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Enantioselective copper-catalyzed cyclopropanation of styrene by means of chiral bispidine ligands

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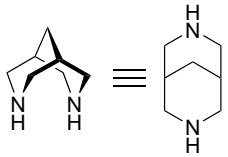
Abstract—Enantiopure C_1- and C_2-symmetric bispidine ligands have been synthesized and screened in the asymmetric copper-catalyzed cyclopropanation of styrene. In order to improve the enantiomeric excesses (ee) of the cyclopropane derivatives, the best performing C_1-symmetric diamine ligand was selected for studies on the reaction conditions. The optimized procedure allowed us to obtain up to 91% ee for the *cis*-cyclopropane derivative and up to 79% ee for the *trans* one.

1. Introduction

The advent of catalytic methods for the controlled decomposition of diazo compounds made the use of carbene reactives a well established tool for synthetic applications.[1] Carbene intermediates can be easily generated starting from diazo alkane derivatives, in the presence of different metals. Cu and Rh complexes have proven to be the most effective and with general applicability.[2] Among the many transformations involving metal carbene species, one of the most studied and exploited reaction is the addition to olefins to afford cyclopropane derivatives. The three-membered ring is found in a wide range of synthetic and naturally occurring compounds and metabolites.[3] Cyclopropanes have also been widely used as versatile synthetic intermediates for the preparation of more functionalized molecules.[4] The development of metal complexes embodying chiral ligands opened the way to the stereoselective cyclopropanation[5] of alkenes, by means of diazo compounds. In the field of copper-catalyzed cyclopropanations, after the first examples by Nozaki et al.[6] and Aratani et al.,[7] many chiral ligands have been proposed. The best results were obtained with bisimine containing C_2-symmetric ligands, such as semicorrins,[8] bisoxazolines,[9] and bipyridines.[10] Only a few examples[11] of strongly basic diamine C_2-symmetric ligands have been reported in the cyclopropanation reaction and, to the best of our knowledge, only one C_1-symmetric diamine ligand[12] has been reported to give moderate results in this reaction.

In our ongoing studies on chiral nitrogen-containing ligands, we were interested in exploring the applicability of molecules containing the 3,7-diazabicyclo[3.3.1]nonane moiety **1**, in copper-catalyzed stereoselective reactions.



bispidine **1**

The 3,7-diazabicyclo[3.3.1]nonane framework is commonly named bispidine and has been thoroughly studied in the past years.[13] Different bispidine derivatives have been previously described both as achiral and chiral ligands, in different metal catalyzed reactions.[14] Herein we report on the applications of C_1- and C_2-symmetric enantiopure bispidines in the copper-catalyzed cyclopropanation of styrene with the use of ethyldiazoacetate (EDA) as a source of the carbene intermediate.

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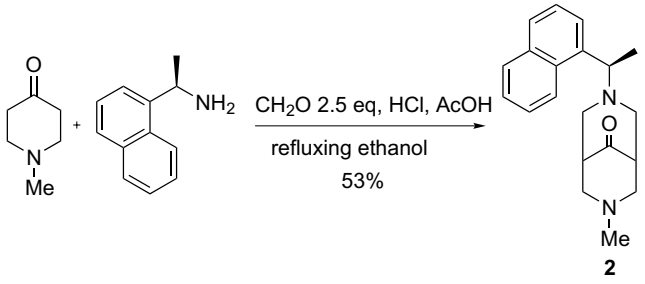
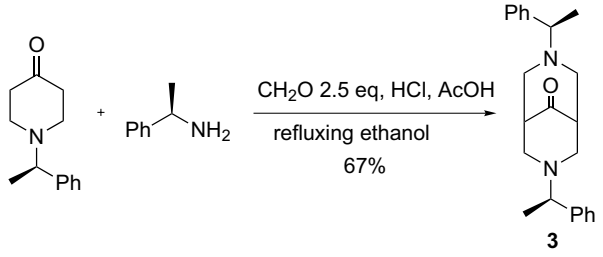
2. Results and discussion

Synthesis of the ligands was achieved through an optimized procedure relying on a double Mannich reaction sequence. The bispidine ring system was made chiral by means of proper substituents at the nitrogen, bearing a stereogenic carbon atom. These chiral residues were introduced in the form of enantiopure primary amines in the double Mannich reaction step. C_1-Symmetric ligand **2** was prepared in a single step, starting from commercially available 1-methyl-piperidin-4-one and (*R*)-1-naphthalen-1-yl-ethylamine, as we recently reported.[14a] After chromatographic purification, bispidinone **2** was isolated in 53% yield (Scheme 1).

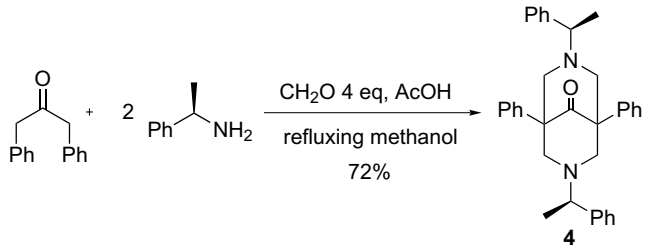
C_2-Symmetric ligand **3** was also prepared through a double Mannich strategy, starting from (*R*)-1-(1-phenylethyl)-piperidin-4-one[15] and (*R*)-1-phenyl-ethylamine, as shown in Scheme 2.



Scheme 1. Synthesis of ligand **2**.



Scheme 2. Synthesis of ligand **3**.



Scheme 3. Synthesis of ligand **4**.

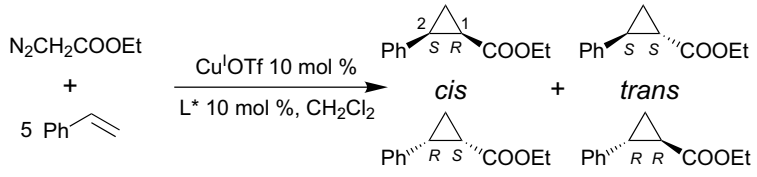
C_2-Symmetric ligand **4** was synthesized in a single one-pot multi-component reaction. Double Mannich condensation of 1,1′-diphenylacetone with (*R*)-1-phenylethylamine and paraformaldehyde in refluxing methanol, cleanly afforded the desired product, which was isolated in 72% yield after crystallization (Scheme 3). The preservation of the enantiomeric purity of ligands **2**–**4** was confirmed by chiral HPLC analysis.[16]

The ligands were then screened in the Cu^I catalyzed cyclopropanation of styrene with ethyldiazoacetate (EDA) as carbene generator. In a typical experimental procedure, the chiral catalyst was first prepared by stirring the chiral ligand (0.1 equiv) and an equimolar amount of commercially available CuOTf·0.5PhH in dry dichloromethane for 30 min. Styrene (5 equiv) was then added, followed by the dropwise addition of ethyl diazoacetate (1 equiv). The reaction mixture was then stirred for 24 h at room temperature. Chromatographic separation afforded *cis*- and *trans*-diastereoisomers, which were analyzed by chiral HPLC[17] to determine the ee. The results of the screening of the ligands are reported in Table 1.

The best outcome was obtained with ligand **2**, giving a 68% global yield, with a 2:3 *cis*/*trans* ratio, as determined by ^{1}H NMR analysis of the crude. Using HPLC, the *cis*-diastereoisomer showed a 41% ee and the *trans*-diastereoisomer 37% ee. A lower enantioselectivity was achieved with C_2-symmetric ligands **3** and **4**, despite the presence of acceptable yields.

In order to improve the results obtained, ligand **2** was tested under various reaction conditions. The influence of

Table 1. Cu^I Catalyzed asymmetric cyclopropanation of styrene



Ligand	Yield[a] (%)	*cis*/*trans*[b]	ee[c] (%) *cis*	ee[c] *trans* (%)
2	68	2/3	41 (1*S*,2*R*)[d]	37 (1*S*,2*S*)[d]
3	66	1/3	17 (1*S*,2*R*)	15 (1*S*,2*S*)
4	51	1/3	17 (1*S*,2*R*)	18 (1*S*,2*S*)

[a] Calculated on the sum of the isolated diastereoisomers after chromatographic purification.
[b] Determined by ^{1}H NMR analysis on the crude.
[c] Determined by HPLC analysis on a chiral column. See Section 4 for details.
[d] The absolute configuration was determined by comparison of the $[\alpha]_D$ sign with data reported in the lit.[9c]

Table 2. Screening of solvents in the asymmetric cyclopropanation of styrene in the presence of ligand **2**

Solvent	Yield (%)	*cis*/*trans*	ee (%) *trans*	ee (%) *cis*
Hexane	12	1/1	0	0
Toluene	48	2/3	32 (1*S*,2*S*)	30 (1*S*,2*R*)
THF	8	1/1	0	0
Benzene	33	2/3	31 (1*S*,2*S*)	35 (1*S*,2*R*)
Dichloroethane	55	1/3	38 (1*S*,2*S*)	40 (1*S*,2*R*)
Acetonitrile	27	2/3	13 (1*S*,2*S*)	18 (1*S*,2*R*)

the solvent was firstly investigated, as reported in Table 2. With hexane and THF, low yields and no stereoselection were detected, probably due to the poor solubility of the ligand in these solvents. As toluene, benzene, and dichloroethane led to results comparable to dichloromethane, this solvent was chosen for the subsequent studies.

An important feature in cyclopropanation reactions is the addition time of the EDA. We performed different tests varying the addition time from 1 h to 24 h through the use of a syringe pump. We observed that the best result was achieved with an addition time of 20 h, affording an ee of 67% for the *cis*-(1*S*,2*R*)-diastereoisomer and of 61% for the *trans*-(1*S*,2*S*)-diastereoisomer. The *cis*/*trans* ratio and the yield were influenced, by varying the time of addition of EDA. When we changed the ligand/Cu^{I} ratio, we could observe that an excess of ligand does not affect the ee values, while an excess of Cu^{I} causes a lowering of the ee. This result can be easily explained by assuming that the presence of an uncomplexed copper catalyst can perform a cyclopropanation reaction in a non-stereoselective manner. We could also observe that the reduction of the excess of styrene did not influence the overall yield. In fact, the use of 1.25 equiv excess of styrene with respect to ethyl diazoacetate, did not cause any change in yield or ee, with reference to the 5 equiv excess previously used. With regard to the ligand/Cu^{I} catalyst loading, we performed different experiments with loadings ranging from 10 mol % to 1 mol % with respect to the EDA reagent (Fig. 1).

The best result was obtained with a 2.5 mol % loading of the ligand/Cu^{I} catalyst, combined with the slow addition of EDA (20 h through a syringe pump) and 1.25 equiv excess of styrene. Under these conditions, a 67% overall yield (*cis*/*trans* ratio: 1/3) for the two diastereoisomers was achieved, with a 91% ee for the *cis*-(1*S*,2*R*) and a 79% ee for the *trans*-(1*S*,2*S*) ones. This result is summarized in Scheme 4.

The best performing ligand **2** was further characterized by X-ray diffraction analysis on a single crystal, isolated after crystallization from *i*-PrOH (Fig. 1). The crystal structure reveals the presence of a boat–chair conformation, with a boat for the *N*-methyl substituted piperidone ring. The large 1-naphthyl ring system is placed in the inner part of the 3,7-diazabicyclo moiety, thus forcing the *N*-methyl piperidone ring in the boat conformation.

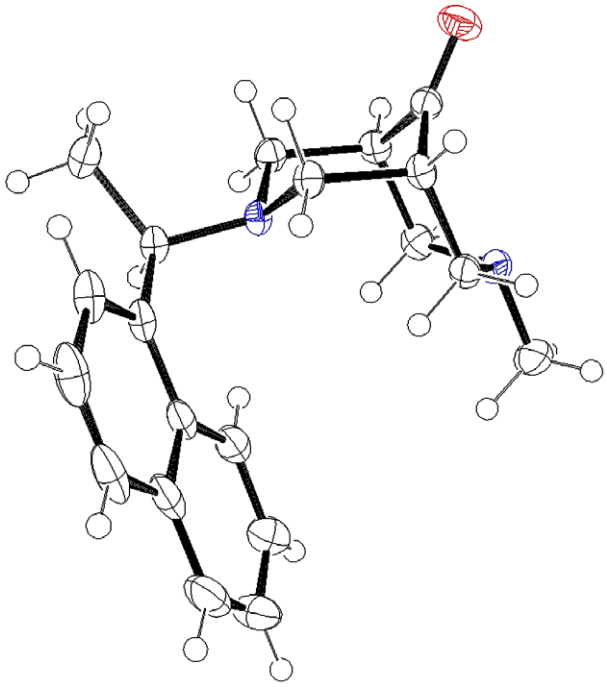
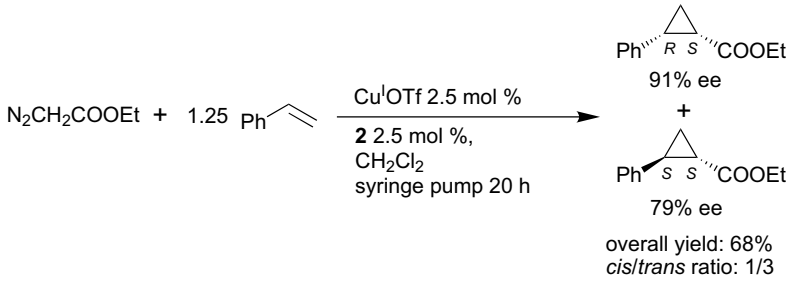


Figure 1. ORTEP projection of compound **2**. Only one of the two independent molecules is shown. Atomic displacement parameters at 50% probability level (see Section 4 for details).

Bispidines and bispidinones are known to act as bidentate chelating agents toward metal cations in a chair–chair conformation. In order to coordinate to the Cu^{I} atom, the *N*-methyl piperidone ring of ligand **2** is required to switch from a boat to chair conformation. The mechanism of the formation of the active catalyst is currently under investigation.

3. Conclusions

The screening of C_1- and C_2-symmetric diamine bispidine ligands in the asymmetric cyclopropanation of styrene



Scheme 4. Optimized conditions for the asymmetric cyclopropanation of styrene in the presence of ligand **2**.

was performed. All ligands were easily prepared in a single step from commercially available products. The C_1-symmetric ligand **2** showed moderate results under the usually referred conditions, but, after fine tuning of the reaction conditions, the outcome was improved up to 91% ee for the *cis* (1*S*,2*R*) cyclopropane derivative and to 79% ee for the *trans* (1*S*,2*S*) one. Ligand **2** represents the first example of a simple C_1-symmetric diamine successfully applied in the asymmetric cyclopropanation of styrene. Further studies on ligand **2** and its modified analogues are currently in progress, in order to expand their applicability in other asymmetric reactions.

4. Experimental

4.1. General

All solvents were distilled and properly dried, when necessary, prior to use. All chemicals were purchased from commercial sources and used directly, unless indicated otherwise. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 (Merck); spots were visualized with UV light or by treatment with 1% aqueous $KMnO_4$ solution. Products were purified by flash chromatography on Merck silica gel 60 (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded with Bruker AC 300 (^1H, 300 MHz; ^{13}C, 75.4 MHz) and 400 MHz Avance (^1H, 400 MHz; ^{13}C, 100 MHz) NMR spectrometers. Chemical shifts are reported in parts per million downfield from $SiMe_4$ ($\delta = 0.0$). HRMS spectra were measured on a Jeol SX 102 instrument equipped with its standard sources. Optical rotations were measured with a Perkin–Elmer 241 polarimeter.

4.2. Synthesis

4.2.1. (1′*R*,1*R*,5*S*)-3-Methyl-7-(1′-naphthalen-1-yl-ethyl)-3,7-diaza-bicyclo[3.3.1]nonan-9-one 2. Compound **2** was prepared according to Ref. 14a. ^1H NMR (400 MHz $CDCl_3$) δ 8.51 (d, $J = 8.0$ Hz, 1H), 7.88 (dd, $J = 8.0$, 2.0 Hz, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.58–7.48 (m, 3H), 7.45 (t, $J = 8.0$ Hz, 1H), 4.37 (q, $J = 6.5$ Hz, 1H), 3.12 (dt, $J = 11.0$, 3.0 Hz, 1H), 3.05 (m, 2H), 3.00 (m, 2H), 2.95 (m, 2H), 2.71 (dd, $J = 11.0$, 3.0 Hz, 1H), 2.55 (m, 2H), 2.23 (s, 3H), 1.53 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1 (1C), 139.7 (1C), 134.2 (1C), 131.5 (1C), 128.7 (1C), 127.8 (1C), 125.6–125.1 (4C), 124.6 (1C), 60.2 (1C), 60.0 (1C), 59.9 (1C), 57.4 (1C), 54.5 (1C), 46.8 (1C), 46.5 (1C), 45.0 (1C), 16.7 (1C); $[\alpha]_D^{20} = -30.6 (c1, CHCl_3)$; HRMS *m*/*z* calcd 308.1889. Found: 308.1893. Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08; O, 5.19. Found: C, 77.92; H, 7.81; N, 9.11.

4.2.2. 3,7-Bis-((*R*)-1′-phenyl-ethyl)-3,7-diaza-bicyclo[3.3.1]-nonan-9-one 3. Compound **3** was prepared by slight modification of a previously reported procedure.[14i] To a suspension of paraformaldehyde (225 mg, 7.5 mmol) in 30 mL of ethanol, (*R*)-1-(1-phenyl-ethyl)-piperidin-4-one[15] (610 mg, 3 mmol), acetic acid (0.171 mL, 3 mmol), and 37% aq HCl (0.120 mL, 1.5 mmol) were added under a nitrogen atmosphere. The mixture was heated at reflux and then a solution of (*R*)-1-phenyl-ethylamine (0.380 mL, 3 mmol) and AcOH (0.171 mL, 3 mmol) in 15 mL of ethanol was added dropwise (15 min). The reaction was refluxed for 6 h and then allowed to reach room temperature overnight. After evaporation of the solvent the residual brown oil was treated with 20 mL of 30% aq NaOH and then extracted with CH_2Cl_2. The crude was purified by flash chromatography (EtOAc/MeOH/TEA, 89:9:2) affording 700 mg of **3** (67% yield). ^1H NMR (400 MHz $CDCl_3$) δ 7.33–7.24 (m, 10H), 3.56 (q, $J = 6.7$ Hz, 2H), 2.99 (m, 4H), 2.79 (m, 4H), 2.50 (m, 2H), 1.35 (d, $J = 6.7$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.4 (1C), 143.4 (2C), 128.2–127.0 (10C), 62.8 (2C), 54.9 (2C), 52.9 (2C), 47.0 (2C), 18.6 (2C); $[\alpha]_D^{20} = +4.2$ (*c* 0.5, $CHCl_3$); HRMS *m*/*z* calcd 348.2202. Found: 348.2209. Anal. Calcd for $C_{23}H_{28}N_2O$: C, 79.27; H, 8.10; N, 8.04; O, 4.59. Found: C, 79.30; H, 8.07; N, 8.01.

4.2.3. 1,5-Diphenyl-3,7-bis-((*R*)-1′-phenyl-ethyl)-3,7-diaza-bicyclo[3.3.1]nonan-9-one 4. A solution of (*R*)-1-phenyl-ethylamine (6.36 mL, 0.05 mol) in 30 mL of ethanol was cooled to 0 °C with an ice bath. Acetic acid (3 mL), paraformaldehyde (3.0 g, 0.1 mmol), and 1,1′-diphenylacetone (5.25 g, 0.025 mol) were added. The mixture was refluxed overnight. After cooling to room temperature, the suspension was filtered affording 9.12 g of **4** (72% yield).^1H NMR (400 MHz $CDCl_3$) δ 7.32–7.15 (m, 20H), 3.80 (q, $J = 6.8$ Hz, 2H), 3.47 (br d, $J = 10.7$ Hz, 4H), 3.13 (br d, $J = 9.8$ Hz, 2H), 3.10 (br d, $J = 10.8$ Hz, 2H), 1.47 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.5 (1C), 143.3 (2C), 142.5 (2C), 129.3–124.5 (20C), 63.2 (2C), 60.9 (2C), 58.3 (2C), 54.5 (2C), 17.8 (2C); $[\alpha]_D^{20} = -8.4$ (*c* 1, $CHCl_3$); HRMS *m*/*z* calcd 500.2828. Found: 500.2821. Anal. Calcd for $C_{35}H_{36}N_2O$: C, 83.96; H, 7.25; N, 5.60; O, 3.20. Found: C, 83.89; H, 7.29; N, 5.68.

4.3. Optimized procedure for the cyclopropanation reaction

A solution of the catalyst was prepared by stirring, under argon, the ligand (0.025 mmol) and commercially available CuOTf·0.5PhH (0.025 mmol) in dry dichloromethane (10 mL) for 30 min. Styrene (1.25 mmol) was added to the solution. Then ethyl diazoacetate (1.0 mmol) was added over a period of 20 h by a syringe pump. After 4 h under stirring, the mixture was concentrated under reduced pressure. The residue oil was purified by flash chromatography with 99:1 hexane/diethyl ether as eluant to isolate the *cis* and the *trans* diastereoisomers. The *cis*/*trans* ratio was evaluated by ^1H NMR on the crude product. Enantiomeric excess was determined by HPLC analysis on chiral stationary phase. Absolute configurations were assigned on the basis of the retention times,[17]and by comparison of the $[\alpha]_D$ sign[9c] with the data reported in the literature.

HPLC analysis conditions. *trans*-isomer: column, Chiralcel OD; eluant 95:5 *n*-hexane/*i*-PrOH; flow rate, 1 mL/min; UV detector, 230 nm; retention time of (*R*,*R*)-isomer, 7.20 min (lit.[17] 5.15 min); retention time of (*S*,*S*)-isomer, 8.45 min (lit.[17] 5.90 min). *Cis* isomer: column, Chiralcel OB; eluant 99:1 *n*-hexane/*i*-PrOH; flow rate, 1 mL/min; UV detector, 230 nm; retention time of (*S*,*R*)-isomer,

27.40 min (lit.[17] 29.00 min); retention time of (*R*,*S*)-isomer, 25.80 min (lit.[17] 26.30 min).

4.4. Crystal data for 2

$M = 308.41$, monoclinic, $P2_1$, $a = 10.776(2)$, $b = 12.421(2)$, $c = 12.452(2)$ Å, $\beta = 99.91(2)°$, $V = 1641.8(5)$ Å^3, $Z = 4$, $T = 123$ K, $D_c = 1.248$ g cm^{-3}, μ(Mo-Kα) $= 0.077$ cm^{-1}, $F(0\,0\,0) = 664$; prism, $0.43 \times 0.29 \times 0.12$ mm, Bruker SMART diffractometer; 29,886 data collected, 5797 unique, $R_{int} = 0.0455$, 5047 with $I_o > 2\sigma(I_0)$. The structure was solved by a direct method,[18] and refined anisotropically by matrix least-squares based on F^2,[19] to give $R_1 = 0.0417$, $wR_2 = 0.0988$ for 5047 observed reflections and 607 parameters and 151 restraints on C–H bond distances. The asymmetric unit contains two independent molecules whose geometrical parameters are nearly equal. The absolute configuration was chosen on the known chirality the (*R*)-1-naphthalen-1-yl group, unchanged by the chemical synthesis. Supplementary crystallographic data were deposited as CCDC 635829 with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

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