Bifunctional N-heterocyclic carbene ligands for Cu-catalyzed direct C–H carboxylation with CO$_2$†

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Diethylene glycol-functionalized imidazo[1,5-α]pyridin-3-ylidene (DEG-ImPy) have been developed as bifunctional N-heterocyclic carbene ligands. The DEG-ImPy Cu(I) complexes efficiently catalyzed the direct C–H carboxylation of benzoxazole with CO$_2$, showing higher isolated yields than those with the $N,N'$-(2,6-diisopropylphenyl)imidazolylidene Cu catalyst.

Introduction

The use of N-heterocyclic carbenes (NHCs) as strong σ-donating ligands has become increasingly popular in homogeneous catalysis.1 Numerous structural variations on the prototypical imidazolylidene skeleton have been used to modulate the electronic and steric properties of NHC ligands. Imidazo[1,5-α]pyridin-3-ylidene (ImPy) ligands, first developed by Glorius2 and Lassaletta3 in 2005, are a rigid bicyclic variant of NHCs. ImPy ligands are strong σ-donors3,4 as the extended π-system can increase the electron density at the carbene center.5 Substituents on the bicyclic ImPy can be projected into the metal coordination sphere, often resulting in bonding interactions with the metal.6,7 Synthesis of ImPy precursors is concise and often allows late-stage incorporation of diverse functional substituents.7 Owing to this feature, a number of ImPy-metal catalysts have been developed for various organic transformations (Fig. 1).8 We envision that ImPy ligands could serve as a versatile framework for bifunctional NHC ligands.9 Polyether units such as polyethylene glycol (PEG) are known as a CO$_2$-philic building block and have been utilized in ionic liquids for CO$_2$ capture10 and as catalysts for CO$_2$ conversion.11 Thus we were wondering whether introduction of diethylene glycol unit (DEG) into the ligand scaffold could render the ImPy bifunctional. Herein, we report the synthesis of diethylene glycol-functionalized imidazo[1,5-α]pyridin-3-ylidene (DEG-ImPy) copper complexes and their application in direct C–H carboxylation of benzoxazoles with CO$_2$. DEG-ImPy Cu exhibits higher catalytic activity than non-functionalized NHC–Cu catalysts.

Results and discussion

Synthesis of ligands and catalysts

Synthesis of imidazopyridinium salts (4a–4g) was accomplished following a modified procedure of the reported method (Scheme 1). 6-Mesitylpicolinaldehyde (3) was prepared by Bouveault aldehyde synthesis,12 followed by Suzuki–Miyaura coupling.13 ImPy precursors (4a–4g) were then synthesized from the functionalized anilines, formalin, and aldehyde 3 by Aron’s method.7 Among the synthesized ImPy ligands, imidazopyridinium salts (4a–4c, 4g) were converted to the corresponding ImPy–copper(i) complexes (5a–5c, 5g) by the reaction with copper chloride(i) in the presence of sodium tert-butoxide or through Ag transmetalation in reasonable isolated yields.

![Fig. 1 Representative examples of metal complexes containing imidazo[1,5-α]pyridin-3-ylidene (ImPy) ligands.](image-url)
X-ray crystallography

The structure of ImPy–Cu complex 5a and 5g were determined by X-ray diffraction analysis (Fig. 2). As with recently reported ImPy–copper complexes,\(^5\) geometry of both complexes is linear; C(1)–Cu(1)–Cl(1) is 173.5(1)° (5a) and 173.7(4)° (5g). In case of 5g, the mesityl group is in close proximity to the Cu metal center as the observed atom distance Cu(1)–C(8) is shorter (2.887 Å) than that of 5a (2.957 Å). The aryl group on the nitrogen atom in 5a is oriented nearly perpendicular to the NHC plane, resulting in a dihedral angle of 80.64° whereas the dihedral angle between the ImPy plane and the DEG-phenyl in 5g is 50.84°.

Catalytic properties of ImPy–Cu complexes

With the various ImPy ligands in hand, the catalytic activities of the ImPy–Cu complexes were evaluated in direct C–H carboxylation of benzoxazole using CO \(_2\) (Table 1). Synthetic utilization of carbon dioxide (CO \(_2\)) as a sustainable C1 feedstock has attracted much attention recently.\(^14\) Catalytic direct C–H carboxylation with CO \(_2\) is an atom-economical transformation that affords carboxylic acid derivatives. Various C–H bonds of alkynes,\(^13\) alkenes/arenes,\(^16,17\) and alkanes,\(^18\) can be substituted with CO \(_2\).H. Coinage–metal complexes with NHC ligands are efficient catalysts for direct C–H carboxylation. Following the procedure reported in the literature,\(^16\) initial studies were carried out using isolated NHC–Cu complexes (entries 1–4). ImPy–Cu complex with a 2,6-diisopropyl phenyl substituent (5e) showed higher catalytic activity in producing the corresponding ester than IPrCuCl under the same conditions (entry 4 vs. entry 1). It was examined whether the catalyst could be generated in situ from CuCl and NHC–HCl salt under the same reaction conditions. In most cases, in situ-formed catalysts from CuCl and NHC ligands showed better yields than the isolated Cu complexes (entries 5–7 vs. entries 1–3). Note that in situ-generated Cu catalysts from alkyloxy-functionalized ImPy ligands exhibited very good yields (entries 10–12). While the hydroxy group (4d) was rather detrimental (entry 9), a methoxy group (4e and 4f) resulted in increased yield (entries 10 and 11). ImPy ligand bearing a diethylene glycol moiety (4g, DEG-ImPy) exhibited excellent activity and afforded the desired product in quantitative yield (entry 12).

Using the optimal DEG-ImPy ligand (4g), the heteroarene substrate scope of the direct C–H carboxylation was examined.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal salt</th>
<th>Ligand</th>
<th>Yield of 7a (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>IPr-CuCl‡</td>
<td>—</td>
<td>80</td>
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<tr>
<td>2</td>
<td>5a</td>
<td>—</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>5b</td>
<td>—</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>5c</td>
<td>—</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>CuCl</td>
<td>IPr-HCl</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>CuCl</td>
<td>4a</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>CuCl</td>
<td>4b</td>
<td>95</td>
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<td>8</td>
<td>CuCl</td>
<td>4c</td>
<td>81</td>
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<tr>
<td>9</td>
<td>CuCl</td>
<td>4d</td>
<td>92</td>
</tr>
<tr>
<td>10</td>
<td>CuCl</td>
<td>4e</td>
<td>94</td>
</tr>
<tr>
<td>11</td>
<td>CuCl</td>
<td>4f</td>
<td>94</td>
</tr>
<tr>
<td>12</td>
<td>CuCl</td>
<td>4g</td>
<td>99</td>
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\(‡\) Reaction conditions: benzoxazole (0.5 mmol), CuCl (5 mol%), ligand (5 mol%), KOtBu (1.15 equiv.), THF (2.5 mL), CO \(_2\) (1 atm), 80 °C, 14 h, then evaporation of THF under vacuum, DMF (2.5 mL), \(\text{C}_6\text{H}_5\text{Cl} (1.0 \text{ mmol}), 80 °C, 6 \text{ h}. \) Yields of the isolated product (average of two runs). IPrCuCl = 1,3-bis(2,6-diisopropylphenyl) imidazolium copper(i) chloride.
Conclusions

Diethylene glycol-functionalized imidazo[1,5-a]pyridin-3-ylidenes (DEG-ImPy) ligands have been developed as a bifunctional NHC ligand. Cu catalyst generated in situ with the DEG-ImPy·HCl salts efficiently catalyzed the direct C–H carboxylation of various heterocyclic compounds with CO₂, resulting in higher yields than those with the imidazolylidene carbene ligand (IPr). Further studies of DEG-ImPy ligands relating to cation-binding capabilities as well as application in other catalysis are currently under way in our laboratory.

Experimental sections

General remarks

All reactions were carried out under an inert argon atmosphere using the Schlenk technique or a glovebox. All reactions using CO₂ were conducted in a 30 mL Schlenk flask equipped with Teflon-valve. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL spectrometer, operating at 400 MHz or 300 MHz for ¹H NMR and at 100 MHz or 75 MHz for ¹³C NMR. All chemical shifts for ¹H and ¹³C NMR spectroscopy were assigned to residual signals from CDCl₃ (¹H) at 7.26 ppm and (¹³C) at 77.16 ppm, CD₂Cl₂ (¹H) at 5.32 ppm and (¹3C) at 53.84 ppm, or DMSO-d₆ (¹H) at 2.50 ppm and (¹³C) at 39.52 ppm. High resolution GC mass spectra were recorded using a JEOL JMS-700 MStation mass spectrometer. Infrared spectra were obtained on a Nicolet iS10 FT-IR spectrometer with an ATR unit and recorded in wave numbers (cm⁻¹).

Materials

Tetrahydrofuran (THF), dichloromethane (CH₂Cl₂), N,N-dimethylformamide (DMF) and diethyl ether (Et₂O) were dried under a positive pressure of dry nitrogen using a J. C. Meyer Solvent Distiller equipped with a cation System prior to use. Toluene and n-hexane were distilled from calcium hydride and ethanol was dried over 4 Å molecular sieves. Unless specified, all the other chemicals were purchased from Sigma-Aldrich Co., Acros Organics, TCI, Alfa Aesar, and Strem Chemicals Inc. and were used as received without further purification. Commercial carbon dioxide (99.99%) was purchased by Sinil Gas Co. and used without further purification. Benzoxazole, 5-methylbenzoxazole, and 5-chlorobenzoxazole were purchased and purified by flash column chromatography. Other benzoxazole derivatives and oxadiazole were synthesized as reported previously. 6-Bromopicolinaldehyde (2), 6-mesitylpicolinaldehyde (3), 4-Methoxy-2,6-dimethylaminine, IPr·HCl, and (IPr)CuCl were prepared according to the literature.

Catalyst preparation

2,5-Dimesityl imidazo[1,5-a]pyridinium chloride (4a). The procedure was modified from a report by Aron et al. ²,⁴,⁶-Tri-methylaniline (84.8 μL, 0.604 mmol), 6-mesitylpicolinaldehyde 3 (136 mg, 0.604 mmol), formalin (65.0 μL, 0.900 mmol) and 1.25 M HCl in EtOH (546 μL, 0.660 mmol) were added to dry...
EtOH (1.20 mL) and stirred at room temperature for 12 hours. The crude product was purified by flash column chromatography (CH₂Cl₂ : MeOH 10 : 1). The product was collected by reprecipitation using Et₂O and CH₂Cl₂ to obtain a product 4a (216 mg, 92%) as an ivory powder. ¹H NMR (400 MHz, CDCl₃): δ 9.30 (s, 1H), 8.87 (dd, J = 9.4 Hz, 1H), 7.93 (s, 1H), 7.46 (dd, J = 9.4, 6.8 Hz, 1H), 7.05 (m, 3H), 6.98 (s, 2H), 2.34 (s, 3H), 2.32 (s, 3H), 2.02 (s, 6H), 1.97 (s, 6H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 141.7, 141.6, 136.6, 133.3, 132.0, 129.7, 126.7, 126.6, 126.4, 120.7, 120.3, 118.8, 21.2, 21.2, 19.1, 17.2 ppm; IR (ATR): ν = 3058, 2919, 1652, 1610, 1553, 1154, 1034, 844, 829, 731, 679 cm⁻¹; HR-MS (EI): calcld for C₂₃H₂₄N₂O [M⁺] 431.2180 found 431.2170.

5-(Mesityl)-imidazo[1,5-a]pyridinum chloride (4c). The same method used in the synthesis of 4a, 4b (86%) was obtained as a white powder from 4-methoxy-2,5-dimesitylimidazo[1,5-a]pyridine 3. ¹H NMR (400 MHz, CDCl₃): δ 9.35 (s, 1H), 9.02 (m, 1H), 7.91 (s, 1H), 7.57-7.53 (m, 2H), 7.31 (m, 2H), 7.13 (d, J = 6.9 Hz, 1H), 1.07 (s, 2H), 2.35 (s, 3H), 2.09 (m, 2H), 2.03 (s, 6H), 1.25 (d, J = 6.8 Hz, 6H), 1.04 (d, J = 6.9 Hz, 6H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 144.9, 141.8, 137.0, 133.0, 132.9, 132.5, 132.2, 130.7, 129.7, 126.5, 125.9, 124.7, 121.5, 120.8, 120.6, 28.8, 24.7, 23.9, 21.3, 19.1 ppm; IR (ATR): ν = 3073, 3041, 2958, 2924, 2867, 1652, 1551, 1449, 1300, 1172, 1109, 853, 799, 754, 681 cm⁻¹; HR-MS (EI): calcld for C₂₃H₂₄N₂O [M⁺] 397.2643 found 397.2648.

5-(Mesityl)-imidazo[1,5-a]pyridinum chloride (4d). Compound 4d was prepared analogously to 4a. 4d was synthesized from 2-aminoenophene and 6-mesitylimidazole 3. The crude product was purified by recrystallization using Et₂O and CH₂Cl₂ to obtain a product 4d (quant.) as an ivory powder. ¹H NMR (400 MHz, DMSO-d₆): δ 11.46 (br s, 1H), 9.38 (s, 1H), 8.70 (s, 1H), 8.01 (d, J = 9.3 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.47 (dd, J = 9.3, 7.0 Hz, 1H), 7.39 (m, 2H), 7.18 (d, J = 6.8 Hz, 1H), 7.10 (s, 2H), 6.98 (m, 1H), 2.33 (s, 3H), 2.03 (s, 6H) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ 151.1, 139.8, 137.1, 133.1, 131.4, 129.7, 128.9, 127.0, 126.6, 125.8, 125.1, 122.5, 119.3, 119.1, 117.4, 117.3, 115.9, 20.8, 18.9 ppm; IR (ATR): ν = 3179, 3166, 3179, 2948, 2688, 2571, 1654, 1607, 1551, 1458, 1464, 1350, 1227, 1173, 805, 752, 654 cm⁻¹; HR-MS (FAB): calcld for C₂₃H₂₄N₂O [M⁺] 329.1654 found 329.1656.

5-(Mesityl)-imidazo[1,5-a]pyridinum chloride (4e). The same method used in the synthesis of 4d, 4e (quant.) was obtained as a white powder from 2-methoxyenophile and 6-mesitylimidazole 3. ¹H NMR (400 MHz, CDCl₃): δ 9.46 (d, J = 6.0 Hz, 1H), 8.58 (dd, J = 9.3, 3.8 Hz, 1H), 8.27 (s, 1H), 7.90 (m, 1H), 7.50 (t, J = 8.4 Hz, 1H), 7.35 (t, J = 9.3 Hz, 1H), 7.18 (t, J = 9.2 Hz, 1H), 7.08 (m, 3H), 6.97 (d, J = 6.8 Hz, 1H), 3.82 (s, 3H), 2.37 (s, 3H), 2.07 (s, 6H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 151.5, 141.4, 137.1, 133.1, 132.4, 131.1, 129.5, 126.6, 124.9, 123.4, 122.3, 119.9, 119.8, 118.0, 112.6, 56.4, 21.2, 19.3 ppm; IR (ATR): ν = 3187, 2995, 2918, 2858, 1654, 1604, 1556, 1518, 1451, 1261, 1130, 1022, 850, 760, 654 cm⁻¹; HR-MS (FAB): calcld for C₂₃H₂₄N₂O [M⁺] 434.1810 found 434.1802.

5-Mesityl-2-(4-methoxy-2,6-dimethylphenyl)-2H-imidazol[1,5-a]pyridinium chloride (4f). With the same method used in the synthesis of 4a, 4f (86%) was obtained as a white powder from 4-methoxy-2,6-dimethylaniline and 6-mesitylimidazole 3.

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17.7 ppm (signal from the carbon bonded metal was not detected); IR (ATR): ν = 3136, 2953, 2915, 2835, 1615, 1491, 1441, 1359, 1315, 1196, 1053, 831, 792, 784, 736, 682 cm⁻¹; HR-MS (EI): calecd for C₂₃H₂₈N₄CuClO₃ [M] 528.1241 found 528.1221.

2-(2-Methoxyethoxy)ethyl 4-methylbenzenesulfonate (8). Diethylen glycol monomethyl ether (6.01 g, 50 mmol), p-toluene sulfonamide (11.4 g, 60 mmol), and pyridine (8.09 mL, 100 mmol) were combined at 0 °C, then stirred for 6 h at the same temperature. The reaction mixture was extracted with Et₂O and water, and washed with 1 N HCl. The organic phase was dried over anhydrous MgSO₄, filtered, and concentrated in a vacuum. The crude product was purified by flash column chromatography (n-hexane : ethyl acetate 3 : 1) to give a product 8 (90%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.79 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 4.15 (m, 2H), 3.67 (m, 2H), 3.56 (m, 2H), 3.46 (m, 2H), 3.33 (s, 3H), 2.43 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): 144.8, 132.8, 129.8, 127.9, 71.7, 70.6, 69.2, 68.6, 59.0, 21.6 ppm.

2-(2-Methoxyethoxy)ethoxy)aniline (9). To a solution of 2-nitrophenol (139 mg, 1.00 mmol) and potassium carbonate (138 mg, 1.00 mmol) in DMF (3.50 mL) was added a solution of 2-(2-methoxyethoxy)4-methylbenzenesulfonate 8 (274 mg, 1.00 mmol) in DMF (2.00 mL) and allowed to reflux overnight. Afterward, the mixture was cooled to room temperature. The solvent was evaporated and the residue was dissolved in ethyl acetate. The organic phase was washed with water, dried over anhydrous MgSO₄, then filtered and concentrated in a vacuum. The crude mixture was subjected to hydrogenation over Pd/C in MeOH (8.00 mL) at room temperature under H₂ atmosphere for 24 h. Pd/C was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (n-hexane : ethyl acetate 1 : 1) to give a product 9 (84%, 2 steps) as a dark orange oil. ¹H NMR (400 MHz, CDCl₃): δ 6.82-6.78 (m, 2H), 6.73-6.67 (m, 2H), 4.16 (m, 2H), 3.86 (m, 2H), 3.71 (m, 2H), 3.57 (m, 2H), 3.39 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 146.1, 136.8, 121.5, 118.0, 115.0, 112.5, 71.7, 70.4, 69.6, 68.0, 58.9 ppm; IR (ATR): ν = 3458, 3358, 3058, 2924, 2876, 2822, 2862, 1616, 1505, 1458, 1277, 1218, 1105, 1053, 927, 848, 738 cm⁻¹; HR-MS (EI): calecd for C₁₁H₁₃N₂O₃ [M] 211.12 found 211.1209.

General procedure for catalytic direct C–H carboxylation with CO₂

General procedures for ImPy Cu-catalyst generated in situ for direct C–H carboxylation of heterocyclic compound. General procedures were adapted from those used by Hou et al.¹⁶e Ligand (5 mol%), copper chloride(Ⅲ) (2.50 mg, 5 mol%), and potassium tert-butoxide (65.1 mg, 0.580 mmol) were added to a 30 mL Schlenk flask equipped with Teflon-valve in a glove box. THF (2.50 mL) was added to the reaction flask and stirred at room temperature for 4 hours. Under an Ar atmosphere, a heterogeneous compound (59.6 mg, 0.500 mmol) was added to the reaction mixture. The mixture was degassed through three freeze–pump–thaw cycles and CO₂ (1 atm) was charged into the reaction flask. The sealed Schlenk flask was stirred at 80 °C for 14 hours. After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure. DMF (2.50 mL) and 1-iodohexane (0.150 mL, 1.00 mmol) were

[The text continues with detailed chemical reactions and spectroscopic data.]
added to the mixture under an Ar atmosphere and stirred at 80 °C for 6 hours. The reaction mixture was dissolved in ethyl acetate and washed with water. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in a vacuum. The crude product was purified by flash column chromatography (n-hexane : ethyl acetate 8 : 1) to give the product.

**General procedures for ImPy Cu-catalyzed carboxylation of benzoxazole with CO₂.** ImPy-Cu complexes (5 mol%) and potassium tert-butoxide (61.7 mg, 0.550 mmol) were added to a 30 mL Schlenk flask equipped with Teflon-valve in a glove box and THF (2.50 mL) was charged into the reaction flask. Benzoxazole (59.6 mg, 0.500 mmol) was added and the mixture was degassed through three freeze–pump–thaw cycles. CO₂ (1 atm) was charged into the reaction flask. The reaction mixture was stirred at 80 °C for 14 hours. After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure. DMF (2.50 mL) and 1-iodohexane (0.150 mL, 1.00 mmol) were added to the mixture under an Ar atmosphere and stirred at 80 °C for 6 hours. Subsequent procedures remained the same as described above.

All compounds were reported materials except for 5-methoxy-benzoxazole-2-carboxylic acid hexyl ester (7e).

5-Methoxy-benzoxazole-2-carboxylic acid hexyl ester (7e).

Yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 7.49 (dd, J = 9.0, 2.3 Hz, 1H), 7.25 (t, J = 2.4 Hz, 1H), 7.08 (dt, J = 9.1, 2.5 Hz, 1H); 4.43 (td, J = 6.8, 2.0 Hz, 2H), 3.82 (d, J = 2.3 Hz, 3H), 1.85–1.77 (m, 2H), 1.43–1.28 (m, 6H), 0.85 (m, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 158.2, 156.6, 153.4, 145.6, 141.5, 118.0, 112.0, 103.5, 67.3, 56.0, 31.4, 28.5, 25.5, 22.5, 14.0 ppm; IR (ATR); ν r = 2932, 2856, 1732, 1609, 1544, 1484, 1438, 1325, 1260, 1205, 1152, 1025, 853, 815 cm⁻¹; HR-MS (EI): calcd for C₁₅H₁₉NO₄ [M] 277.1314 found 277.1312.

**Conflicts of interest**

There are no conflicts to declare.

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**Notes and references**


