the H₂ atmosphere (6 Mpa) at 30 °C until the reaction was finished (<6 h). Then, Pd/C was removed by filtration and washed with CH₂Cl₂. The filtrate was concentrated and directly used for the next step (100% yield).

To a solution of (*S*)-*N*-Boc-ramipril acid **3** (3.83 g, 15 mmol) in THF (35 mL) was added Et₃N (18 mmol), isobutyl carbonochloridate (18 mmol) at 0 °C under stirring. After 30 min, 2,6-diisopropylaniline (18.0 mmol) was added. The reaction was stirred at 40 °C and detected by TLC. After 36 h, the mixture was concentrated, added with CH₂Cl₂ (100 mL), washed with 1 N KHSO₄ solution, saturated NaHCO₃ solution, brine, dried over anhydrous Na₂SO₄, concentrated and purified through flash chromatograph (EtOAc:petroleum ether = 1:10) to give the white solid **4** (5.0 g, 80% yield).

TFA (10 mL) was added to the solution of the amide **4** in CH₂Cl₂ (20 mL) and stirred at 30 °C until reaction was finished (1 h). Then, the solvent was evaporated, and CH₂Cl₂ (50 mL) was added. The pH value of the mixture was brought into the range of 10-12 by the addition of 2 M NaOH solution. The aqueous phase was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic phase was washed with brine, dried over anhydrous MgSO₄

and evaporated in vacuo. The residue **5** was directly used for the next step (3.77 g, 100% yield).

K₂CO₃ (4.98 g, 36 mmol) and 1,3-dibromopropane (7.0 mmol) was added to a solution of (*S*)-*N*-(2,6-diisopropylphenyl)-ramipril-2-carboxamide **5** (12.0 mmol) in CH₃CN (15 mL) under stirring. It was refluxed and monitored by TLC (24 h). Then, CH₂Cl₂ (20 mL) was added, the solid was removed by filtration and washed by CH₂Cl₂. The filtrate was concentrated and purified by silica gel column chromatography (EtOAc:petroleum ether = 1:2 to 1:1) to give the desired product **6** (3.13 g, 78% yield).

Finally, **6** was oxidated by *m*-CPBA (11.7 mmol, 2.5 eq.) in CH₂Cl₂ (30 mL) at -20 °C for 1 h and purified through aluminum oxide (alkalinescence) chromatograph (EtOAc : petroleum ether = 1 : 1 to EtOAc) to provide the *N,N'*-dioxide ligand **L2** (2.95 g, 90% yield).

3. X-ray structures of *N,N'*-dioxide-metal complexes

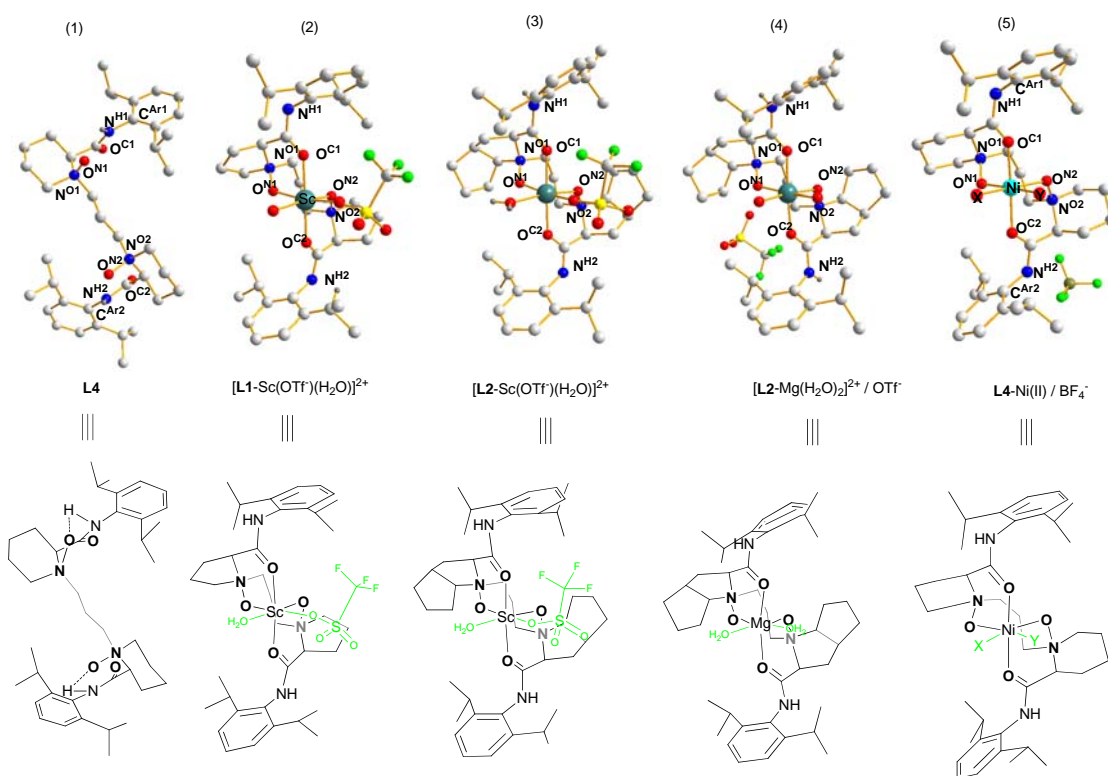


Figure 2. Molecular structures of the ligand **L4** (1), $[\mathbf{L1}\text{-Sc}(\text{OTf})(\text{H}_2\text{O})]^{2+}$ (2), $[\mathbf{L2}\text{-Sc}(\text{OTf})(\text{H}_2\text{O})]^{2+}$ (3), and $[\mathbf{L2}\text{-Mg}(\text{H}_2\text{O})_2]^{2+}$ (4), $\mathbf{L4}\text{-Ni}(\text{II})[\text{tetrahydrofuran-2-yl)methanol}](\text{BF}_4)_2$ (5). (H atoms, the ancillary bidentate ligand and counter-ion are omitted for clarity)

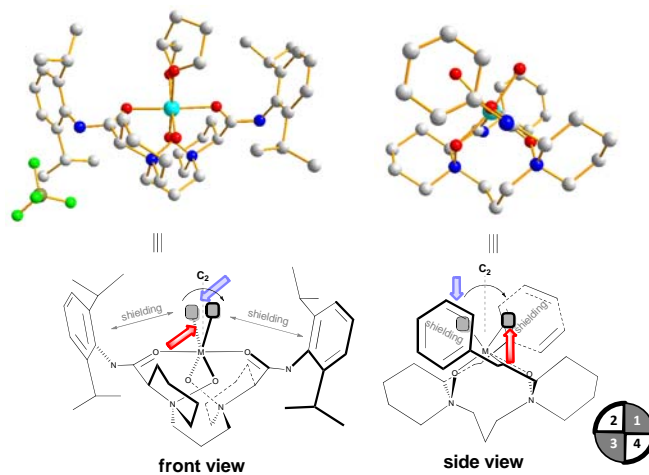
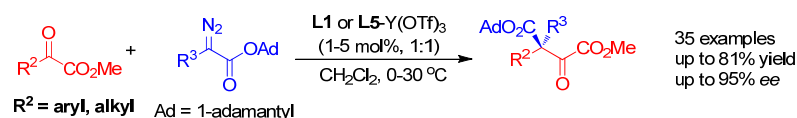


Figure 2. Molecular models of **L4**-metal complex (The isopropyl substituents of amides are omitted in the side view for clarity)

4. Full scheme for the depiction of the asymmetric reactions mentioned in the text

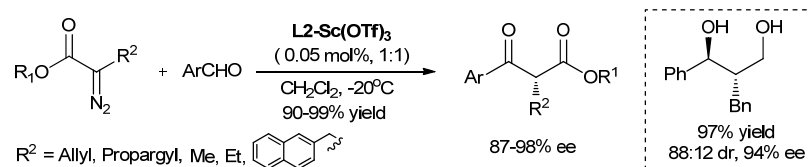
(1) L1/Y(OTf)₃

homologation of α -ketoesters and α -diazoesters

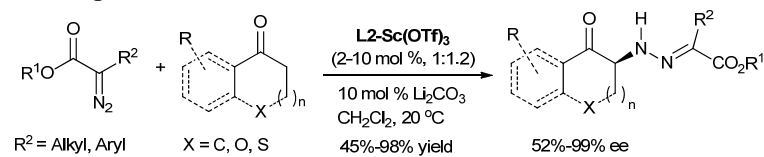


(2) L2/Sc(OTf)₃

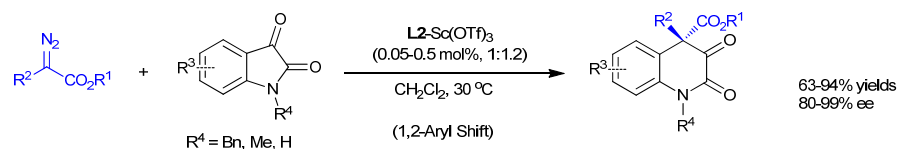
Roskamp–Feng reaction



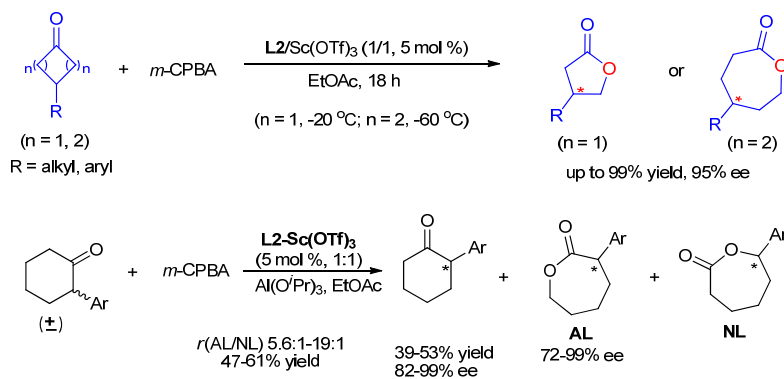
electrophilic addition of α -diazoesters to ketones



ring expansion of isatins with α -diazoesters



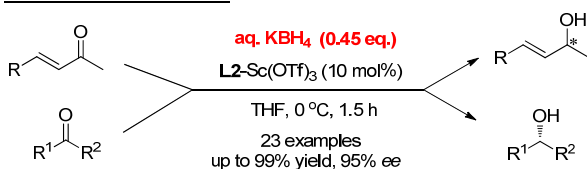
Baeyer–Villiger oxidation



inverse electron-demand aza-Diels–Alder reaction

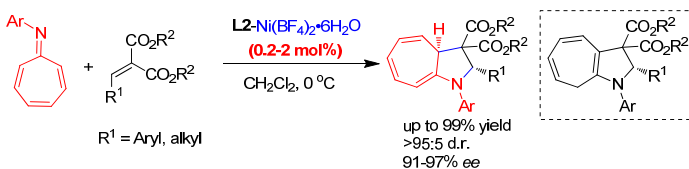


reduction reaction



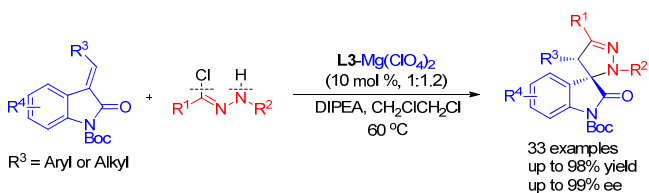
(3) **L2/Ni(BF₄)₂**

[8+2] cycloaddition



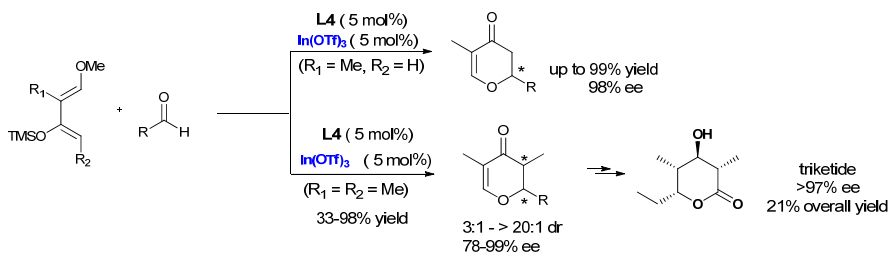
(4) **L3/Mg(ClO₄)₂**

1,3-dipolar cycloaddition of nitrile imines



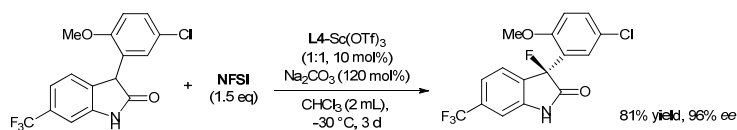
(5) **L4/In(OTf)₃**

Hetero-Diels–Alder reaction



(6) **L4/Sc(OTf)₃**

α -functionalization of 3-substituted oxindoles

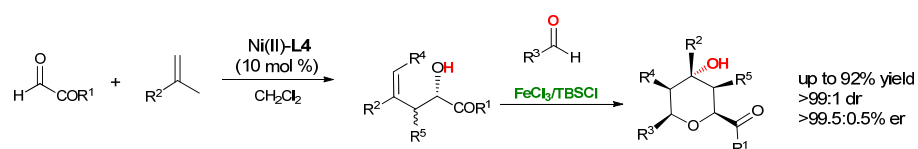


epoxidation of enones with H₂O₂



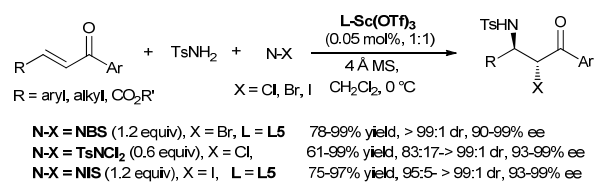
(7) L4/Ni(ClO₄)₂

Ene reaction



(8) L5/Sc(OTf)₃

Bromoamination and iodoamination reaction



(9) L6/Sc(OTf)₃

α -Arylation of 3-substituted oxindoles

