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SYNTHESIS OF OCTAHYDROPYRROLO[3,2-*c*]PYRIDINE DERIVATIVES BY THE CATALYTIC ASYMMETRIC INTRAMOLECULAR CYCLOADDITION OF AZOMETHINE YLIDES

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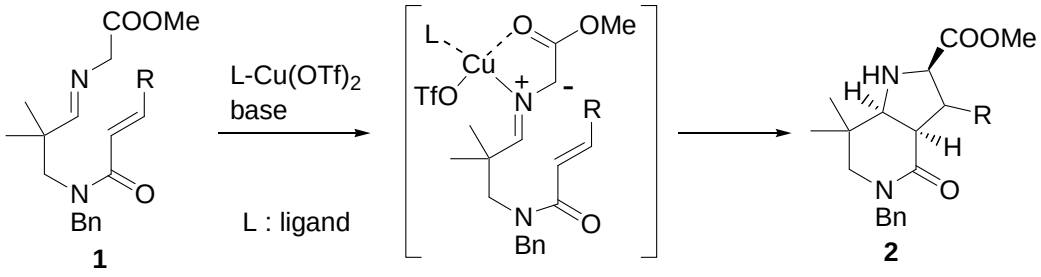
Abstract – The synthesis of optically active octahydropyrrolo[3,2-*c*]pyridine derivatives was achieved via the asymmetric intramolecular cycloaddition of azomethine ylides using copper-bisphosphine complexes. $Cu(OTf)_2$─(*R*,*R*)-CHIRAPHOS is a suitable catalyst for the reactions.

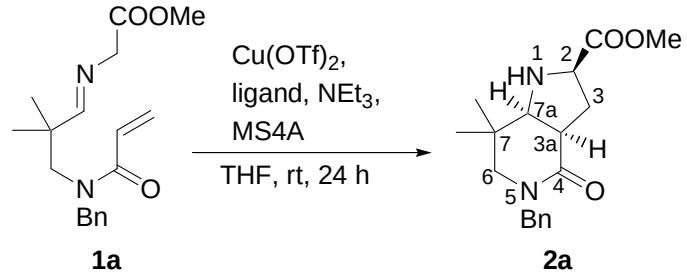
The development of effective methods for the synthesis of optically active octahydropyrrolo[3,2-*c*]pyridine derivatives, intermediates in the synthesis of naphthyridinomycin[1] and cyanocycline A,[2] is an important topic. The catalytic asymmetric intramolecular 1,3-dipolar cycloaddition of azomethine ylides would be a powerful tool for the synthesis of optically active octahydropyrrolo[3,2-*c*]pyridine derivatives. An intermolecular version of this type of cycloaddition has recently been reported.[3] We recently reported the *exo*-selective asymmetric intermolecular cycloaddition of azomethine ylides generated from *N*-alkylidene glycine esters using Cu(II)-BINAP complexes.[4] In the field of asymmetric intramolecular cycloaddition, only one example[5] has been reported, namely the reaction of azomethine ylides generated from *N*-arylmethylidene amino acids. However, the method has limitations, in that an aromatic ring is involved in the framework of the cycloadduct. The reaction of azomethine ylides with no aryl group on the dipoles would lead to octahydropyrrolo[3,2-*c*]pyridine derivatives. Herein we report asymmetric intramolecular cycloaddition of azomethine ylides generated from *N*-alkylidene glycine esters containing a carbon-carbon double bond using chiral copper(II) complexes for the synthesis of optically active octahydropyrrolo[3,2-*c*]pyridine derivatives (Scheme 1).

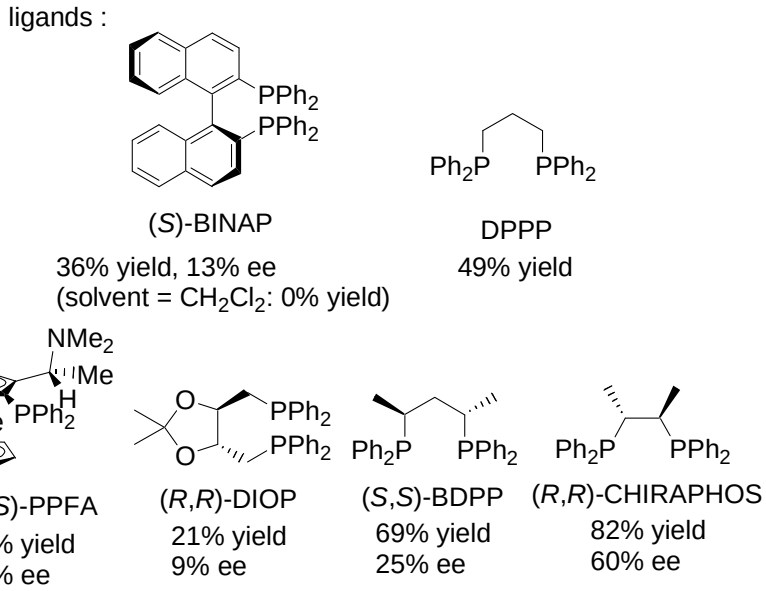
In a first attempt, according to the reaction conditions used in our previous study,[4] the reaction of imine



Scheme 1

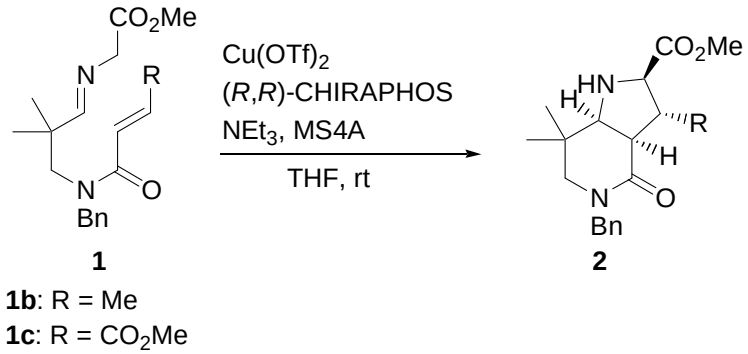
(**1a**)[6] in the presence of copper(II) triflate (20 mol%), (*S*)-BINAP (22 mol%), triethylamine (40 mol%), and MS4A in dichloromethane was examined, but the reaction did not proceed at all (Scheme 2). To find suitable reaction conditions, reactions using 1,3-diphenylphosphinopropane (DPPP) instead of (*S*)-BINAP in dichloromethane, benzene, acetonitrile, and THF were examined. Among the solvents tested, THF was found to be the best for the intramolecular cycloaddition (yields of **2a**; CH_2Cl_2: 32%, C_6H_6: 36%, CH_3CN: 0%, THF: 49%). The cycloadduct (**2a**) was obtained as a single diastereomer, the stereochemistry of which was determined by nOe measurement (*cis*-orientation [H(3a)-H(7a) (12%) and H(2)-H(7a) (8%)]). The structure of the product indicates that the reaction proceeded via an *endo* approach.





Scheme 2

Asymmetric reactions of imine (**1a**) catalyzed by copper(II) triflate and some bidentate chiral phosphine ligands in THF were also investigated. A low enantioselectivity was observed in the reaction catalyzed by $Cu(OTf)_2$─(*S*)-BINAP which was used in our previous work.[4] The absolute configuration of the cycloadduct has not been assigned so far. The reaction using (*R*)-(*S*)-PPFA, a *P*-*N* ligand, gave cycloadduct (**2a**) in low chemical yield and ee. When $Cu(OTf)_2$─(*R*,*R*)-DIOP, derived from tartaric acid was employed, a low yield and ee also resulted. The use of (*S*,*S*)-BDPP led to an increase in both the yield and ee of the cycloadduct (**2a**). Furthermore, when the reaction was catalyzed by $Cu(OTf)_2$─(*R*,*R*)-CHIRAPHOS cycloadduct (**2a**) was produced in good yield and ee (82% yield, 60% ee).[7]



1

1b: R = Me

1c: R = CO_2Me

2

Scheme 3

The reactions of imines (**1b,c**) bearing substituents on the β-position of the *N*-acryloyl amide in imine (**1**) were also carried out (Scheme 3). The reaction of imine (**1b**) gave the corresponding cycloadducts (**2b**) in low yield and ee (24 h, 44%, 6% ee). When imine (**1c**) was employed, an electron withdrawing methoxy carbonyl group, accelerated the reaction of imine (**1c**) and good yield and ee were obtained (12 h, 89%, 59% ee).

In summary, the synthesis of optically active octahydropyrrolo[3,2-*c*]pyridine derivatives was achieved via the asymmetric intramolecular cycloaddition of azomethine ylides using copper-bisphosphine complexes. $Cu(OTf)_2$─(*R*,*R*)-CHIRAPHOS is a suitable catalyst for the reactions. The cycloaddition would be applicable to the synthesis of N-containing fused heterocycles.

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6. Imines (**1a-c**) were synthesized by a known procedure.[8]

   Imine (**1a**): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.10-7.33 (m, 5H), 6.49 (dd, *J* = 10.3, 16.7 Hz, 1H), 6.28 (dd, *J* = 2.2, 16.7 Hz, 1H), 5.59 (dd, *J* = 2.2, 10.3 Hz, 1H), 4.71 (s, 2H), 4.14 (s, 2H), 3.71 (s, 3H), 3.56 (s, 2H), 1.12 (s, 6H).

   Imine (**1b**): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.10-7.36 (m, 5H), 6.87 (dq, *J* = 6.8, 14.6 Hz, 1H), 6.18 (dq, *J* = 1.6, 14.6 Hz, 1H), 4.69 (s, 2H), 4.14 (s, 2H), 3.73 (s, 3H), 3.56 (s, 2H), 1.78 (dd, *J* = 1.6, 6.8 Hz, 3H), 1.12 (s, 6H).

   Imine (**1c**): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.64 (d, *J* = 15.4 Hz, 1H). 7.16-7.39 (m, 5H), 6.78 (d, *J* = 15.4 Hz, 1H), 4.80 (s, 2H), 4.16 (s, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.62 (s, 2H), 1.21 (s, 6H).
7. General Procedure: Copper(II) trifluoromethane sulfonate (18.1 mg, 0.050 mmol), and molecular sieves 4A (100 mg) were added to a THF (1.0 mL) solution of (*R*,*R*)-CHIRAPHOS (23.5 mg, 0.055 mmol). After stirring the solution for 1 h, triethylamine (10.1 mg, 0.10 mmol) and a THF (1.5 mL) solution of imine (**1**) (0.25 mmol) were added. The mixture was stirred for the indicated time, and the reaction was quenched with a saturated ammonium chloride aqueous solution (10 mL). The mixture was extracted with dichloromethane (10 mL x 3), and the combined extracts were washed with brine. The organic layer was dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by silica gel chromatography to give the corresponding cycloadduct (**2**). The stereochemistry of cycloadducts (**2a-c**) was determined by difference noe experiments. The ees of

the cycloadducts were determined by HPLC with DAICEL CHIRALCEL OD.

Cycloadduct (**2a**): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.24-7.34 (m, 5H), 4.82 (d, *J* = 14.9 Hz, 1H), 4.28 (d, *J* = 14.9 Hz, 1H), 3.80 (dd, *J* = 6.8, 9.5 Hz, 1H), 3.70 (s, 3H), 3.53 (d, *J* = 12.4 Hz, 1H), 3.06 (dd, *J* = 1.4, 6.8 Hz, 1H), 2.92 (ddd, *J* = 4.6, 6.8, 9.5 Hz, 1H), 2.63 (dd, *J* = 1.4, 12.4 Hz, 1H), 2.55 (td, *J* = 9.5, 13.8 Hz, 1H), 2.33 (ddd, *J* = 4.6, 6.8, 13.8 Hz, 1H), 1.83 (br, 1H), 0.93 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 174.0, 171.0, 136.9, 128.4, 128.2, 127.2, 65.7, 58.5, 53.4, 52.1, 50.5, 42.4, 34.2, 32.7, 24.6, 24.2; HRMS (EI) calcd for $C_{18}H_{24}N_2O_3$, 316.1787, found 316.1790.

Cycloadduct (**2b**): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 4.83 (d, *J* = 14.3 Hz, 1H), 4.25 (d, *J* = 14.3 Hz, 1H), 3.72 (s, 3H), 3.53 (d, *J* = 12.2 Hz, 1H), 3.35 (d, *J* = 6.8 Hz, 1H), 3.15 (dd, *J* = 1.4, 6.8 Hz, 1H), 2.66 (dd, *J* = 1.4, 12.2 Hz, 1H), 2.50 (dd, *J* = 6.8, 13.5 Hz, 1H), 2.05 (br, 1H), 1.78 (m, 1H), 1.37 (d, *J* = 6.5 Hz, 3H), 0.92 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.6, 171.2, 137.0, 128.5, 128.4, 127.3, 67.7, 66.2, 64.1, 53.1, 52.0, 50.4, 43.5, 32.7, 24.4, 23.2, 20.2; HRMS (EI) calcd for $C_{19}H_{26}N_2O_3$, 330.1943, found 330.1947.

Cycloadduct (**2c**): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.28-7.16 (m, 5H), 4.81 (d, *J* = 14.6 Hz, 1H), 4.15 (d, *J* = 14.6 Hz, 1H), 4.06 (d, *J* = 5.4 Hz, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 3.55 (d, *J* = 5.4 Hz, 1H), 3.43 (d, *J* = 11.9 Hz, 1H), 3.13 (s, 2H), 2.58 (d, *J* = 11.9 Hz, 1H), 2.10 (br s, 1H), 0.85 (s, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.8, 172.7, 169.3, 136.8, 128.5, 128.3, 127.4, 65.1, 61.7, 53.4, 52.7, 52.4, 51.3, 50.6, 46.8, 32.4, 24.4, 24.1; HRMS (EI) calcd for $C_{20}H_{26}N_2O_5$, 374.1842, found 374.1846.

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