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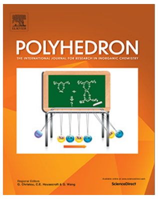

Larger scale Stahl oxidation with instant Cu removal in convenient synthesis of chiral bidentate N–heterocyclic carbene precursor

Krzysztof Grudzień [a,1], Wojciech Nogaś [a], Grzegorz Szczepaniak [a], Karol Grela [a,*]

[a] *Biological and Chemical Research Centre, Faculty of Chemistry, University of Warsaw, Żwirki i Wigury Street 101, 02-089 Warsaw, Poland*

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ABSTRACT

Commercially available *N*-Boc protected L-proline can be efficiently converted into a chiral, bidentate, aminoalkyl *N*-heterocyclic carbene ligand precursor in high yield (50% total after 4 steps) without column chromatography purification at any moment. The developed synthetic path includes: (1) redox step leading to an aldehyde, (2) imine condensation and *in situ* reduction to 1,2-diamine; (3) heterocyclization; (3) removal of the protecting group. Instant separation of Cu traces after the key Stahl oxidation at gram-scale was facilitated by the use of bis(isocyanide) scavenger, SnatchCat, forming insoluble, easy to remove RNC:→[Cu] complexes that allowed usto obtain crude intermediate suitably pure for next steps without tedious purification.

1. Introduction

Over the last three decades *N*-heterocyclic carbenes (NHCs, Fig. 1) have become a versatile tool in homogeneous organo- and organometallic catalysis [1,2]. Their exceptional tunability, based on a broad range of possible and convenient to achieve structural modifications, enabled multiple interesting applications in "smart" catalytic systems [3]. One of the most basic and universally pursued goals in the field of synthetic organic chemistry is the ability to perform certain transformations in enantiocontrolled fashion. Chiral NHCs can serve both, as (organo)catalysts and as ligands in transition metal complexes [4], the latter function is fulfilled by mono- and polidentate NHC molecules [2]. In a very recent review showing application of NHCs bearing additional chelating group(s) in asymmetric organometallic catalysis, Fiedel and Labande report that so far the most frequently used ligands contain various types of oxygen donor (over 200 examples), while those containing alkylamine nitrogen donors are limited to a few [5]. Intensive research, especially by Mauduit and Alexakis teams, resulted in the development of a number of useful bidentate hydroxyalkyl imidazolium and imidazolinium NHCs based on natural, enantiomerically pure α-amino acids (Fig. 1a), which turned out to be especially useful in copper-catalyzed enantioselective conjugated addition [6] and allylic substitution [7]. Some amino acid-based imidazolinium and triazolium ligands developed by Fiksdahl were also applied in enantioselective organocatalysis and gold catalysis [8], while hydroxyalkyl-amidate benzimidazolium precursors developed by Sakaguchi and Jung were also used in palladium-catalyzed asymmetric, oxidative Heck reaction [9], metal-catalyzed asymmetric transfer hydrogenation [10], iridium-catalyzed asymmetric hydrosilylation [11], copper-catalyzed asymmetric conjugated addition [12] and palladium-catalyzed asymmetric allylic substitution [13]. In 2005 Arnold presented a synthesis of silver(I) complexes with structurally similar, yet non-chiral, aminoalkyl imidazolium carbenes [14], while in 2008 Chao and Ong used one of its analogues to obtain mono- and bis-carbene nickel(II) complexes [15]. Application of such ligands in enantioselective synthesis was showed by Roland (palladium-catalyzed asymmetric allylic substitution) [16] and Williams (copper-catalyzed asymmetric conjugated addition, Fig. 1b) [17a]. Beside catalysis organometallic complexes of such aminoalkyl carbenes were also studied as potential anti-cancer drugs [18]. In this work we document a short and efficient synthesis of a model imidazolinium NHC precursor bearing a chiral alkylamino side-arm derived from L-proline (Fig. 1d). This structure was arbitrarily selected by us as a general platform for further modifications, based on its similarity to the known imidazolium NHC precursors derived from amino-acids (Fig. 1b,c) developed by Williams17a and by Suzuki and Sato [17b]. We believe that designing a new convenient route to such chiral (amino)imidazolinium NHCs can find use in asymmetric organic and organometallic catalysis, where similar (amino)carbenes proved exceptional utility in a broad scope of applications [2].

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* Corresponding author.
E-mail addresses: k.grudzien@cent.uw.edu.pl (K. Grudzień), karol.grela@gmail.com (K. Grela).

[1] Current address: Centre of New Technologies, University of Warsaw, Banacha 2C, 02-097 Warszawa, Poland.

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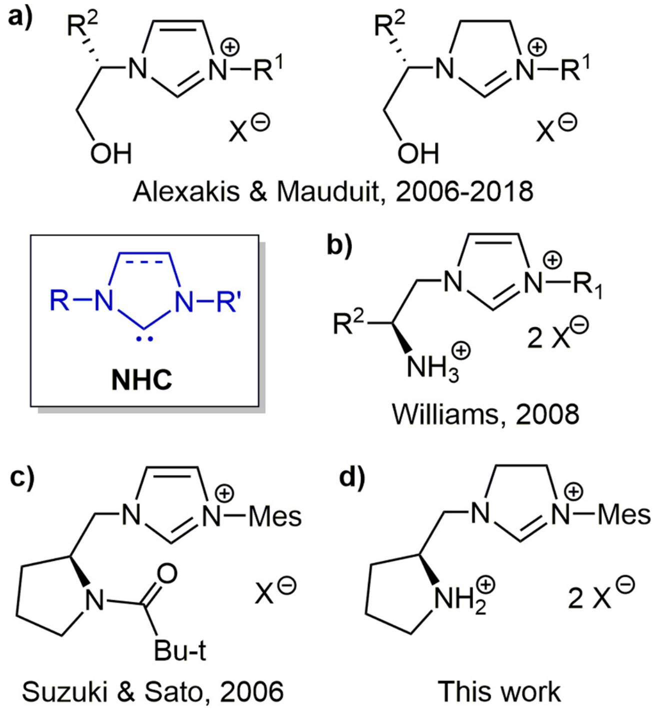


Fig. 1. General structure of *N*-heterocyclic carbene (NHC, insert) and selected precursors of chiral: a) (hydroxyalkyl)imidazolinium and imidazolium NHCs; b) (aminoalkyl)imidazolium NHCs useful in catalysis; c) imidazolium NHC derived from L-proline; d) closely related imidazolinium NHC selected for this study.

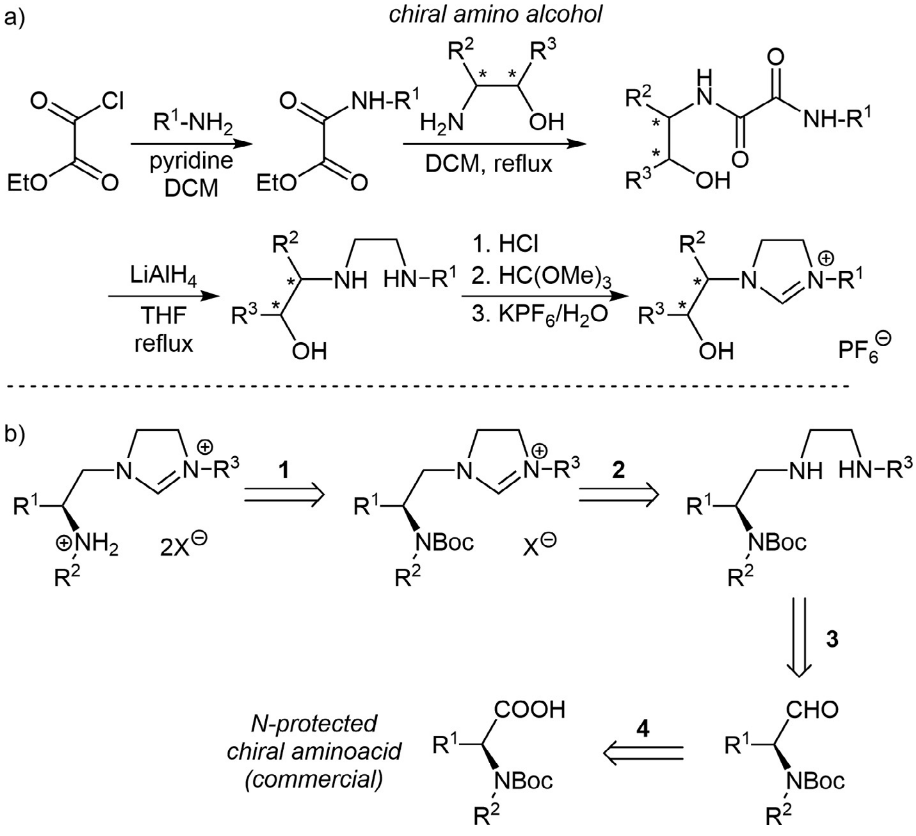
2. Results

State of the art. The reported syntheses of related *hydroxyalkyl*-NHC precursors are quite straightforward and do not employ costly reagents (Scheme 1a) [7]. Therefore, our aim was to develop a route leading to chiral *aminoalkyl*-NHC precursors that is also easily scalable and relies on readily available substrates and reagents. The presence of L-proline function in the target compound requires usage of the suitable protecting group throughout the synthesis (Scheme 1b).

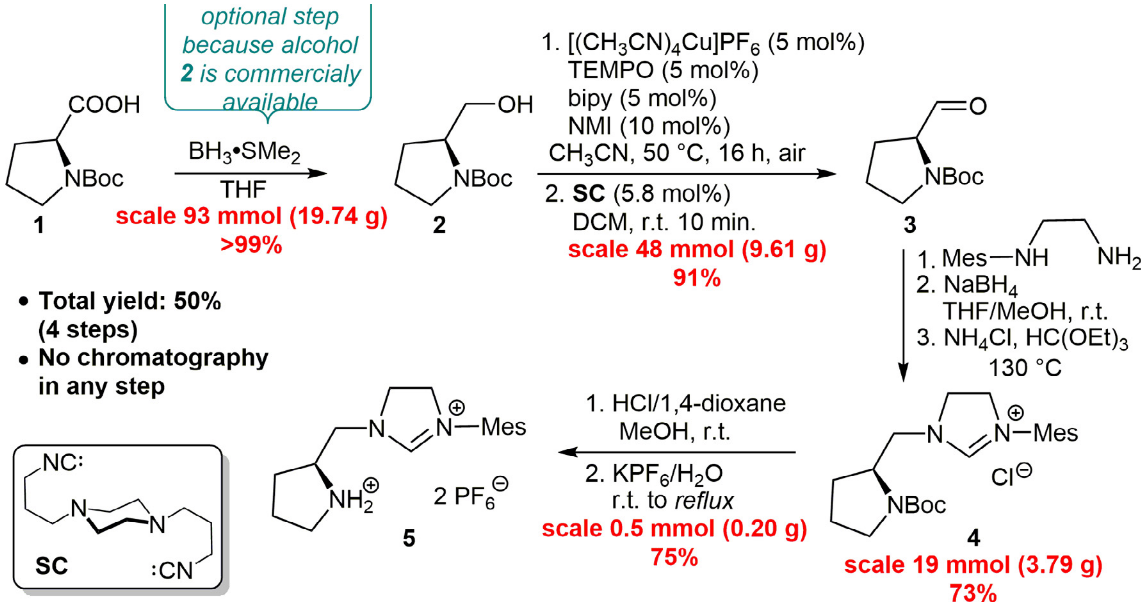
Our synthesis. Retrosynthesis of this new family of ligands (Scheme 1b) includes following elementary transformations of general character: (1) removal of the *N*-Boc protecting group; (2) heterocyclization; (3) imine condensation and *in situ* reduction; (4) selective reduction or reduction/oxidation. This analysis was then reduced to practice using the arbitrarily *selected* proline-based NHC ligand precursor Fig. 1d). The synthesis of the ligand precursor is presented on Scheme 2 (for detailed experimental procedures and analytical data see Supporting Information, SI). Both *N*-Boc-L-proline **1** and *N*-Boc-L-prolinol **2** are commercially available, but due to a much higher price of **2** as compared with **1** we decided to convert the former into the latter, which was made possible in quantitative yield using simple reducing reagent ($BH_3\cdot SMe_2$). Next we faced a challenge to perform a selective oxidation of **2**. Fortunately, this particular reaction can be carried out in aerobic conditions using Cu(I)-TEMPO-bipy-NMI system, described by Hoover and Stahl, giving > 98% yield of aldehyde **3** on a 1.0 mmol scale after silica-gel purification [19]. We found it a particularly interesting procedure as it uses atmospheric oxygen as a stoichiometric oxidant and earth-abundant metal as a catalyst. A convenient way of monitoring of the reaction progress is another advantage: the initial solution of the reaction is dark red, which turns blue upon completion (the change in brown to green colour indicating a change in the resting state of the copper species) [19]. Unfortunately, when we repeated this process on a bigger scale (48 mmol) we observed a significant drop in yield (48%), presumably due to the partial decomposition of **3** during rather tedious silica-gel purification.

To solve this problem, we opted to modify the work-up procedure so it would allow us to omit the potentially problematic chromatographic purification step. After some exploratory experiments, we derived a new protocol that avoids silica-gel purification. After full conversion of **2**, the solvent (CH_3CN) was removed *in vacuo* and replaced by dichloromethane (DCM). Then a newly developed, commercially available isocyanide metal scavenger **SC** (SnatchCat) [20] (5.8 mol%; 1.16 equiv. relative to Cu) was added. The colour of the mixture immediately changed from blue to green, and after a while, large amounts of green, sticky, glutinous solid formed, while the solution turned clear yellow (Fig. 2). This mixture was filtered through a short pad of neutral Al_2O_3 placed in a funnel and the pale-yellow coloured clear filtrate was concentrated yielding 91% of crude aldehyde **3** (48.0 mmol scale, Scheme 4). Such produced **3** was directly converted into imidazolinium chloride **4** in 73% total yield (19.0 mmol scale) via 3-step sequence consisted of (*i*) condensation with *N*-Mes-ethylenediamine; (*ii*) $NaBH_4$ reduction and (*iii*) cyclisation using triethyl orthoformate. No chromatography separation was performed and salt **4** was isolated by precipitation with Et_2O and filtration. Finally, *N*-Boc group was removed by reaction with a dioxane solution of HCl. The resulting product turned out to be extremely hygroscopic. Therefore we decided to exchange Cl^- anions with hydrophobic PF_6^- by reaction with KPF_6 in water, which yielded in beige, crystalline, non-hydrophilic solid **5** which was conveniently purified and isolated by crystallization from hot water. The total yield of deprotection and anion exchange steps was 75% (0.5 mmol scale; Scheme 2).

Attempts to explain the Cu-scavenger mode of action. Despite the use of SnatchCat (**SC**) to scavenge copper complexes was very recently disclosed [20d], no information about the exact nature of Cu/**SC** complexes was reported. We speculate that during the oxidation step work-up the bis(isocyanide) fragment might have formed with Cu ions a kind of coordination polymer, which is easily removable from the reaction mixture, due to its very low solubility and high polarity [21]. Unfortunately, because of the physical properties of this product (green, sticky, glutinous, insoluble solid – see: Fig. 2. picture 4. and 5.) we were not able to characterize it and thus its structure remains unknown. To shed some light on the possible structure of such complex we switched to mono-isocyanide analogue [17a] (**SC'**, Fig. 3) in a hope that in this case non-polymeric material will be formed that will be easier to characterise. Copper(I) iodide was selected as a source of metal in this model study. Fortuitously, it was relatively easy to grow a single crystal of a complex formed when CuI was reacted with **SC'**. The complex crystallizes in the trigonal R3c space group with one third of the molecule in the asymmetric unit of the crystal lattice (for bond lengths, valence and torsion angles bond lengths, see SI). The solidstate structure, presented in Fig. 3 shows that three molecules of isocyanide **SC'** bond to the copper cation forming $(\mathbf{SC'})_3CuI$ type of complex (Fig. 1). We are aware that this molecule can be understood as only a very approximate model for the real complexes formed between bis(isocyanide) **SC** and a variety of Cu species present in solution after the Stahl oxidation. Nonetheless, one can assume that because Cu ion was found to bond to more than one isocyanide group, and SnatchCat (**SC**) molecule has two opposite isocyanide groups available, the complexes formed shall be of polymeric nature $([Cu]\leftarrow:CN\text{-}A\text{-}NC:\rightarrow[Cu]\leftarrow:CN\text{-}A\text{-}NC:\rightarrow)_n$. This can explain the formation of a sticky glutinous insoluble mass observed by us, which was then very easy to be separated, leading to clear solution of the aldehyde product (cf. photographs in Fig. 2).



Scheme 1. a) Original synthesis of chiral (hydroxyalkyl)imidazolinium NHCs precursor according to Mauduit; b) our retrosynthetical analysis of chiral (aminoalkyl) imidazolinium NHCs precursor synthesis. Boc = *tert*-butyloxycarbonyl.



Scheme 2. Synthetic pathway for the transformation of *N*-Boc-L-proline (**1**) into new chiral NHC ligand precursor (**5**). NMI = *N*-methylimidazole; bipy = 2,2′-bipyridine; Boc = *tert*-butyloxycarbonyl.

We believe that the instant purification method utilizing SnatchCat (**SC**) studied herewith is of general nature and can be used not only in Stahl oxidation used in ligands and building blocks preparation, but also in medicinal chemistry context [20d].

3. Conclusion

In conclusion, we have developed a simple and short synthetic pathway to transform L-proline into a bifunctional carbene precur-

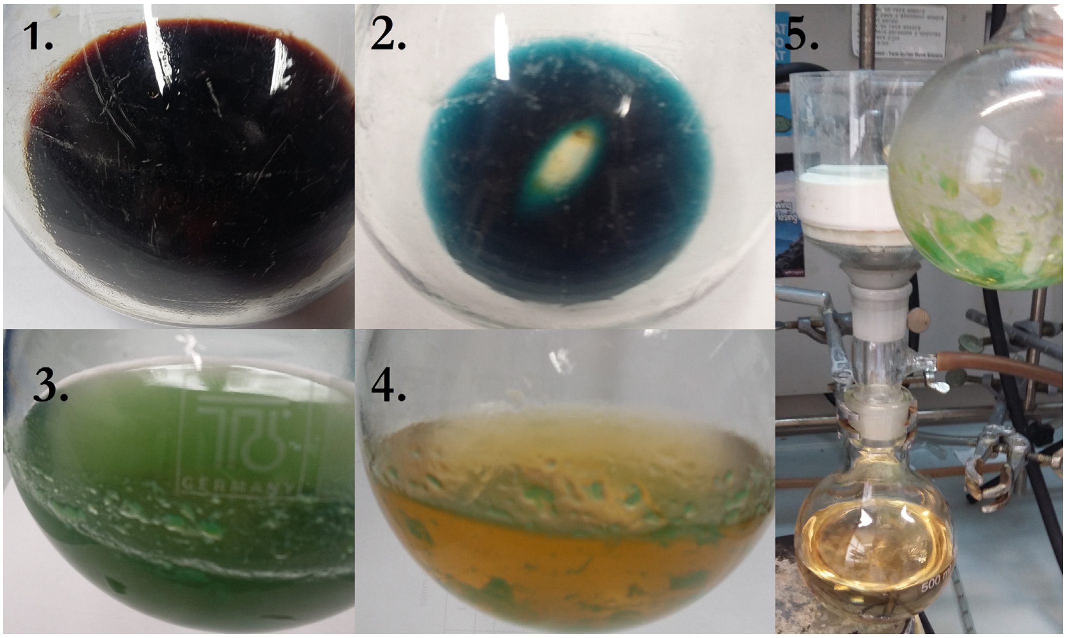


Fig. 2. Instant purification of the Cu-catalyzed aerobic oxidation mixture using **SC** scavenger. (1) before reaction; (2) after reaction is completed; (3) 30 s after addition of **SC**; (4) 10 min after addition of **SC**; (5) Cu/**SC** sticky residue stays in the reaction flask (top), clear filtrate in the bottom flask.

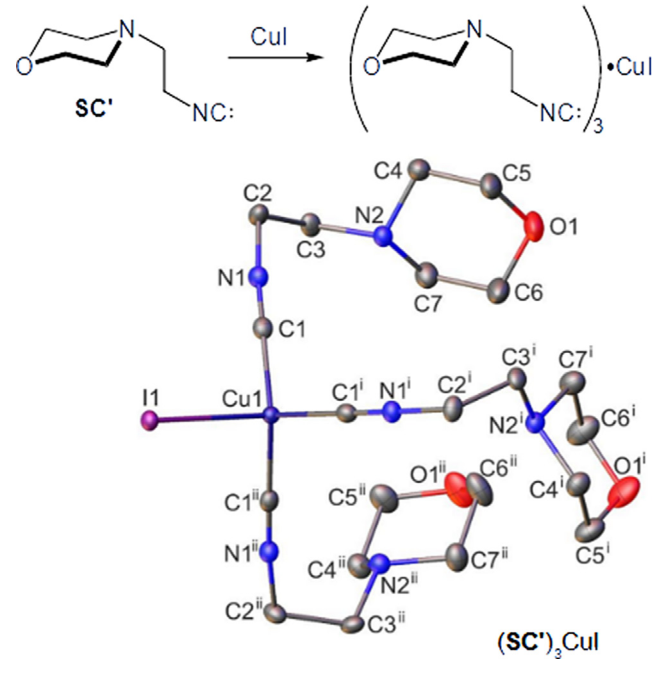


Fig. 3. Solid state crystallographic structure of complex formed in reaction between isocyanide **SC'** and CuI. Displacement ellipsoids are drawn at the 50% probability level. H-atoms were omitted for clarity.

sor of a chiral (amino)imidazolinium NHC in 50% total yield, avoiding usage of costly reagents and column chromatography purification. Separation of Cu traces after Stahl oxidation was facilitated by use of bis(isocyanide) scavenger, SnatchCat. This bifunctional isocyanide, forming insoluble polymeric RNC:→[Cu] complexes allowed us to remove traces of Cu substantially simplifying the purification step. We believe that this new convenient route to such chiral (amino)imidazolinium NHCs can find use in asymmetric organic and organometallic catalysis, where similar (amino)carbenes proved exceptional utility in a broad scope of applications. Therefore applications of the present ligand precursor as well as its analogues possible to be synthesized via presented strategy in metal-catalyzed asymmetric transformations will be studied by us independently in due time.

Authors contribution

K. Grudzień – Planned and executed complete synthesis of target compound **5**; **W. Nogaś** – performed synthesis of (**SC'**)$_3$CuI complex; **G. Szczepaniak** – originated research on **SC** family of scavengers and prepared samples of **SC** and **SC'**; **K. Grela** and **K. Grudzień** wrote the paper.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.poly.2021.115090.

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