From Prochiral N-Heterocyclic Carbenes to Optically Pure Metal Complexes New Opportunities in Asymmetric Catalysis


To cite this version:
Lingyu Kong, Jennifer Morvan, Delphine Pichon, Marion Jean, Muriel Albalat, et al.. From Prochiral N-Heterocyclic Carbenes to Optically Pure Metal Complexes New Opportunities in Asymmetric Catalysis. Journal of the American Chemical Society, 2020, 142 (1), pp.93-98. 10.1021/jacs.9b12698. hal-02442228

HAL Id: hal-02442228
https://univ-rennes.hal.science/hal-02442228
Submitted on 24 Jan 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
From Prochiral N-Heterocyclic Carbenes (NHC) to Optically Pure Metal Complexes: New Opportunities in Asymmetric Catalysis

Lingyu Kong,† Jennifer Morvan,† Delphine Pichon,‡ Marion Jean,§ Muriel Albalat,§ Thomas Vives,† Sophie Colombel-Rouen,‡ Michel Giorgi,§ Vincent Dorcet,‡ Thierry Roisnel,‡ Christophe Crévisy,† Didier Nuel,§ Paola Nava,§ Stéphane Humbel,§ Nicolas Vanthuyne,§ Marc Mauduit*,† and Hervé Clavier*§

Supporting Information Placeholder

ABSTRACT: Well-defined optically pure Transition Metal-complexes bearing C1- and C2-symmetric N-Heterocyclic Carbene (NHC) ligands were prepared from prochiral NHC precursors. As predicted by DFT calculations, our strategy capitalizes on the formation of a metal-carbene bond which induces an axis of chirality. Configurationally stable atropisomers of various NHC containing TM-complexes were isolated by preparative HPLC on a chiral stationary phase in good yields and excellent optical purities (up to 99.5% ee). The carbene transfer from an optically pure Cu-complex to gold or palladium center reveals, for the first time, a full stereoretentive mechanism for the transmetalation. The potential of these new chiral TM-complexes was illustrated in asymmetric catalysis with up to 98% ee.

Due to their unique topology along with a highly modular steric environment around the metal, chiral N-heterocyclic carbenes (NHCs) rapidly emerged as stereo-directing ligands.† Since the first report of a highly enantioselective reaction in 2001,‡ chiral NHCs were intensively studied in enantioselective catalysis with resounding breakthroughs.§ Advantageously, their versatile and easy synthetic access led to the development of a plethora of chiral NHCs containing various elements of symmetry. Among them, chiral Transition Metal (TM) complexes containing C2- or C1-symmetric NHC precursors 1 and 2 proved to be quite efficient, thanks to the effective chiral relay from the stereogenic substituents of carbene backbone to the N-aryl ortho-substituent that induces a trans-relationship (Figure 1,a). The resulting chiral environment close to the metal enabled to reach remarkable stereo-inductions (up to >99% ee) in numerous asymmetric catalytic transformations.§ Despite these notable achievements, the technology remains somewhat costly as optically pure starting materials are required (in both enantiomers if possible) for the synthesis of NHCs.

Consequently, reducing the cost of chiral technology remains a longstanding goal for chemists. Moreover, the chiral relay generates a mismatch effect which might be detrimental to chiral inductions.† We report herein the synthesis of many optically pure (>98% ee) well-defined C1- and C2-symmetric NHC-TM complexes containing an axial chirality, which may be readily synthesized from prochiral NHC precursors (Figure 1,b). The chiral resolution of resulting stable atropisomers is efficiently achieved by HPLC on a preparative scale.§

(a) The chiral relay strategy for C1- and C2-symmetric chiral NHC precursors

(b) New access to chiral TM-complexes from prochiral NHCs (This work):

Figure 1. Design of chiral NHC-TM catalysts
These new C1- and C2-symmetric chiral Cu- and Pd-complexes display excellent performances in asymmetric catalysis (up to 98% ee). Importantly, and for the first time, we demonstrate that the carbene transfer from an optically pure Cu-complex to gold or palladium center occurred with a full stereoretentivity giving experimental insights to the NHC transmetalation mechanism.

Our study began with the design of prochiral NHC precursors, i.e. imidazolium salts 3-Cl (Figure 2). Given the infinite substitution patterns that could be considered either on the carbene backbone or on N-aryl substituents, prior theoretical calculations appeared useful to determine with accuracy the expected rotational barriers of the N-aryl bond after coordination to copper(I) chloride (>93 kJ mol⁻¹; t₁/₂ >1000 s at 25 °C to observe atropisomers, but ideally >110 kJ mol⁻¹; t₁/₂ >12 days at 25 °C). With a bulky isopropyl group on ortho position of the aryl group (Cu-3a), the rotation barrier values are too low to obtain stable atropisomers (Figure 2a; ΔG°C= 51.0 kJ mol⁻¹ and ΔG°(BB) = 42.6 kJ mol⁻¹). Of note, despite the methyl groups on the backbone, a methyl substituent in ortho position of the aryl group (Cu-3c) did not prevent the arylation rotation (Figure 2c, ΔG°C= 94.4 kJ mol⁻¹ and ΔG°(BB) = 123.1 kJ mol⁻¹). In order to assess experimentally these data obtained from theoretical calculations, Cu-3b complex was synthesized from the prochiral imidazolium salt 3b-Cl (Scheme 1, see Supporting Information; SI). The deprotonation of the latter by K₂CO₃ in the presence of CuCl afforded the desired complex Cu-3b in 57% yield after silica gel purification. The HPLC analysis on chiral stationary phase confirmed clearly that stable atropisomers were formed in a racemic mixture (Scheme 1).

**Scheme 1. Synthesis of optically pure complex Cu-3b from prochiral imidazolium 3b-Cl**

![Scheme 1](image)

**Figure 2. DFT calculations of rotational barriers for NHC-copper complexes Cu-3a,3b,3c.** ΔG°C and ΔG°(BB) are the values of rotation barriers on backbone (BB) and copper (Cu) sides, respectively.

Nevertheless, the backbone substitution with methyl groups (Cu-3b) leads to a substantial increase of the rotation barriers values up to expect configurationally stable enantiomers (Figure 2b, ΔG°C= 116.4 kJ mol⁻¹ and ΔG°(BB) = 144.1 kJ mol⁻¹). Of note, despite the methyl groups on the backbone, a methyl substituent in ortho position of the ary group (Cu-3c) could not prevent the arylation rotation (Figure 2c, ΔG°C= 94.4 kJ mol⁻¹). Thanks to the robustness of copper-NHC complexes toward silica gel, the chiral resolution of (rac)-Cu-3b by HPLC on a preparative scale (80 mg, flow-rate = 5 mL min⁻¹; see SI) enabled to isolate both atropisomers (+)-Cu-3b and (−)-Cu-3b in excellent yields and remarkable >99% optical purities. Moreover, the Electronic Circular Dichroism (ECD), affording chiroptical properties of the copper complex, showed expected mirror-image spectra for both enantiomers (see SI, Figure S4). X-ray diffraction analysis of the second eluted atropisomers (+)-Cu-3b confirmed its structure but also enabled to determine its absolute configuration (S, Scheme 1). Furthermore, kinetic of enantiomerization of (S)-Cu-3b in 1,2-dichloroethane at 83.5 °C gave access to the experimental rotation barrier value (ΔG° = 117.2 kJ mol⁻¹) which fits with the predicted lowest value (ΔG° = 116.5 kJ mol⁻¹, see Figure 2b,b). This validates the use of theoretical calculations as a reliable tool to design the NHC structures.

We next turned our attention to the synthesis of other optically pure atropisomeric NHC transition metal complexes. On this concern, the transmetalation represents a fundamental organometallic reaction as numerous transition-metal complexes were and are synthesized via this process. Furthermore, the elucidation of its mechanism, notably when coinage NHC-TM complexes are involved, remains a longstanding goal for organometallic chemists. The stable optically pure atropisomers of copper-NHC complexes, in which the axis of chirality is induced by the metal-carbene bond, represents an oppor-
tunity to generate other TM-complexes and to gain valuable insights about the mechanistic route of transmetalation (vide infra). In that respect, the optically pure \( \text{(S)}_3\)\(+\)-Cu-3b complex (>99.5% ee) was treated with AuCl-SMe₂ complex in dichloromethane at 40 °C over 2 h (Scheme 2, a). To our delight, the corresponding gold complex Au-3b was isolated in quantitative yield. HPLC analysis confirmed the high enantiopurity of the newly formed gold complex (>99.5% ee) attesting that no racemization occurred during the transmetalation.

**Scheme 2. Stereoretentive transmetalation affording optically pure gold and palladium complexes**

![Diagram of Scheme 2](image)

\( ^{\text{a}}\text{Determined by chiral-stationary phase HPLC analysis.}\)

Moreover, X-ray diffraction analysis allowed us to confirm the complex structure and determine its absolute configuration \( \text{(S)}_3\). Similarly, the transmetalation starting from \( \text{(R)}_3\)\(\text{(-)}\)-Cu-3b afforded the corresponding gold enantiomer \( \text{(R)}_3\)\(\text{(-)}\)-Au-3b in quantitative yield and full optical purity, indicating unambiguously the stereoretentivity of the transmetalation (Scheme 2, b). Importantly the rotation barriers of Au-3b were assessed both by DFT calculations \( (\Delta \text{G}^0=\text{exp}) = 145.5 \text{ kJ mol}^{-1} \) and \( \Delta \text{G}^0=\text{cal} = 158.5 \text{ kJ mol}^{-1} \) and experimentally \( (\Delta \text{G}^0 = 142.4 \text{ kJ mol}^{-1} \text{ at } 132^\circ \text{C in chlorobenzene}) \), showing their enhancement over the analogous Cu-complex. The transmetalation process was then successfully extended to \( \pi\)-allyl palladium chloride (Scheme 2, c). Nevertheless, a prolonged reaction time (24 h) was required to reach a good 86% isolated yield. The optical purity of the newly formed Pd-complex (98% ee) was confirmed by HPLC analysis attesting that no racemization occurred during the transmetalation. In order to shorten the reaction time, the media was heated up to 80 °C. Satisfactory, similar isolated yields could be reached with a duration dropping to 2 h. However, a slight erosion of the optical purity was observed from 95% ee at 40 °C to 81% ee at 80 °C. This behavior could be relied to a racemization of the starting copper complex occurring at this temperature. Indeed, the rotation barriers of Pd-3b obtained from DFT calculations \( (\Delta \text{G}^0=\text{exp}) = 133.4 \text{ kJ mol}^{-1} \) and \( \Delta \text{G}^0=\text{cal} = 159.4 \text{ kJ mol}^{-1} \) and experimentally \( (\Delta \text{G}^0 = 131.5 \text{ kJ mol}^{-1} \text{ at } 132^\circ \text{C in chlorobenzene}) \) are higher than for Cu-3b. \( \text{(R)}_3\)\(\text{(-)}\)-Cu-3b is quite stable at 40 °C with a half-life time of 22 days, but at higher temperatures, the enantiomerization occurs rapidly \( (t_{1/2} = 3 \text{ h at } 80^\circ \text{C}) \). Regarding palladium and gold counterparts, they show greatly higher stabilities, even at 80 °C, with half-life times up to 15 days and 2 years respectively. Considering the aforementioned experimental results, a hypothetic reaction pathway for the transmetalation process is depicted in Figure 4. First, the observed stereoretentivity supports that an associative pathway could occur for the transmetalation of coinage NHC-TM complexes (Figure 3, A).

**Figure 3. Proposed associative (A) vs dissociative (B) transmetalation pathway.**

Indeed, a dissociative pathway (Figure 3, B) that would involve a transient free carbene seems incompatible with stereoretention as partial to full racemization could happen due to the free rotation around the N-Aryl bond, as demonstrated by DFT calculations with low values for rotational barriers on free NHC \( (\Delta \text{G}^0=\text{free}) = 60.9 \text{ kJ mol}^{-1} \text{ at } 40^\circ \text{C}) \). Second, considering the steric hindrance within the metal coordination sphere, a four-center transition state is suspected for the associative pathway, probably in the less sterically hindered pocket in opposite side to that of \( \pi\)-aryl substituents (Figure 3, A). DFT calculations related to the formation of Au-3b from Cu-3b are currently underway to provide useful information regarding the transmetalation pathway. Of note, Au-3b and Pd-3b could be also prepared as heterochiral complexes from the corresponding imidazolium and then efficiently separated by chiral HPLC on preparative scale.
Following the aforementioned protocol depicted in scheme 1, various optically pure C-centered Cu-complexes were synthesized from NHC precursors 3b,d-h featuring bulky ortho-substituents (Scheme 3). In all cases, stable atropisomeric complexes were formed and each enantiomer was isolated in moderate to excellent yields and high optical purities. Moreover, the absolute configuration of each complex was assigned via X-ray diffraction analysis.6 The methodology was then extended to synthesis of C-centered NHC complexes from symmetric NHC precursors 4a-c (Scheme 4). Nevertheless, the formation of meso complexes could complicate the chiral HPLC resolution in addition to lower the quantity of expected chiral complexes. Indeed, with imidazolium 4a-CI and 4a-BF₃, meso and heterochiral complexes Cu-4a and Pd-4a were respectively isolated with ratios of 1:1.8 and 2:2:1 (Scheme 4). Fortunately, the preparative chHPLC allowed their efficient separations and the expected C-centered homochiral Pd-4a and Cu-4a complexes were isolated in moderate to good yields (27-34%) and remarkable optical purities (>99.5% ee), highlighting the versatility of the concept. Heterochiral salts could easily be separated from the meso stereoisomers and used to prepare complexes Pd-4b and Pd-4c, which were isolated free of meso isomers, and very efficiently resolved on preparative chHPLC. For instance, both enantiomers of Pd-4b were separated with 91% yield on 580 mg-scale in only 3 hours. DFT calculations confirmed that an additional ortho-substituent, even a fluorine, is sufficient to restrict the aryl rotation along the N-C bond which leads to configurationally stable NHC precursors (lowest rotation barriers: for 4a-BF₃: $\Delta G^\circ_H$ = 69.7 kJ mol⁻¹; for 4b-BF₃: $\Delta G^\circ_H$ = 155.9 kJ mol⁻¹; for 4c-BF₃: $\Delta G^\circ_H$ = 108.7 kJ mol⁻¹).17

**Scheme 3. Library of optically pure C-centered NHC-copper complexes**

\[
\text{Cu-3d (70% yield)} \quad \text{Cu-3e (53% yield)} \quad \text{Cu-3f (75% yield)} \quad \text{Cu-3g (50% yield)} \quad \text{Cu-3h (60% yield)}
\]

**Scheme 4. Library of optically pure C-centered NHC-copper and -palladium complexes**

<table>
<thead>
<tr>
<th>$\text{Cu-4a (62% yield)}$</th>
<th>$\text{Cu-4b (35% yield)}$</th>
<th>$\text{Cu-4c (27% yield)}$</th>
<th>$\text{Cu-4d (21% yield)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{meso-Cl (1:1.8 yield)}$</td>
<td>$\text{meso-Cl (1:2.2:1 yield)}$</td>
<td>$\text{meso-Cl (2:2:1 yield)}$</td>
<td>$\text{meso-Cl (2:2:1 yield)}$</td>
</tr>
</tbody>
</table>

$\text{Pd-4a (95% yield)}$ $\text{Pd-4b (75% yield)}$ $\text{Pd-4c (72% yield)}$ $\text{Pd-4d (72% yield)}$

<table>
<thead>
<tr>
<th>$\text{Cu-4a (62% yield)}$</th>
<th>$\text{Cu-4b (35% yield)}$</th>
<th>$\text{Cu-4c (27% yield)}$</th>
<th>$\text{Cu-4d (21% yield)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{meso-Cl (1:1.8 yield)}$</td>
<td>$\text{meso-Cl (1:2.2:1 yield)}$</td>
<td>$\text{meso-Cl (2:2:1 yield)}$</td>
<td>$\text{meso-Cl (2:2:1 yield)}$</td>
</tr>
</tbody>
</table>

**Scheme 4. Library of optically pure C-centered NHC-copper and -palladium complexes**

*Diastereomers were separated by SiO₂ chromatography. *Isolated yields after preparative chiral resolution. * Determined by chiral HPLC analysis.

X-ray diffraction analysis of homochiral complexes confirmed their structure and enabled to determine their related absolute configurations (Scheme 4).16 Having these new C-centered and C-centered NHC TM-complexes in hands, we next investigated their catalytic performances in asymmetric catalysis. First, the copper-catalyzed asymmetric allylic alkylation8 of diethylzinc to allyl phosphates 8 was explored (Scheme 5a).

**Scheme 5. Catalytic performances of optically pure NHC Cu- and Pd-complexes in asymmetric catalysis**

From the copper-catalysts library, optically pure C₁-symmetric \((\text{S})_2\)-(+)\,-Cu\,-3h and C₂-symmetric \((\text{R})_2\)-(+)\,-Cu\,-4a featuring respectively ortho-F/CHPh₂ and ortho-H/CHPH₂ substituents were found to be the best catalysts. The desired γ-adducts 9a,b were produced with complete regioselectivity and up to 90% ee, and isolated in excellent yields.²² Advantageously, by using opposite enantiomers of Cu-complexes, the γ-adducts (ent)-9b could also be produced with similar efficiencies. The second asymmetric transformation investigated was the asymmetric intramolecular α-arylation of amides 10 (Scheme 5,b). Among C₂-symmetric Pd-complexes, the homochiral \((\text{S},\text{S})\)-(−)-Pd\,-4b afforded the highest enantioselectivity. Resulting adducts \((\text{R})\,-11\text{a,b}\) were isolated in good to excellent yields and remarkable chiral inductions (95 to 98% ee). Of note, \((\text{S})\,-11\text{a}\) was also obtained in similar good yield and ee using \((\text{R},\text{R})\)-(+)\,-Pd\,-4b.

In summary, a novel access to chiral C₁- and C₂-symmetric NHC-TM complexes from readily accessible prochiral NHC precursors was developed. As predicted by DFT calculations, the appropriate choice of the N-aryl ortho-substituents and the NHC backbone substituents induced an axis of chirality which is constrained by the carbene-metal coordination. Resulting configurationally stable atropisomers of TM-complexes were successfully separated by preparative chiral HPLC in good yields and up to >99.5% ee. For the first time, an optically pure Cu-complex was successfully transmetalated to gold and palladium counterparts in excellent yields with a full stereoretentivity (>99.5% ee). Valuable insights to the transmetalation pathway were therefore obtained, supporting the hypothesis of an associative mechanism. The catalytic performances of these Cu- and Pd-complexes were illustrated in Cu-AAA and Pd-AIA with up to 98% ee.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the website.

NMR spectra of products, HPLC traces, experimental procedures and single crystal X-ray diffraction (PDF)

X-ray crystallographic data (CIF)

AUTHOR INFORMATION

Corresponding Authors
* E-mail: hervé.clavier@univ.amu.fr
* E-mail: marc.mauduit@ensc-rennes.fr

ORCID

Lingyu Kong: 0000-0002-7125-680X
Jennifer Morvan: 0000-0003-1210-7975
Delphine Pichon: 0000-0002-2307-6388
Marion Jean: 0000-0003-0524-8825
Muriel Albatal: 0000-0002-0215-0999
Thomas Vives: 0000-0001-6533-0703
Sophie Colombel-Rouen: 0000-0003-2603-2783
Michel Giorgi: 0000-0002-4367-1985

Vincent Dorcet: 0000-0001-9423-995X
Thierry Roisnel: 0000-0002-6088-4472
Christophe Crévisy: 0000-0001-5145-1600
Didier Nuel: 0000-0002-5055-0583
Paola Nava: 0000-0002-8909-8002
Stéphane Humbel: 0000-0001-5405-1848
Nicolas Vanthuyne: 0000-0003-2596-7940
Marc Mauduit: 0000-0002-7801-9708
Hervé Clavier: 0000-0002-2458-3015

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We are grateful to the CNRS, Aix-Marseille Université, the ECM and the ENSCR. L.K. thanks the China Scholarship Council for a Ph.D. grant. This work was supported by the Region Bretagne (ARED 2018 “Biometa” N° 601, grant to J.M.) and D.P. thank the Agence Nationale de la Recherche (ANR-16-CE07-0019 Hel-NHC). Umicore AG & Co is acknowledged for a generous gift of complexes.

REFERENCES


(9) Imidazolium salts were prepared in moderate yields by adapting protocols from the literature, see: (a) Zhang, J.; Fu, J.; Su, X.; Wang, X.; Song, S.; Shi, M. Synthesis of Various Saturated and Unsaturated N-Heterocyclic Carbene Precursors by Triflic Anhydride Mediated Intramolecular Cyclization. Chem. Asian J. 2013, 8, 552–555;


(16) See Supporting Information, Scheme SX and SX.

(17) See Supporting Information, Scheme S9.


(19) See Supporting Information, Table S22.

(20) It is noteworthy that the chiral induction reached here is one of the best reported so far regarding the class of C2-symmetric monodenimate NHCs, see ref. 3.

(21) For a selected example of successful Pd-AAA promoted by chiral NHC ligands, see: Kündig, E.P.; Seidel, T.M.; Jia, Y.-X.; Bernardinelli, G. Bulky Chiral Carbene Ligands and Their Application in the Palladium-Catalyzed Asymmetric Intramolecular α-Arylation of Amides. Angew. Chem. Int. Ed. 2007, 46, 8484–8487. See also ref. 4.
1) Base, [M]

2) Chiral Resolution (HPLC)

AuCl⋅SMe₂ (R\text{a})-Au (>99% ee)

1st stereoretentive transmetalation

Both enantiomers available

Wide library of optically pure \( \text{C}_1 \) and \( \text{C}_2 \)-symmetric TM-complexes

Up to 98% ee in asymmetric catalysis