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# Syntheses of $C_1$-symmetric bidentate ligands having pyridyl and 1,3-Thiazolyl, 1-methylimidazolyl or pyrazinyl donor groups for enantioselective palladium-catalyzed allylic substitution and copper-catalyzed cyclopropanation

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**Abstract**

New chiral $C_1$-symmetric bidentate ligands, which possess two different nitrogen heterocycles, 1,3-thiazolyl, 1-methylimidazolyl or pyrazinyl and one pyridyl group, were prepared by Kröhnke condensation in 36–59% overall yield. Stable Pd(II)-allyl and Cu(II) chloride complexes formed by some of the ligands were obtained in 60–65% yields. X-ray crystal structure analysis of a copper(II) complex having 1-methylimidazolyl group indicated that it is a μ-chloro bridge dimer. The Pd(II)-allyl complexes were found to be active catalysts in the asymmetric allylic substitution of 1,3-diphenylprop-2-enyl acetate. The best result observed was 85% e.e. and 99% isolated yield. In addition, the in situ generated $Cu(OTf)_2$ complexes were found to be active catalysts in cyclopropanation of styrene with ethyl diazoacetate.


*Keywords:* Pyridyl; Allylic Substitution; Cyclopropanation; Palladium; Copper

## 1. Introduction

The use of nitrogen heterocycles in metal-catalyzed reactions has received great attention in recent years [1]. Chiral $C_2$-symmetric bidentate ligands of this class, like bisoxazoline and bipyridine, have especially enjoyed success [2–5]. $C_2$-Symmetric ligand can, in principle, reduce the number of possible transition states of a reaction thus increasing the chances of success [6]. In certain applications, however, good results have been achieved with chiral bidentate $C_1$-symmetric ligands. For example, the monoterpene-derived $C_1$-bipyridyls **L1** and amino-alcohol-derived $C_1$-pyridinooxazolines **L2** have been employed in Pd-catalyzed asymmetric allylic substitutions [7]. In addition, **L2** has been successfully utilized in hydrosilylation [8a] and Diels–Alder [8b] reactions. Our group recently reported the use of $C_1$-symmetric pyridine ligands **L3** in Cu-catalyzed allylic oxidation reactions [9]. In spite of these results, heterocycles other than oxazoline and pyridine are relatively unexplored in the synthesis of chiral $C_1$-symmetric ligand [10]. Aromatic heterocycles which have different electron density compared to that of pyridine have different coordination chemistry and environment. Recently, we reported bidentate ligand having 1,3-thiazolyl and pyridyl donors for asymmetric allylic oxidation of cyclohexene [11] To further develop this class of ligand, we report here several new bidentate $C_1$-symmetric pyridine ligands, which have heterocycles such as 1,3-thiazole (**1** and **2**), imidazole (**3**) or pyrazine (**4**) coupled to a chiral pyridyl unit. Their applications in the asymmetric Pd-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate and Cu-catalyzed cyclo-

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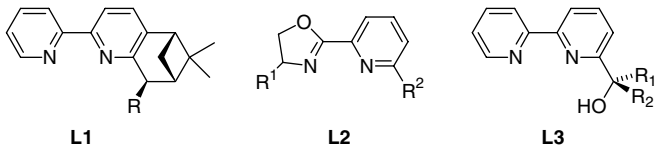
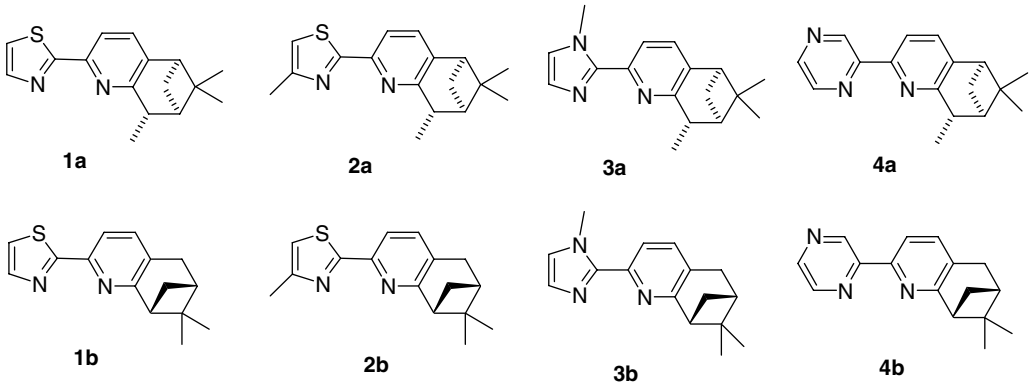
propanation of styrene with ethyl diazoacetate were investigated.




chiral rigid substituent fused to the pyridine ring were easily prepared by two step synthesis using 2-acetyl-1,3-thiazole, 2-acetyl-4-methyl-1,3-thiazole, 2-acetyl-1-methylimidazole or 2-acetyl-pyrazine as the starting material and pyridinium iodide **7**–**10** as intermediates (Scheme 1). For example, the 1,3-thiazolyl-pyridine ligand **1a** was prepared by the cyclization of acetylheterocycle pyridinium iodide **7** with α,β-unsaturated ketone **5** in the presence of ammonium acetate and acetic acid under reflux conditions. The




## 2. Results and discussion

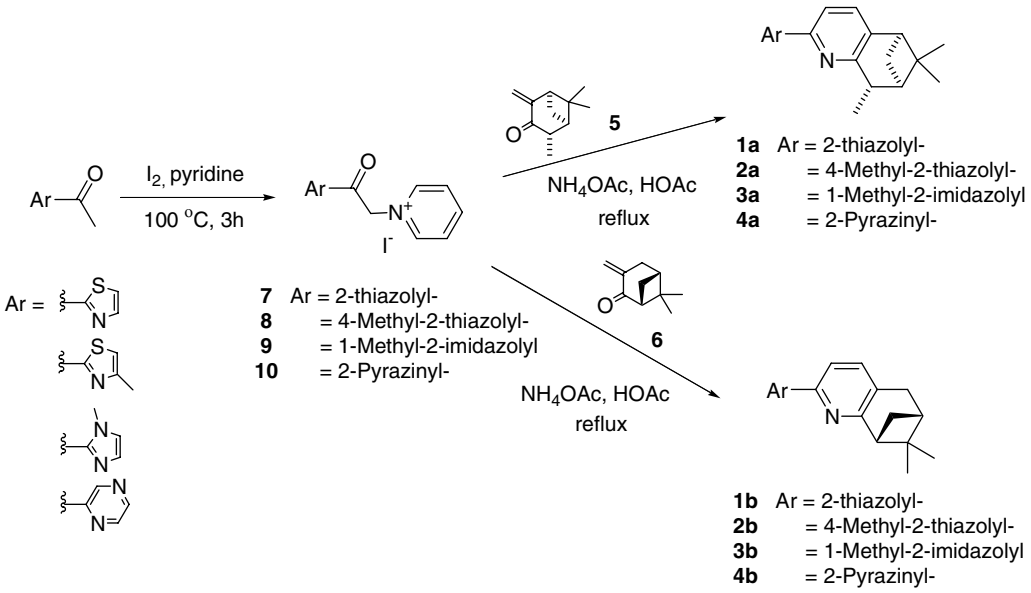
### 2.1. Synthesis of 1,3-thiazolyl-, imidazolyl- and pyrazinyl-pyridines ligands

The key step in the synthesis of the ligands is the assembly of the pyridine unit, which involves reaction of a 1-(2-hetaryl-2-oxoethyl)pyridinium salt with chiral α,β-unsaturated ketones [12]. This synthetic approach, first reported by von Zelewsky and co-worker [13], has been widely utilized for preparation of chiral terpyridine [14], bipyridine [7a,7b,7c] and phenyl-pyridine [15]. Ligands **1-4** having a

pure compound **1a** was obtained with 67% yield after purification by flash column chromatography. Modification of the fused chiral substitute can be successfully carried out by using a different chiral α,β-unsaturated ketone **6**. Reaction of **6** with heterocycle pyridinium iodide **7**–**10** leads to ligands in moderate yields (28–48%).

### 2.2. Synthesis and characterization of palladium complex

The $C_1$-symmetric ligands formed a variety of complexes with transition metals. Their coordination property with palladium was demonstrated by reacting with




Scheme 1.

$[Pd(allyl)Cl]_2$. The $[Pd(allyl)Cl]_2$ was mixed with ligand **1a** in $CH_2Cl_2$ for 2 h and treated with $AgPF_6$. The complex was isolated as $[Pd(allyl)(\mathbf{1a})][PF_6^-]$ in 60% yield. The $^1H$ NMR spectra of the complex exhibited characteristic differences in chemical shifts as compared with the free ligand and the elemental analyses of the complex showed good agreement with the theoretical calculated value.

### 2.3. Synthesis and X-ray structure of copper complex

The coordination property of the ligands with copper was demonstrated by reacting with $CuCl_2$ with **3b**. A $CH_2Cl_2$ solution of **3b** was added to a solution of hydrated $CuCl_2$ in MeOH and a clear greenish-blue solution was observed immediately. Evaporation of the solvent and addition of diethyl ether led to green precipitates. Crystals of the complex $[Cu_2(\mathbf{3b})_2(\mu\text{-}Cl)_2Cl_2]$ for X-ray analysis were obtained by slow diffusion of diethyl ether into a $CH_2Cl_2$ solution. The crystallographic data are summarized in Table 1. The perspective view and atomic numbering of the crystal structure are shown in Fig. 1. The Cu complex exists as a dimer which is bridged by two chloride ligands and results in a distorted trigonal bipyramidal geometry. Selected bond distances and bond angles for the complex are listed in Table 2. The N donor from the *N*-methylimidazole, one of the bridging chlorides and one terminal chloride form the trigonal plane (Cl(2)–Cu(1)–Cl(1): 115.0°, N(2)–Cu(1)–Cl(1): 139.2°, N(2)–Cu(1)–Cl(2): 105.7°; Cl(3)–Cu(2)–Cl(4): 109.7°, N(5)–Cu(2)–Cl(3): 109.0°, N(5)–Cu(2)–Cl(4): 141.1°, while the N donor of the pyridine ring and the remaining bridging chloride form the apex. The two nonbridging chloro ligands are arranged in an *anti*-fashion. The Cu···Cu separation is 3.193 Å. The geometry of the copper(II) centres is intermediate between square pyramidal and trigonal bipyramidal. This is more precisely described by Reedijk's $\tau$ factor, which averages 0.67 ($\tau = 0$ for exact square pyramidal and $\tau = 1$ for exact trigonal bipyramidal) [16].

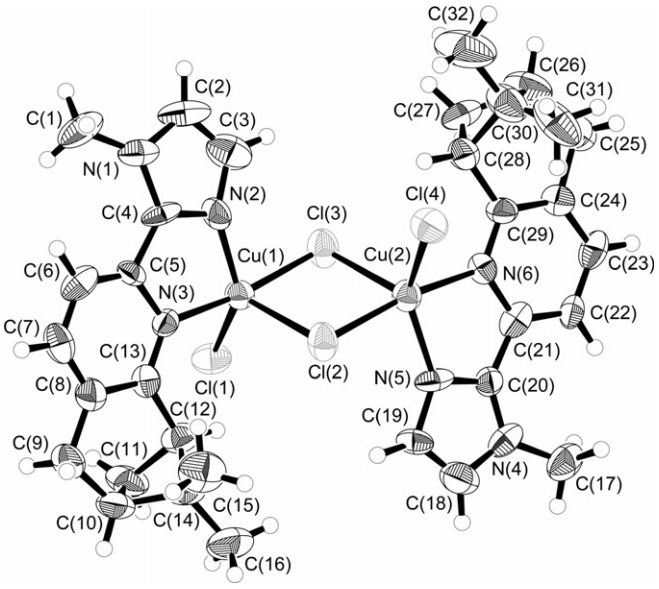



Fig. 1. X-ray crystal structure of $[Cu_2(\mathbf{3b})_2(\mu\text{-}Cl)_2Cl_2]$.

Table 1
Crystallographic data for $[Cu_2(3b)_2(\mu\text{-}Cl)_2Cl_2]$

| Empirical formula | $Cu_2Cl_4C_{32}N_6H_{38}$ |
|---|---|
| Formula weight | 775.60 |
| Temperature (°C) | 30 |
| Wavelength (Å) | 0.71073 |
| Crystal color | Green |
| Crystal system | Trigonal |
| Space group | *R*3(#146) |
| Unit cell dimensions | |
| *a* (Å) | 29.017(4) |
| *c* (Å) | 10.655(2) |
| α (°) | β = 90 |
| γ (°) | 120 |
| Volume (Å$^3$) | 7769(2) |
| *Z* value | 9 |
| Density (calcd.) (g/m$^3$) | 1.492 |
| Absorption coefficient (mm$^{-1}$) | 0.991 |
| $F_{000}$ | 3582 |
| Crystal size (mm$^3$) | 0.12 × 0.23 × 0.28 |
| Theta range for data collection | 1.52–28.48°. |
| Index ranges | $-12 <= h <= 12$, $-24 <= k <= 24$, $-14 <= l <= 25$ |
| Reflections collected | 16182 |
| Independent reflections [$R_{int}$] | 3914 = 0.030 |
| Completeness to theta = 28.48° | 95.6% |
| Absorption correction | Semi-empirical from equivalents |
| Maximum and minimum transmission | 1.00 and 0.67 |
| Refinement method | Full-matrix least-squares on *F* |
| Data/restraints/parameters | 7976/0/433 |
| Goodness-of-fit indicator | 0.975 |
| Final *R* indices [$I > 2\sigma(I)$] | $R_1 = 0.0567$, $wR_2 = 0.0987$ |
| *R* indices (all data) | $R_1 = 0.1093$, $wR_2 = 0.1152$ |
| Absolute structure parameter | −0.022(16) |
| Largest difference in peak and hole | 0.953 and −0.625 e Å$^{-3}$ |

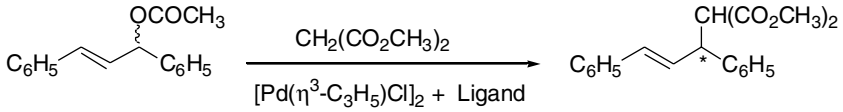
### 2.4. Pd-catalyzed asymmetric allylic substitution

The $[Pd([allyl)(\mathbf{1a})]^+PF_6^-$ complex was found to be active catalyst in the substitution reaction with dimethyl malonate, *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and cat-

Table 2
Selected bond angles and bond distances for $[Cu_2(\mathbf{3b})_2(\mu\text{-}Cl)_2Cl_2]$ complex

| Atoms | Bond angles (°) | Atoms | Bond distances (Å) |
|---|---|---|---|
| Cl(2)–Cu(1)–Cl(1) | 115.0(1) | Cu(1)–Cl(1) | 2.281(4) |
| Cl(3)–Cu(1)–Cl(1) | 94.3(2) | Cu(1)–Cl(2) | 2.576(4) |
| N(2)–Cu(1)–Cl(1) | 139.2(3) | Cu(1)–Cl(3) | 2.311(6) |
| N(3)–Cu(1)–Cl(1) | 94.6(3) | Cu(1)–N(2) | 1.94(4) |
| Cu(1)–Cl(2)–Cu(2) | 92.9(1) | Cu(1)–N(3) | 2.07(1) |
| Cl(3)–Cu(1)–Cl(2) | 87.4(2) | Cu(2)–Cl(2) | 2.325(6) |
| N(2)–Cu(1)–Cl(2) | 105.7(3) | Cu(2)–Cl(3) | 2.588(4) |
| N(3)–Cu(1)–Cl(3) | 90.5(4) | Cu(2)–Cl(4) | 2.249(4) |
| N(3)–Cu(1)–Cl(3) | 170.4(3) | Cu(2)–N(5) | 2.007(9) |
| N(3)–Cu(1)–N(2) | 80.4(5) | Cu(2)–N(6) | 2.13(2) |

Table 3
Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate[a]




| Entry | Ligands | Solvents | Salts | Time[c], h | Yield[d] | % ee[e] | Config.[f] |
|---|---|---|---|---|---|---|---|
| 1[b] | **1a** | $CH_2Cl_2$ | KOAc | 30 | 96 | 79 | *S* |
| 2 | **1a** | $CH_2Cl_2$ | KOAc | 12 | 98 | 78 | *S* |
| 3 | **1a** | $CH_2Cl_2$ | NaOAc | 20 | 78 | 76 | *S* |
| 4 | **1a** | $CH_2Cl_2$ | LiOAc | 12 | 87 | 68 | *S* |
| 5 | **1a** | $CH_3CN$ | KOAc | 72 | 99 | 85 | *S* |
| 6 | **1a** | THF | KOAc | 84[g] | 63 | 79 | *S* |
| 7 | **1b** | $CH_2Cl_2$ | KOAc | 14 | 99 | 24 | *S* |
| 8 | **2a** | $CH_2Cl_2$ | KOAc | 16 | 99 | 77 | *S* |
| 9 | **2b** | $CH_2Cl_2$ | KOAc | 15 | 94 | 18 | *S* |
| 10 | **3a** | $CH_2Cl_2$ | KOAc | 48 | 77 | 67 | *S* |
| 11 | **3b** | $CH_2Cl_2$ | KOAc | 12 | 91 | 31 | *S* |
| 12 | **4a** | $CH_2Cl_2$ | KOAc | 22 | 99 | 63 | *S* |

[a] Reaction conditions: Ligand (10 mol%) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%) with 1,3-diphenylprop-2-enyl acetate (0.4 mmol), $CH_2(CO_2Me)_2$ (1.2 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (1.2 mmol) and Salt (3.5 mol%) in 2 mL solvent at room temperature.
[b] *b*$[Pd(allyl)(\mathbf{1a})]^+PF_6^-$ was used.
[c] Reaction time of reactions was monitored by TLC.
[d] Isolated yields.
[e] Determined by HPLC analysis using a chiral column (Chiralcel-OD).
[f] Assigned by the comparison with sample of known configuration.
[g] The reaction was not complete.

alytic amounts of potassium acetates at room temperature [17]. When the loading of $[Pd(allyl)(\mathbf{1a})]^+PF_6^-$ complexes used at 5 mol%, the reaction was completed after 30 h in 96% isolated yield and 79% e.e. (Table 3, entry 1). For a more convenient procedure, the Pd(allyl)-complex can be prepared *in situ* by reacting the ligand with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ in $CH_2Cl_2$ solution under nitrogen. The complexes formed are effective catalysts for asymmetric allylic substitution with a similar enantioselectivity and slightly higher reactivity compared to isolated complex $[Pd(allyl)(\mathbf{1a})]^+PF_6^-$ as the reaction completed within 12 h even with 2.5 mol% of catalysts (Table 3, entry 2). Better results are summarized in Table 3. Ligand **1a** exhibited the best results in terms of enantioselectivity (up to 85% e.e.) and reactivity (12 h for complete conversion). In addition, the reaction rates of allylic substitution were much faster in $CH_2Cl_2$ than $CH_3CN$ and THF (entries 4–6). The acetate salts (LiOAc, NaOAc and KOAc) showed some effects in the reaction in which the KOAc was the best in terms of yields and enantioselectivity (entries 2–4). Other ligands such as imidazolyl-pyridine **3** and pyrazinyl-pyridine **4** were examined in order to compare the heterocyclic effects in the allylic substitution (entries 10–12). However, the results were not as good as the 1,3-thiazolyl-pyridine **1a**. Chiral ligands from α,β-unsaturated ketone **6** in general gave lower enantioselectivity but faster reaction when compared with ligands from α,β-unsaturated ketone **5** (entry **6** vs **7, 8** vs **9** and **10** vs**11**).

All allylic substitutions in this study favored the (*S*)-configuration. This preference can be readily explained if one look at the steric environment of the ligand **3b**. Fig. 2 shows the steric environment of the ligand in the crystal structures of $[Cu_2(\mathbf{3b})_2(\mu\text{-}Cl)_2Cl_2]$. The bulkiness of the ligand comes from the lower side of the ligand, which has the dimethyl group. The distance of the two methyl carbons, C(15) and C(16), are 5.149 and 5.501 Å from the metal center respectively whereas carbons C(11) and C(14) are 4.605 and 4.808 Å away from the metal. In this environment, the methyl group of carbon C(16) points into the open space in the direction of the π-allyl ligand of the palladium metal. In order to minimize the steric hindrance between phenyl group of the π-allyl group and the methyl group, the π-allyl would favor a "W" orientation shown in the proposed intermediate in Fig. 3. Nucleophilic attack through pathway b, which should be more favored because of the favorable arrangement of the product, would then afford the observed allylic product.

### 2.5. Cu-catalyzed asymmetric cyclopropanation

Apart from the Pd-catalyzed asymmetric allylic substitution, the application of the $C_1$-pyridine ligands in the copper-catalyzed asymmetric cyclopropanation of styrene with ethyl diazoacetate was also investigated. The copper complexes were generated *in situ* by stirring 2.2 mol% of ligand and 2 mol% of $Cu(OTf)_2$ in dry $CH_2Cl_2$ under nitrogen.

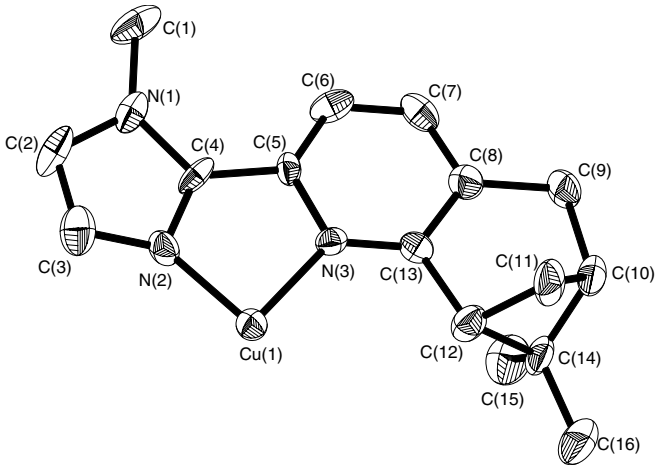



Fig. 2. Crystal structures of $[Cu_2(\mathbf{3b})_2(\mu\text{-}Cl)_2Cl_2]$ with only the ligand and Cu centre shown and hydrogen atoms omitted.

The complex was then activated with 0.2 equivalents of EDA as catalysts for cyclopropanation reaction. All complexes were found to be active catalysts in the reaction and cyclopropyl esters were isolated from 46% to 90% yields. The *trans*/*cis* ratios of the products were found between 60:40 and 70:30. In all cases, the Cu-catalysts favored the formation of *trans*-cyclopropyl esters. Selected results are listed in Table 4. Only moderate enantioselectivities were obtained. The best case is obtained by ligand **2a** with 70% isolated yield of cyclopropyl esters and 38% e.e. for *trans*-isomer and 30% e.e. for *cis-isomer* (Table 4, entry 3). The methyl substitutient on the 1,3-thiazole ring increases the e.e. and six member ring pyrazine is better compared to unsubstituted five membered 1,3-thiazolyl- and 1-methylimidazolyl rings.

The absolute configurations of cyclopropyl ester products formed were determined to be (1*R*,2*R*) for the *trans-isomer* and (1*R*,2*S*) for *cis-isomers* from the (1*R*,2*R*,3*R*,5*S*)-(-)-isopinocampheol derived ligands (Table 4, entries 1,3,5,7). Opposite absolute configurations (1*S*,2*S*) for the *trans-isomer* and (1*S*,2*R*) for *cis-isomers* were obtained in the nopinone-fused pyridine ligands (Table 4, entries 2,4,6,8). This trend is different from that of the allylic substitution which shows the same absolute configuration. However, similar trend has been observed previously with chiral terpyridine ligand in asymmetric cyclopropanation [14c]. Further analysis of the steric environment of ligand **3b** in Fig. 2 indeed sheds some light on the difference. The bulky methyl group of C(16) is pointing away from the metal center, whereas the bulky methyl group at the 8-position of the tetrahydroquinoline ring of **3a** should be pointing more towards the metal center. This may hinder the approach of alkene from pathway d and favors pathway c (Fig. 4). On the other hand, approach of alkene should favor pathway c with **3a** because of the hindered rotation of the carbene moiety towards the methyl group at the 8-position. However, as the enantioselectivities obtained are not high, the exact reason for the difference may require further investigation.

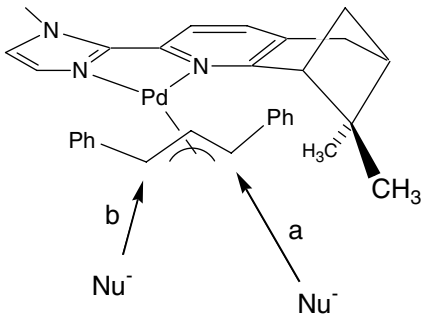



Fig. 3. Proposed Pd-allyl intermediate with ligand **3b**.

In summary, a number of new chiral $C_1$-symmetric 1,3-thiazolyl-, imidazolyl- and pyrazinyl-pyridines were successfully synthesized in moderate to good yields by using Kröhnke condensation reaction. The ligands were good for asymmetric Pd-catalyzed allylic substitution and Cu-catalyzed cyclopropanation reactions. The best enantioselectivity of the allylic substituted product was 85% e.e. with 99% isolated yield. Moreover, in the cyclopropanation of styrene with EDA, the enantioselectivity was up to 38% e.e. The coordination properties of the ligands with transition metals and the applications in other catalytic asymmetric reactions are under investigation in our laboratory.

## 3. Experimental

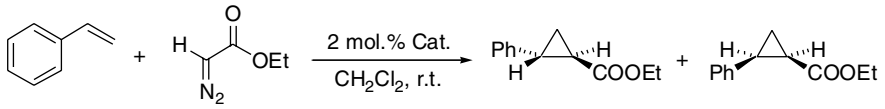
### 3.1. General methods

Toluene was distilled over sodium under dry nitrogen. $CH_2Cl_2$ was distilled under $N_2$ over calcium hydride. 4-Methyl-1,3-thiazole, 1-methylimidazole, 2-acetyl-1,3-thiazole and 2-acetylpyrazine were purchased from Aldrich and used as received. Chiral α,β-unsaturated ketones **5** and **6** were prepared according to the literature procedures [14c]. 2-Acetyl-4-methyl-1,3-thiazole and 2-acetyl-1-methylimidazole were readily obtained through lithiation of 4-methyl-1,3-thiazole and 1-methylimidazole with LDA and acylation with *N*,*N*-dimethylacetamide in THF and $Et_2O$ respectively. Infrared spectra in the range 500–4000 $cm^{-1}$ as KBr plates were recorded on a Perkin Elmer Model FTIR-1600 spectrometer. $^1H$ and $^{13}C$ NMR spectra were recorded on a Varian 300 MHz Mercury instrument. ESMS were recorded using a PE SCIEX API 365 mass spectrometer. Electron ionization mass spectra were recorded on a Hewlett–Packard 5890II GC instrument coupled with a 5970 mass selective detector. Elemental analyses were performed on a Vario EL elemental analyzer.

### 3.2. Crystallographic studies

Crystal of sample was mounted on a glass fiber. All measurements were made on a Bruker SMART CCD area detector with graphite monochromated Mo Kα radiation. Cell constants and an orientation matrix for data collection

Table 4
Asymmetric cyclopropanation of styrene with ethyl diazoacetate catalyzed by $C_1$-heterocyclic copper complexes.




| Entry | Ligand | *trans*:*cis* | *trans*% e.e. (config.)[a] | *cis*% e.e. (config.)[a] | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **1a** | 68 : 32 | 19 (1*R*,2*R*) | 11 (1*R*,2*S*) | 66 |
| 2 | **1b** | 70 : 30 | 16 (1*S*,2*S*) | 16 (1*S*,2*R*) | 51 |
| 3 | **2a** | 68 : 32 | 38 (1*R*,2*R*) | 30 (1*R*,2*S*) | 70 |
| 4 | **2b** | 70 : 30 | 14 (1*S*,2*S*) | 14 (1*S*,2*R*) | 46 |
| 5 | **3a** | 66 : 34 | 10 (1*R*,2*R*) | 20 (1*R*,2*S*) | 89 |
| 6 | **3b** | 69 : 31 | 14 (1*S*,2*S*) | 12 (1*S*,2*R*) | 90 |
| 7 | **4a** | 65 : 35 | 24 (1*R*,2*R*) | 6 (1*R*,2*S*) | 79 |
| 8 | **4b** | 67 : 33 | 8 (1*S*,2*S*) | 4 (1*S*,2*R*) | 85 |

[a] Enantiomeric excesses were determined by HPLC with Daicel Chiralcel OJ column. Absolute configurations were determined by comparing the order of elution of sample with known configuration [18].
[b] Isolated yield after chromatography.

corresponded to a R-centered trigonal cell (laue class: $-3$). Based on the systematic absences of: *hkil*: $-h + k + l \pm 3n$, packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be: R3 (#146). The data were collected at a temperature of $30 \pm 1$ °C to a maximum $2\theta$ value of 55.0°. A total of 16 182 oscillation images were collected. Of the 16 182 reflections that were collected, 3914 were unique ($R_{int} = 0.030$). Data were collected and processed using CrystalClear (Rigaku). The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed at geometrical sites with C–H = 0.95 Å and refined using the riding model. All calculations were performed using the CrystalStructure crystallographic software package. The structure has been solved using space group R-3 (#148), however, the $R$ and $R_w$ values are larger with some of the C & H atoms showing signs of disorder, which support the selection of space group R3 (#146).

### 3.3. Synthesis of pyridinium iodide salt

To a pyridine solution (6 mL) of 2-acetylheterocycle (8 mmol) was added a solution of iodine (2.03 g, 8 mmol) in pyridine (6 mL). The mixture was heated at 110 °C for 3 h. After cooling to room temperature, the dull brown-yellow solid was filtered and then washed with cold ethanol. The collected products were dried under vacuum.

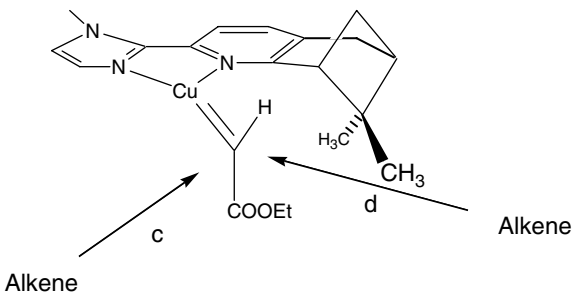



Fig. 4. Proposed Cu carbenoid intermediates with ligand **3b**.

### 3.4. Pyridinium iodide salt 7

2-Acetyl-1,3-thiazole (1.02 g) was used. Yield: 85% (2.26 g). $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 6.48 (s, 2H), 8.05 (t, $J = 6.9$ Hz, 1H), 8.28–8.37 (m, 3H), 8.76 (t, $J = 7.2$ Hz, 1H), 9.04 (d, $J = 6.3$ Hz, 2H).

### 3.5. Pyridinium iodide salt 8

2-Acetyl-4-methyl-1,3-thiazole (1.13 g) was used. Yield: 90% (2.49 g). $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 2.56 (s, 3H), 6.44 (s, 2H), 8.04 (t, $J = 7.5$ Hz, 1H), 8.27–8.32 (m, 2H), 8.75 (t, $J = 7.8$ Hz, 1H), 9.02 (d, $J = 6.6$ Hz, 2H).

### 3.6. Pyridinium iodide salt 9

2-Acetyl-1-methyl-imidazole (0.87 g) was used. Yield: 85% (2.24 g). $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 3.94 (s, 3H), 6.35 (s, 2H), 7.33 (s, 1H), 7.74 (s, 1H), 8.27 (t, $J = 7.8$ Hz, 2H), 8.73 (t, $J = 7.8$ Hz, 1H), 9.01 (d, $J = 5.7$ Hz, 2H).

### 3.7. Pyridinium iodide salt 10

2-Acetylpyrazine (0.98 g) was used. Yield: 88% (2.30 g). $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 6.50 (s, 2H), 8.31 (t, $J = 6.9$ Hz, 2H), 8.76 (t, $J = 7.8$ Hz, 1H), 8.99–9.01 (m, 3H), 9.09 (s, 1H), 9.25 (s, 1H).

### 3.8. Synthesis of chiral heterocyclyl-pyridine ligands by Kröhnke condensation

The pyridinium iodide salt (1.5 mmol), chiral α,β-unsaturated ketone (4.5 mmol) and ammonium acetate (2 g)

were added to the glacial acetic acid (2 mL). The mixture was heated to reflux at 120 °C overnight. The saturated $NaHCO_3$ solution was added to the reaction mixture slowly and the resulting solution was adjusted to pH 8. The mixture then was extracted with $Et_2O$ ($3 \times 50$ mL). The combined organic layers were dried over $MgSO_4$. After removal of solvents under reduced pressure, a brown residue was obtained and then purified by flash column chromatography.

*Ligand **1a***: α,β-Unsaturated ketone **5** and pyridinium iodide **7** were used. Purification by flash column chromatography (petroleum ether-EtOAc = 20:1) gave 67% yield (0.27 g) of **1b**. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.68 (s, 3H), 1.31 (d, $J = 9.9$ Hz, 1H), 1.43 (s, 3H), 1.44 (d, $J = 6.9$ Hz, 3H), 2.15–2.20 (m, 1H), 2.55–2.62 (m, 1H), 2.81 (t, $J = 5.7$ Hz, 1H), 3.22–3.26 (m, 1H), 7.29 (d, $J = 7.8$ Hz, 1H), 7.37 (d, $J = 3.3$ Hz, 1H), 7.86 (d, $J = 7.8$ Hz, 1H), 7.87 (d, $J = 3.3$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 18.16, 20.97, 26.31, 28.53, 38.71, 41.49, 46.64, 47.326, 116.58, 120.44, 133.54, 143.28, 148.39, 152.21, 161.00, 170.64; ESI-MS *m*/*z*: 271 ($M^+$+H).

*Ligand **1b***: α,β-Unsaturated ketone **6** and pyridinium iodide **7** were used. Purification by flash column chromatography gave 45% yield (0.17 g) of **1c**. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.71 (s, 3H), 1.33 (d, $J = 9.6$ Hz, 1H), 1.45 (s, 3H), 2.33–2.38 (m, 1H), 2.71–2.78 (m, 1H), 2.98 (d, $J = 2.4$ Hz, 2H), 3.08 (t, $J = 5.4$ Hz, 1H), 7.38 (d, $J = 3.0$ Hz, 1H), 7.51 (d, $J = 7.5$ Hz, 1H), 7.88 (d, $J = 3.3$ Hz, 1H), 7.97 (d, $J = 7.5$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 21.51, 26.18, 31.02, 31.62, 39.36, 40.30, 50.43, 117.49, 120.61, 131.95, 136.10, 143.93, 147.60, 166.67, 170.34; ESI-MS *m*/*z*: 257 ($M^+$+H).

*Ligand **2a***: α,β-Unsaturated ketone **5** and pyridinium iodide **8** were used. Purification by flash column chromatography (petroleum ether-EtOAc = 20:1) gave 65% yield (0.28 g) of **2a**. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.67 (s, 3H), 1.31 (d, $J = 9.9$ Hz, 1H), 1.43 (s, 3H), 1.44 (s, 3H), 2.14–2.21 (m, 1H), 2.54 (s, 3H), 2.56–2.61 (m, 1H), 2.80 (t, $J = 5.4$ Hz, 1H), 3.21–3.25 (m, 1H), 6.95 (d, $J = 0.9$ Hz, 1H), 7.27 (s, 1H), 7.95 (d, $J = 7.5$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 17.30, 18.11, 20.91, 26.28, 28.50, 38.66, 41.42, 46.61, 47.24, 115.12, 116.26, 133.33, 143.08, 148.60, 153.62, 160.80, 169.64; ESI-MS *m*/*z*: 285 ($M^+$+H).

*Ligand **2b***: α,β-Unsaturated ketone **6** and pyridinium iodide **8** were used. Purification by flash column chromatography gave 48% yield (0.19 g) of **2b**. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.68 (s, 3H), 1.33 (d, $J = 9.9$ Hz, 1H), 1.40 (s, 3H), 2.27–2.36 (m, 1H), 2.51 (s, 3H), 2.64–2.88 (m, 1H), 2.97 (d, $J = 2.4$ Hz, 2H), 3.07 (t, $J = 5.7$ Hz, 1H), 6.92 (s, 1H), 7.49 (d, $J = 7.8$ Hz, 1H), 7.93 (d, $J = 7.8$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 17.34, 21.26, 26.10, 31.03, 31.37, 39.24, 40.30, 50.21, 115.12, 117.22, 131.49, 135.77, 147.43, 153.85, 161.33, 166.38; ESI-MS *m*/*z*: 271 ($M^+$+H).

*Ligand **3a***: α,β-Unsaturated ketone **5** and pyridinium iodide **9** were used. Purification by flash column chromatography gave 0.21 g (52%) of **3a**. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.66 (s, 3H), 1.31 (d, $J = 10.8$ Hz, 1H), 1.40 (d, $J = 7.2$ Hz, 3H), 1.43 (s, 3H), 2.15–2.19 (m, 1H), 2.54–2.61 (m, 1H), 2.72–2.80 (m, 1H), 3.18–3.21 (m, 1H), 4.15 (s, 3H), 6.95 (s, 1H), 7.09 (s, 1H), 7.28 (d, $J = 9.3$ Hz, 1H), 7.83 (d, $J = 8.1$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 18.10, 20.81, 26.28, 26.83, 28.61, 38.84, 40.18, 46.76, 47.10, 119.51, 123.68, 127.71, 133.46, 140.67, 145.65, 147.81, 159.30; ESI-MS *m*/*z*: 268 ($M^+$+H).

*Ligand **3b***: α,β-Unsaturated ketone **7** and pyridinium iodide **9** were used. Purification by flash column chromatography gave 28% yield (0.11 g) of **3b**. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.68 (s, 3H), 1.33 (d, $J = 9.6$ Hz, 1H), 1.44 (s, 3H), 2.30–2.37 (m, 1H), 2.70–2.77 (m, 1H), 2.89–2.92 (m, 1H), 2.97–3.00 (m, 2H), 4.11 (s, 3H), 6.94 (s, 1H), 7.09 (s, 1H), 7.50 (d, $J = 7.8$ Hz, 1H), 7.91 (d, $J = 8.1$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 21.51, 26.07, 30.80, 31.19, 36.05, 40.22, 40.32, 50.42, 120.47, 123.64, 127.83, 129.02, 135.77, 145.61, 146.46, 164.92; ESI-MS *m*/*z*: 254 ($M^+$+H).

*Ligand **4a***: α,β-Unsaturated ketone **5** and pyridinium iodide **10** were used. Purification by flash column chromatography gave 48% yield (0.19 g) of **4a.** $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.69 (s, 3H), 1.34 (d, $J = 9.9$ Hz, 1H), 1.45 (s, 3H), 1.48 (d, $J = 6.9$ Hz, 3H), 2.14–2.25 (m, 1H), 2.57–2.64 (m, 1H), 2.78–2.85 (m, 1H), 3.24–3.34 (m, 1H), 7.35 (d, $J = 7.5$ Hz, 1H), 8.04 (d, $J = 7.8$ Hz, 1H), 8.55–8.59 (m, 2H), 9.68 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 18.16, 20.88, 26.25, 28.50, 38.85, 41.39, 46.64, 47.20, 118.24, 133.53, 143.05, 143.20, 143.34, 143.62, 151.18, 151.82, 160.73; ESI-MS *m*/*z*: 266 ($M^+$+H).

*Ligand **4b***: α,β-Unsaturated ketone **6** and pyridinium iodide **10** were used. Purification by flash column chromatography gave 48% yield (0.19 g) of **4b**. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.70 (s, 3H), 1.34 (d, $J = 10.2$ Hz, 1H), 1.45 (s, 3H), 2.33–2.39 (m, 1H), 2.73–2.80 (m, 1H), 3.00–3.04 (d, $J = 2.4$ Hz, 1H), 3.10–3.14 (t, $J = 5.7$ Hz, 1H), 7.55 (d, $J = 7.8$ Hz, 1H), 8.10–8.13 (d, $J = 7.8$ Hz, 1H), 8.54–8.58 (d, $J = 12.3$ Hz, 2H), 9.60 (s, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 21.27, 25.96, 30.74, 31.28, 39.11, 39.97, 50.32, 119.24, 131.64, 136.03, 143.14, 143.49, 143.62, 149.77, 151.72, 166.32 ppm; ESI-MS *m*/*z*: 252 ($M^+$+H).

### 3.9. Preparation of palladium allyl complex $[Pd(\eta^3 - C_3H_5)(1a)]^+PF_6^-$

The $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ complex (40 mg, 0.11 mmol) and ligand 1a (62 mg, 0.23 mmol) were dissolved a in $CH_2Cl_2$ (6 mL) solution at room temperature and a THF solution (5 mL) of $AgPF_6$ (60 mg, 0.24 mmol) was then added. After reaction for 10 min, the resulting solution was filtered through a Celit-packed column. The filtrate was washed with saturated NaCl solution. After drying with $MgSO_4$ and evaporation of solvent, the $[Pd(\eta^3 - C_3H_5)(1a)]^+PF_6^-$ complex was isolated as a white solid in 60% yield (78 mg). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.71 (s, 3H), 1.34 (d,

$J = 6.6$ Hz, 1H), 1.45–1.47 (m, 6H), 2.25–2.38 (m, 1H), 2.62–2.29 (m, 1H), 2.96 (t, $J = 5.4$ Hz, 1H), 3.17–3.29 (m, 3H), 4.42–4.45 (m, 2H), 5.67–5.82 (m, 1H), 7.60 (d, $J = 7.8$ Hz, 1H), 7.82 (s, 1H), 7.93 (d, $J = 7.8$ Hz, 1H), 8.08 (d, $J = 3$ Hz, 1H).

### 3.10. Preparation of copper chloride complexes

#### 3.10.1. Cu(3b)$Cl_2$ complex

A solution of ligand 3b (25 mg, 0.1 mmol) in $CH_2Cl_2$ (5 mL) was added to a solution of $CuCl_2u2H_2O$ (18 mg, 0.1 mmol) in EtOH (5 mL). The mixture was stirred for 2 h. Greenish blue solution was observed immediately. The solvent was evaporated and the resulting solid was recrystallized from $CH_2Cl_2$/diethyl-ether mixture to give 65% yield (25 mg) of Cu(3b)$Cl_2$ complex as a yellow solid. Anal. Calcd for $CuN_3Cl_2C_{16}H_{19}$: C, 49.56; H, 4.94; N, 10.84. Found: C, 48.47; H, 4.95; N, 10.69%. ESI-MS *m/z*: 351 (M−Cl).

### 3.11. General procedures for Pd-catalyzed allylic substitution

The [Pd($\eta^3$-$C_3H_5$)Cl]$_2$ complex (4 mg, 0.01 mmol) and the chiral ligand (0.04 mmol) were dissolved in dry $CH_2Cl_2$ solvent (1 mL) under $N_2$ and stirred for 1 h at room temperature. The racemic 1,3-diphenyl-2-propenyl acetate (0.10 g, 0.4 mmol) in dry $CH_2Cl_2$(1 mL) was added dropwise into the solution. The dimethylmalonate (0.105 mL, 1.2 mmol), BSA (0.37 mL, 1.2 mmol) and acetate salts (1.4 mg, 3.5 mol%) were added sequentially to the reaction mixture at room temperature. The reaction was then monitored by TLC. After complete reaction, the mixture was diluted with $H_2O$ and $CH_2Cl_2$. The organic layer was separated, washed with brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure. The product of dimethyl 1,3-diphenylprop-2-enylmalonate was purified by flash column chromatography. The e.e. were determined by HPLC (Daicel chiralcel-OD column; mobile phase: 2-propanol/hexane = 1/100, flow rate: 0.5 mL/min, UV 254 nm, $t_R$: 28.5 min, $t_S$: 31.5 min).

### 3.12. General procedures for Cu-catalyzed cyclopropanation

To a two-neck round-bottom flask were added Cu(OTf)$_2$ (7 mg, 0.02 mmol) and ligand (0.022 mmol) with $CH_2Cl_2$ (2 mL) under nitrogen and then stirred for 2 h at room temperature. Styrene (0.46 mL, 4 mmol) and ethyl diazoacetate (23 μL, 0.2 mmol) were added and the mixture was warmed in an oil bath (40 °C) for 30 min. A solution of ethyl diazoacetate (0.11 mL, 1 mmol) in $CH_2Cl_2$ (0.5 mL) was added to the reaction mixture over a period of 4 h using a syringe pump. After the addition, the mixture was allowed to stir for 16 h at room temperature. The reaction was work-up by removing the solvent and the crude product obtained was purified by flash column chromatography (petroleum ether/EtOAc). The enantioselectivities of the cyclopropanes were determined by HPLC with Daicel Chiralcel OJ column. Absolute configurations were determined by comparing the order of elution with samples of known configurations [18]. The diastereoselectivities (*trans*/*cis* ratio) were measured by GC with Ultra 2-crosslinked 5% PhMesilcone (25 m × 0.2 mm × 0.33 μm) column.

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## Appendix A. Supplementary data

CCDC 606930 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk. CCDC . Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2006.06.050.

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