From Prochiral N-Heterocyclic Carbenes (NHC) to Optically Pure Copper Complexes: New Opportunities in Asymmetric Catalysis

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Supporting Information Placeholder

ABSTRACT: Well-defined optically pure copper-complexes are obtained from prochiral *N*- Heterocyclic Carbene (NHC) ligands. As predicted by DFT calculations, our strategy capitalizes on the formation of a metal-carbene bond which induces axial chirality. Configurationally stable (S_a)- and (R_a)-atropisomers of various Cu-complexes are isolated by preparative chiral HPLC in nearly quantitative yields and excellent optical purities (>99.5%). Their catalytic performances are illustrated in asymmetric allylic alkylation with high regioselectivity and enantioinductions. Importantly, the carbene transfer from an optically pure Cu-complex to gold or palladium center reveals, for the first time, a full stereoretentivity, supporting the hypothesis of an associative mechanism for the transmetalation.

With a unique topology along with a highly modular steric environment around the metal, the use of chiral *N*-heterocyclic carbenes (NHCs) as stereo-directing ligands has rapidly emerged.[1] Since the first report of highly enantioselective reaction in 2001,[2] chiral NHCs were intensively studied in enantioselective catalysis with resounding breakthroughs.[3] 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 TM-complexes containing C_2- or C_1-symmetric NHC precursors **1** and **2** have proved to be quite efficient, thanks to the effective chiral relay transfer from the stereogenic substituents of carbene backbone to the *N*-aryl *ortho*-substituent that induces a *trans*-relationship (Figure 1,a).[4] The resulting chiral environment close to the metal enabled to reach remarkable stereo-inductions (up to >99% ee) in numerous asymmetric catalytic transformations (Figure 1,b).[3] 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. We report herein the synthesis of many optically pure (>98% ee) well-defined NHC-copper complexes containing an axial chirality, which may be readily synthesized from prochiral NHC precursors **3**·Cl (Figure 1-c).[5] The chiral resolution of resulting stable (S_a)- and (R_a)-atropisomers is efficiently achieved by HPLC on a preparative scale.[6]

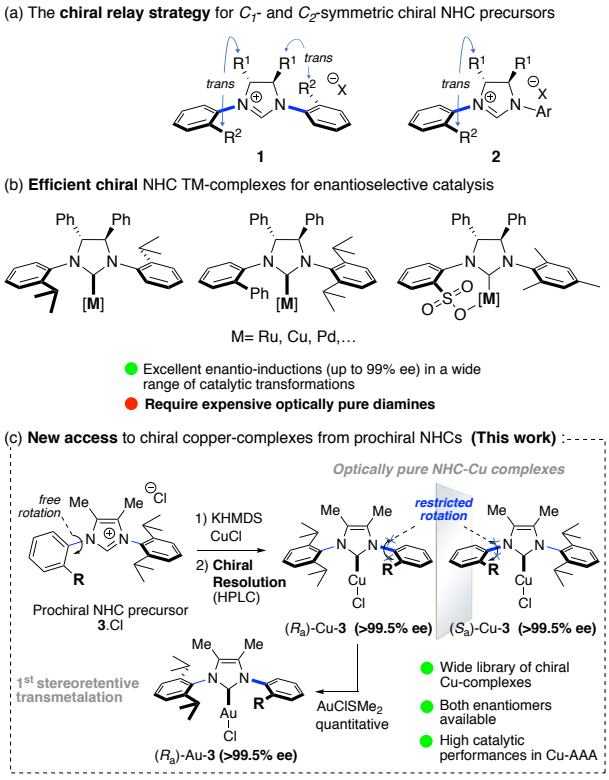
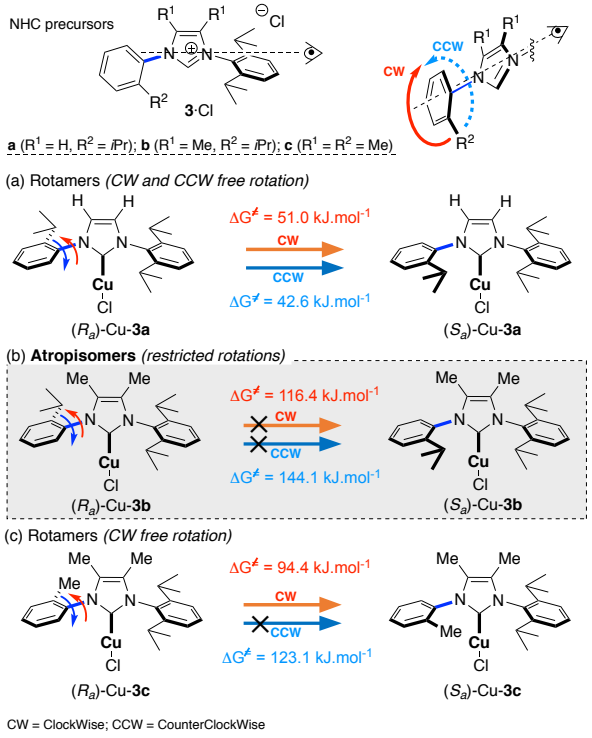


Figure 1. (a) The chiral relay concept for C_2-**1** or C_1-**2** symmetric chiral NHCs. (b) Stereodirecting NHCs successfully used in asymmetric catalysis. (c) New access to optically pure Cu-NHC complexes from prochiral NHC precursors **3** (this work).

These new copper complexes show excellent catalytic performances in AAA[7] with high selectivities. 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 NHC transmetalation mechanism.

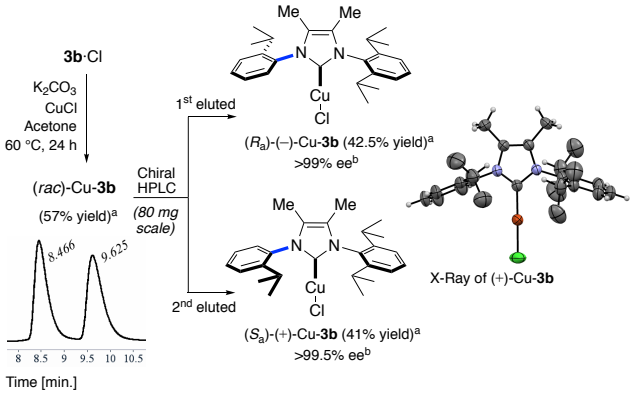
Our study began with the design of prochiral NHC precursors, i.e. imidazolium salts **3**·Cl (Figure 2). Given the infinite substitution patterns that could be considered either on the carbene backbone or on *N*-aryl substituents, prior DFT calculations appeared useful to determine with accuracy the expected rotational barriers of the *N*-aryl bond after coordination to copper(I) chloride (>93 kJ mol^{-1}; $t_{1/2}$ >1000 s at 25 °C to observe atropisomers, but ideally >110 kJ mol^{-1}; $t_{1/2}$ >12 days at 25 °C).[8] With a bulky isopropyl group on *ortho* position of *N*-aryl substituents (Cu-**3a**), the rotation barrier values are too low to obtain stable atropisomers (Figure 2-a; ClockWise CW: 51.0 kJ mol^{-1} and CounterClockWise CCW: 42.6 kJ mol^{-1}).

Figure 2. DFT calculations of rotational barriers for NHC-copper complexes Cu-**3a**,-**3b**,-**3c**.



Nevertheless, the backbone substitution with methyl groups (Cu-**3b**) leads to substantially increase of rotation barriers values up to expect configurationally stable enantiomers (Figure 2-b, CW:116.4 and CCW:144.1 kJ.mol^{-1}). Of note, despite the methyl groups on the backbone, a methyl substituent in *ortho* position of the aryl group (Cu-**3c**) could not prevent the aryl rotation (Figure 2-c, CW: 94.4 kJ.mol^{-1} and CCW: 123.1 kJ.mol^{-1}). In order to assess experimentally these accurate data, Cu-**3b** complex was synthesized from the prochiral imidazolium salt **3b**·Cl (Scheme 1, see Supporting Information; SI).[9] The deprotonation of the latter by K_2CO_3 in the presence of CuCl afforded the desired complex Cu-**3b** in 57% yield after silica gel purification. After a screening of various experimental conditions, the HPLC analysis on chiral stationary phase (Chiralpak® IG) using a mixture of heptane/isopropanol/dichoromethane (80/5/15) as the eluent at room temperature confirmed clearly that stable atropisomers were formed in a racemic mixture (Scheme 1).

Scheme 1. Synthesis of optically pure copper-complexes Cu-3b from prochiral imidazolium 3b·Cl.



[a]Isolated yields. [b]Determined by chiral-stationary phase HPLC analysis.

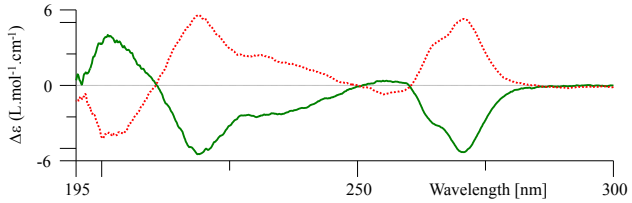
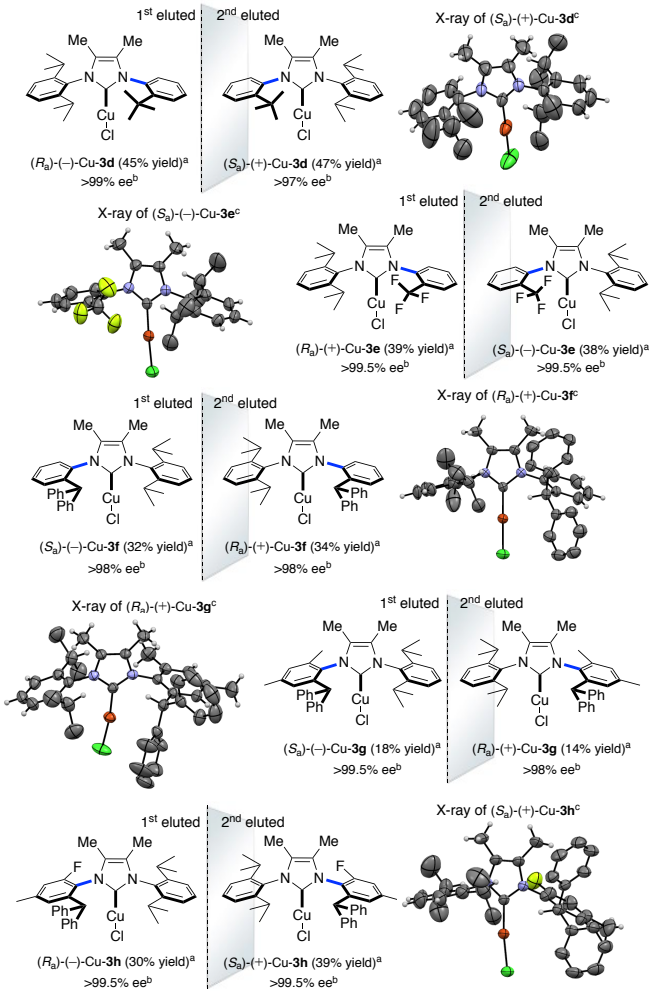


Figure 3. Electronic Circular Dichroism (ECD) of (–)-Cu-**3b** (green solid line) and (+)-Cu-**3b** (red dotted line).

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 nearly quantitative 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 (Figure 3). For instance, (–)-Cu-**3b** displayed a positive ECD-active band at 200 nm ($\Delta\varepsilon$ = +4) and two negative ones at 220 ($\Delta\varepsilon$= –5.5), and 270 nm ($\Delta\varepsilon$ = –5.5). X-ray diffraction analysis of the second eluted atropisomers (+)-Cu-**3b** confirmed its structure but also enabled to determine its related absolute configuration (S_a, Scheme 1). Furthermore, kinetic of enantiomerization of (S_a)-(+)-Cu-**3b** in 1,2-dichloroethane at 83.5 °C gave access to the experimental rotation barrier value ($\Delta G^{\neq}$ = 117.2 kJ.mol^{-1}) which fits perfectly with the predicted lowest value ($\Delta G^{\neq}$ = 116 kJ.mol^{-1}, see Figure 1, b). This validates the use of

theoretical calculations as a reliable tool to design the NHC structures. Following this efficient methodology, we were able to synthesize various optically pure Cu-complexes containing NHC ligands that featured bulky *ortho*-substituents (Scheme 2). In all cases, stable atropisomeric Cu-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.

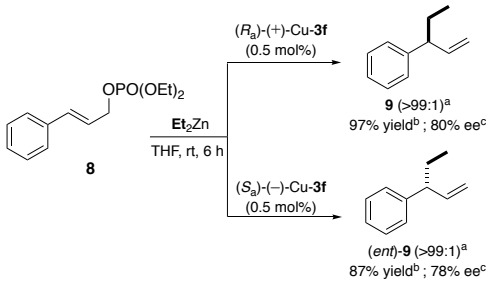
Scheme 2. Library of optically pure NHC-copper complexes[a]



[a]Isolated yields after preparative chiral resolution. [b]Determined by chiral-stationary phase HPLC analysis. [c]Solid-state structures from single crystal X-ray diffraction.

Their catalytic performances were next evaluated in the asymmetric allylic alkylation of diethylzinc to cinnamyl phosphate **8** (Scheme 3). Optically pure Cu-**3b**,**d-h** complexes showed excellent reactivity leading to the exclusive formation of the desired γ-adduct **9** in good to excellent yields (see SI, Table S14). Nevertheless, significant differences of enantioselection were observed depending on the *ortho*-substituents of the *N*-aryl unit. (R_a)-(+)-Cu-**3f**, featuring a benzhydryl substituent produced the highest 80% ee for **9**, close to those previously reported with chiral NHC-Cu complexes (Scheme 3).[10]

Scheme 3. AAA of diethylzinc to allyl phosphate 8 catalyzed by optically pure Cu-3f complex

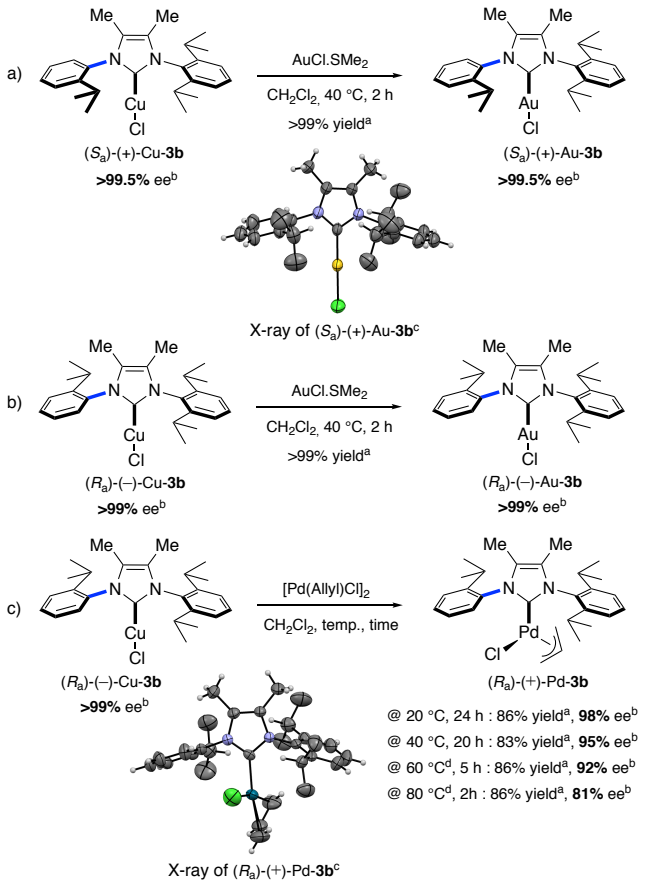


[a]Molar ratio of γ/α adduct were monitored by ^{1}H NMR spectroscopy analysis (see SI for details). [b]Isolated yields after silica gel chromatography. [c]Determined by chiral-phase GC analysis.

Advantageously, by using (S_a)-(–)-Cu-**3f**, the enantiomer of γ-adduct **9** could also be obtained with similar efficiency.

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.[11] 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 opportunity to generate other TM-complexes and to gain valuable insights about the mechanistic route of transmetalation. Indeed, two possible ways could be postulated: i) a dissociative mechanism involving first the free NHC release and then the coordination to the second metal center or ii) an associative mechanism. In that respect, the optically pure (S_a)-(+)-Cu-**3b** complex (>99.5% ee) was treated with AuCl·SMe$_2$ complex in dichloromethane at 40 °C over 2 h (Scheme 4, a). To our delight, the corresponding transmetalated 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. Moreover, X-ray diffraction analysis allowed us to confirm the complex structure and determine its related absolute configuration (S_a, Scheme 4). Similarly, the transmetalation starting from (R_a)-(–)-Cu-**3b** afforded the corresponding gold enantiomer (R_a)-(–)-Au-**3b** in quantitative yield and full optical purity, indicating unambiguously the stereoretentivity of the transmetalation (Scheme 4, b). Importantly the rotation barriers of Au-**3b** were assessed both by DFT calculations (CW: 145.5 kJ.mol^{-1} and CCW: 158.5 kJ.mol^{-1}) and experimentally ($\Delta G^{\neq}$ = 142.4 kJ.mol^{-1} at 132 °C in chlorobenzene), showing their enhancement over the analogous Cu-complex. The transmetalation process was then successfully extended to π-allyl palladium chloride (Scheme 4, c). Nevertheless, a prolonged reaction time (24 h) was required to reach a good 86% isolated yield.

Scheme 4. Stereoretentive transmetalation affording optically pure gold and palladium complexes



[a]Isolated yields. [b]Determined by chiral-stationary phase HPLC analysis. [c]Solid-state structures from single crystal X-ray diffraction. [d]Reaction performed in dichloroethane.

The optical purity of the newly formed Pd-complex (98% ee) was confirmed by HPLC analysis attesting again 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 occurred from 95% ee at 40 °C to 81% ee at 80 °C. This behavior could be relied to the atropisomer stability of the starting copper complex (Table 1).

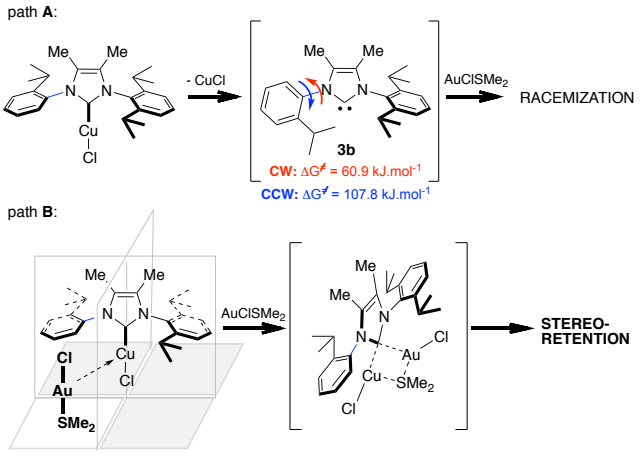
Table 1. Atropisomer stability of Cu-3b,[a] Pd-3b[b] and Au-3b[c] complexes

entry	T (°C)	(R_a)-(–)-Cu-**3b** $t_{1/2}$	(R_a)-(–)-Pd-**3b** $t_{1/2}$	(R_a)-(–)-Au-**3b** $t_{1/2}$
1	40	22 d	14 y	951 y
2	50	5 d	3 y	170 y
3	60	33 h	239 d	34 y
4	70	9 h	58 d	7 y
5	80	3 h	15 d	2 y

[a]$\Delta G^{\neq}$ = 117.2 kJ.mol^{-1}. [b]$\Delta G^{\neq}$ = 131.5 kJ.mol^{-1}. [c]$\Delta G^{\neq}$ = 142.4 kJ.mol^{-1}.

Indeed, the rotation barriers of Pd-**3b** observed by DFT calculations (CW: 133.4 kJ.mol^{-1} and CCW: 159.4 kJ.mol^{-1}) and experimentally ($\Delta G^{\neq}$ = 131.5 kJ.mol^{-1} at 132 °C in chlorobenzene) are higher than for Cu-**3b**. The (R_a)-(–)-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 h at 80 °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 plausible reaction pathway for the transmetalation process is depicted in Figure 4.

Figure 4. Dissociative (path A) vs associative (path B) transmetalation mechanism.



First, the observed stereoretentivity supports that an associative mechanism could occur for the transmetalation of coinage NHC-TM complexes (Figure 4, path B). Indeed, a dissociative pathway that would involve a transient free carbene seems incompatible as partial to full racemization could happen due to the free rotation around the *N*-Aryl bond,[12] as demonstrated by DFT calculations with low values for rotational barriers on free NHC **3b** (Figure 4, path A; 60.9 and 107.8 kJ.mol^{-1}; $t_{1/2}$ = 4 ms at 20 °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 *i*Pr-aryl substituents (Figure 4, path B). DFT calculations about the formation of Au-**3b** from Cu-**3b** are currently underway to provide useful information regarding the transmetalation pathway.

In summary, a practical access to chiral NHC-TM complexes from accessible and inexpensive prochiral NHCs was developed. As predicted by DFT calculations, the appropriate choice of the *N*-aryl *ortho*-substituent and the NHC backbone substituents induced an axe of chirality which is frozen by the carbene-metal coordination. Resulting configurationally stable (S_a)- and (R_a)-atropisomers of Cu-complexes were successfully separated by preparative chiral HPLC in good yields and

up to >99.5% ee. Their catalytic performances were illustrated in asymmetric allylic alkylation with high regio- and enantioinductions. Furthermore, and for the first time, an optically pure Cu-complex was successfully transmetaled 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. This concept could boost the development of chiral NHC-TM complexes and offer new opportunities in asymmetric catalysis.

ASSOCIATED CONTENT

Supporting Information

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

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

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Notes

The authors declare no competing financial interests.

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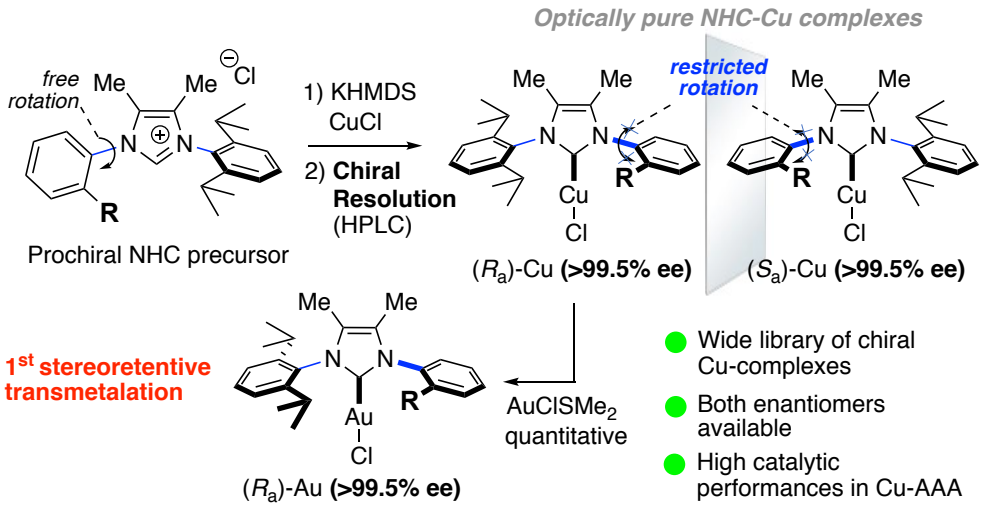
Optically pure NHC-Cu complexes
free rotation
Me
Me
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Prochiral NHC precursor
1) KHMDS
CuCl
2) Chiral Resolution
(HPLC)
restricted rotation
Cu
Cl
(Ra)-Cu (>99.5% ee)
(Sa)-Cu (>99.5% ee)
1st stereoretentive transmetalation
Au
AuClSMe2
quantitative
(Ra)-Au (>99.5% ee)
Wide library of chiral Cu-complexes
Both enantiomers available
High catalytic performances in Cu-AAA