Combining NHC *bis*-Phenolate Ligands with Oxophilic Metal Centers: A Powerful Approach for the Development of Robust and Highly Effective Organometallic Catalysts

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Abstract: The present paper describes an overview of a novel family of tridentate NHC pincer ligand in which two phenoxide moieties are directly connected to the nitrogen atoms of a central N-heterocyclic carbene. It was envisioned that such a structure might be suitable for coordination to a variety of metal centers across the periodic table, including oxophilic metals. Various metal complexes bearing such ligand are indeed readily accessible in high yields via straightforward routes. Interestingly, a robust zirconium–NHC complex was found to polymerize *rac*-lactide in a highly controlled, living and stereoselective manner to afford heterotactic PLA.

Keywords: N-Heterocyclic carbene · Organometallic catalysis · Ring-opening polymerization · Transition metal complexes

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From left to right: PS, RD, SD, SBL, and Prof. Kündig, President of the Swiss Chemical Society.

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Introduction

Over the past two decades, *N*-heterocyclic carbenes (NHC) have attracted tremendous attention and are now considered as *privileged* ligands for coordination to metal complexes due to their exceptional ligating properties.[1] Their bonding to late transition metals has been proven to yield kinetically inert, remarkably stable as well as air-/moisture-tolerant metal complexes, which obviously contributed to their development. NHC metal derivatives have found widespread applications in catalysis and more recently in medicinal chemistry (antimicrobial and cytotoxic agents) or material sciences (luminescence, liquid crystal, conducting polymer, *etc*.).[2]

During the mid-90s, the similarities between *N*-heterocyclic carbenes and phosphines regarding ligand properties were used as *guidelines* to study the coordination chemistry of the NHCs and the potential applications of the derived metal complexes. As a consequence, the use of NHC ligands for coordination to early-transition metals has been much less studied, which may explain the rather limited number of NHC early-transition metal complexes synthesized thus far.

Phosphine ligands display a soft base nature in the HSAB theory and therefore are better suited for late-transition metals. In contrast, *N*-heterocyclic carbenes have no necessary requirement for backbonding and, due to the strongly nucleophilic singlet lone pair, are suitable for a wider range of metals. However, to limit NHC dissociation in high-oxidation-state metals complexes, polydentate NHC-donor systems have been designed and synthesized to improve robustness of such coordination compounds. Potentially bidentate or tridentate systems, which include a neutral carbene surrounded by one or two oxygen or nitrogen-based anionic ligands appear to be promising candidates to afford stable early-transition metal complexes.[3]

In search of new tridentate pincer-type NHC dianionic ligand, we focused our attention on *bis*-phenolate-NHC chelating ligand as shown on Fig. 1. We envisioned that such a L,X₂-type ligand structure would be well suited for oxophilic high-oxidation-state metals. In particular, (i) the use of phenolate arms would bring a rigid ligand platform and also avoid potential decomposition pathways of the ligand; (ii)

the introduction of substituents in the *ortho*- and *para* positions of the phenolates will insure solubility and also disfavor the formation of undesirable metal aggregates and (iii) such a NHC tridentate chelating ligand may be readily modified *via* the introduction of saturated or unsaturated heterocycles (including chiral backbones).
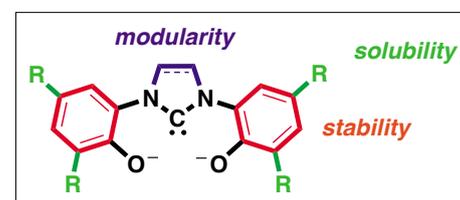

Fig. 1. General structure of the NHC *bis*-phenolate ligand.

Ligand Precursor Synthesis

We thus developed a straightforward synthesis of the corresponding azolium proligands with bulky substituents (R = *t*Bu).[4,5] The key step is the coupling between the 3,5-di-tert-butylcatechol and ethylene diamine to form N,N-*bis*(3,5-di-tert-butyl-2-hydroxyphenyl)-ethylenediamine (Scheme 1).[6] The originality of this approach is to take advantage of the keto-enol equilibrium in the starting catechol. The scope of application is illustrated by the selected examples depicted in Scheme 1. It is thus possible to access various azolium salts upon changing the nature of the starting diamine (including the use of chiral diamine precursors). For instance, benzimidazolium salts and/or cyclic formamidiniums with a fully saturated back-
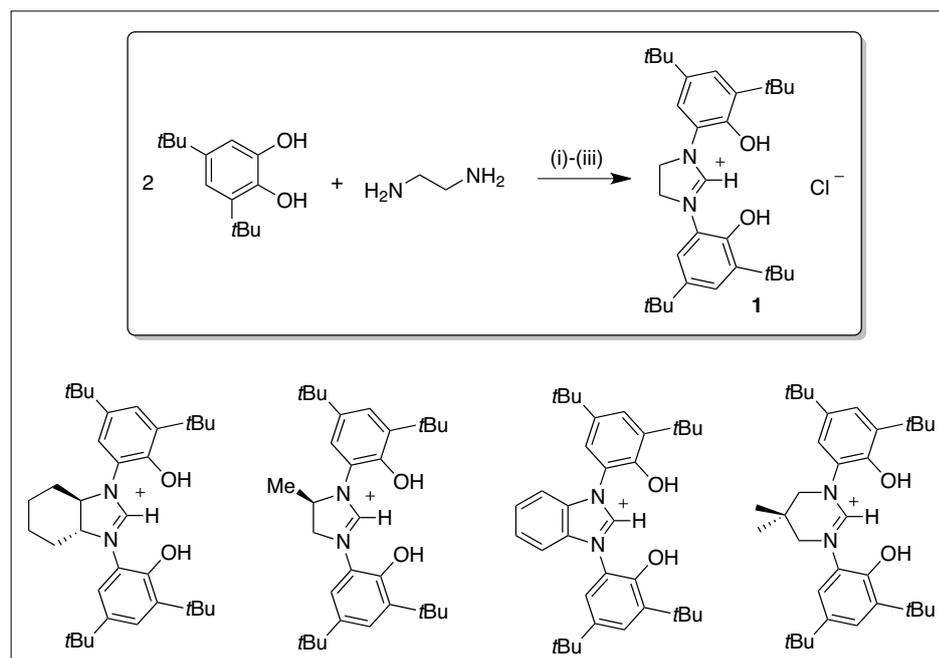
Scheme 1. Synthesis of symmetrical azolium chloride precursors starting from 3,5-di-*tert* butylcatechol. Conditions for **1**: (i) acetonitrile, Δ; (ii) HCl_{aq.}, MeOH (iii) (EtO)₃CH.

bone are easily accessible. Interestingly, such azolium chloride salts typically precipitate during the course of the reaction and may therefore be easily isolated *via* simple filtration with no further purification required.

Synthesis of Metal NHC Complexes

Several routes are known for the preparation of NHC complexes.[2] The most common approach involves the deprotonation of an azolium pro-ligand by an external strong base to generate the corresponding free carbene with a subsequent binding to a metal center. The use of an internal base is also a simple and practical method to implement since it may avoid the generation of air- and moisture-sensitive free carbenes. In that case, a ligand of the metal precursor will act as a base and *in situ* deprotonate the azolium salt with a direct complexation onto the metal center. We found that the alcohol elimination route involving the reaction of the imidazolium precursor **1** and one equivalent of a metal alkoxide precursor allows a straightforward access (and under mild conditions) to early transition metal complexes supported by NHC *bis*-phenolate ligands (Scheme 2).

Using the alcohol elimination approach, various NHC metal complexes could be readily produced in high yields and some representative examples are depicted in Fig. 2. The analytically pure vanadium (V) oxo complex **2** was prepared upon combining the corresponding azolium precursor with (O*i*Pr)$_3$V=O, followed by evaporation of the volatiles *in vacuo*.[7] The titanium, zirconium and hafnium complexes **3–5** were obtained in the same way from ClTi(O*i*Pr)$_3$, Zr(O*i*Pr)$_4$ and HfBn$_4$, respectively.[8–10] It is noteworthy that the NHC *bis*-phenolate ligand provides a remarkable stability to the resulting metal chelates. Complexes **2** and **3** are robust and could be handled under air. Noticeably, such a ligand structure can also readily coordinate mid- and late transition metals (with the species **6** and **7**) or group 13 metal derivatives (**8**) (Fig. 2).[7,11,12]

Several molecular structures of these NHC metal complexes were determined by X-ray crystallography, which confirmed the effective chelation of the NHC bisphenolate moiety to the metal center. For example, as illustrated in Fig. 3, the zirconium atom in complex **4** adopts a distorted octahedral geometry as a result of the *mer* coordination of the ligand.
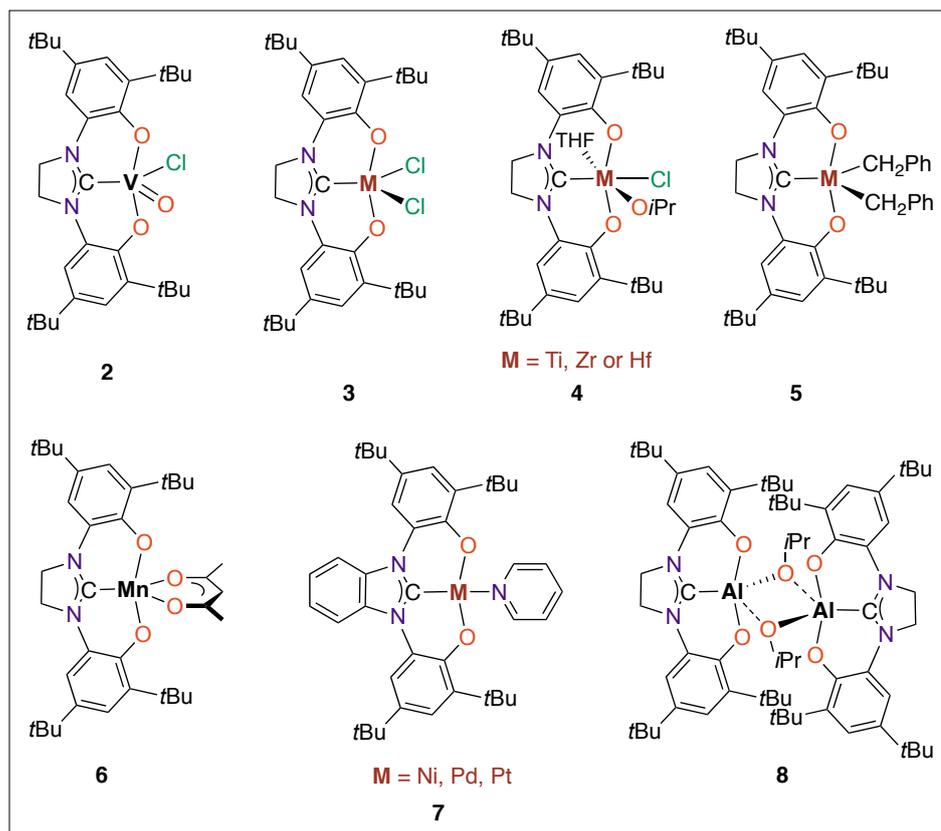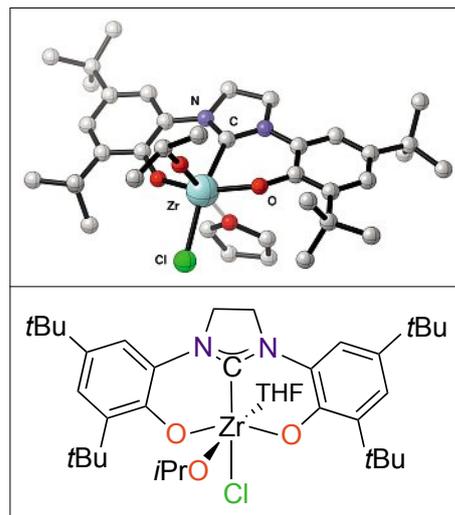

Fig. 3. Molecular structure of the zirconium complex **4**.

Application to the Living and Stereoselective Polymerization of Cyclic Esters/Carbonates

Biodegradable polyesters and polycarbonates, such as polylactide, polycaprolactone or poly-trimethylene carbonate are of current interest due their various applications in numerous domains including their use in the biomedical and pharmaceutical fields. The ring-opening polymerization (ROP) of cyclic esters or carbonates constitutes the most efficient approach to access well-defined polyesters or polycarbonates in a controlled manner.[13] Typically, the ring-opening process is driven thermodynamically by release of the ring strain and the process may be finely controlled to access precise molecular weights, narrow molecular weight distribution and also, when appropriate, regio- and stereoselectivity. All these parameters are of primary importance since, in general, a low polydispersity index with a high tacticity level are prerequisites for such biodegradable polymers to be commercialized.

Commercial polylactide is currently produced industrially by ROP of L-lactide using tin(II) octanoate.[14] Increasing efforts are being devoted towards the development of single-site metal-based initiators to access polymers under the most efficient conditions. Discrete ligand-supported alkoxide complexes of oxophilic metals (Mg, Ca, Zn, Al or rare-earth metals) are well-established initiators for the ROP of lactide.[13] Comparatively, group 4 analogues have been less studied prompting us to investigate the potential utility of group 4 metal NHC species in this field and, in particular, to study the added value that the carbene ligand might provide in this area.

It was thus found that a Ti monoalkoxide chloro derivative of type **4** polymerizes *rac*-lactide in a controlled manner

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NHC.HCl + M(OR)L$_n$ ⟶ [**NHC**]ML$_n$-Cl + R-OH   Scheme 2. Formation of [NHC]M complexes.

Fig. 2. Some representative examples of metal complexes bearing a NHC *bis*-phenolate ligand of type **1**.

(polydiversity index (pdi) <1.1) albeit with no stereoselectivity, thus producing atactic polylactide (PLA) (89% conversion to PLA of 100 equiv. of *rac*-lactide, toluene, 15 h, 90 °C).[8] Surprisingly, going from titanium to zirconium led to highly active systems under mild conditions.[9] The Zr iso-propoxy chloro derivative of **4** polymerizes *rac*-lactide at room temperature and, most importantly, in a controlled and highly stereoselective manner to yield narrowly disperse and highly heterotactic PLA (pdi <1.1 and P_r > 0.95, Table 1).[15] In addition, the direct use of commercial *rac*-lactide without further purification has little effect on the activity and selectivity (commercial lactide typically contains protic impurities such as lactic acid). It is worth highlighting that the prepared polymers were isolated as semicrystalline materials due to the high level of the heterotacticity of the produced PLA.

The good activity and selectivity of the Zr-NHC complex along with its apparent robustness encouraged further investigations of this system to develop its attractive features for possible industrial application (*i.e.* simple and cost-effective catalyst synthesis, low catalyst cost and low trace of residual metal in the final product). In the presence of various alcohols, the Zr-NHC complex **4** polymerizes *rac*-lactide in a controlled and immortal manner to afford narrowly dispersed corresponding PLA. Scheme 3 displays some representative examples. Under these conditions, it is thus possible to generate well-defined and tailor-made block copolymers such as amphiphilic PEG-PLA, PDMS-PLA or polymers with specific liquid crystal properties (*i.e.* PLA with a cholesteryl end group).

Finally, the excellent polymerization performances of the Zr-NHC initiator **4** were further exploited for the synthesis of co-polymeric materials. Indeed, block copolymers, such as PTMC-PLA [PTMC = poly(trimethylene carbonate)], hold interest in many applications including biomaterials.[16] In particular, the micro-structure of block copolymers may potentially be controlled and fine tuned, which in turn impacts the properties of biomaterials. Such properties (biological, physical, mechanical, degradation…) can be controlled by modulating the nature of the block polymers. Also, the tacticity of the PLA fragment is obviously a parameter that will affect the final properties of the material. The Zr-NHC complex **4** was found to readily polymerize ε-caprolactone (CPL), glycolide (GA) or 1,3-trimethylene carbonate (TMC):[17] it is thus possible to generate well-defined heterotactic PLA-PCPL, PLA-PGA or PLA-PTMC (Fig. 4). These block copolymers were simply prepared by the initial ring-opening polymerization of ε-caprolactone, glycolide or 1,3-tri-
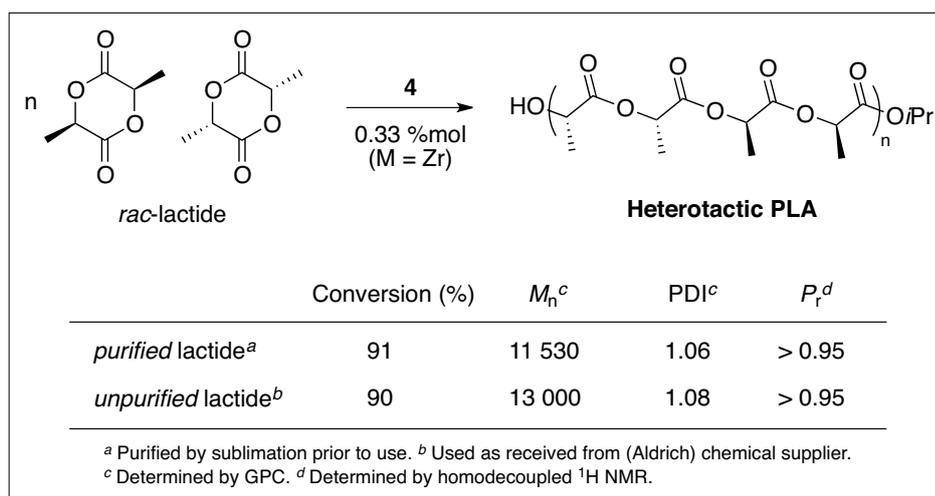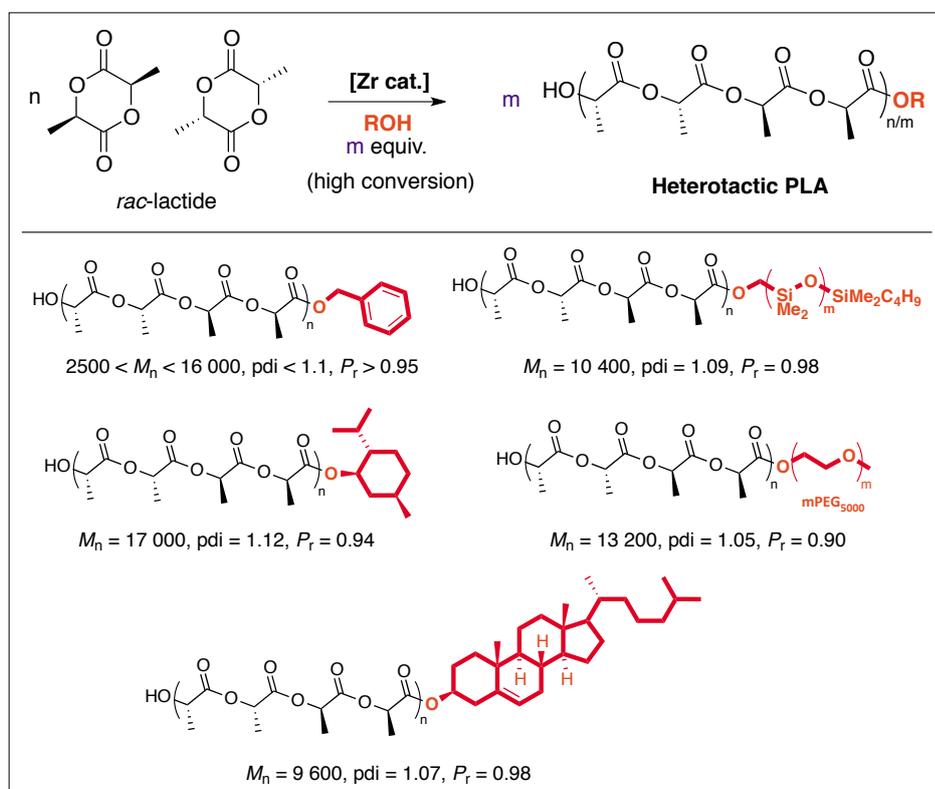

	Conversion (%)	$M_n{}^c$	PDI^c	$P_r{}^d$
purified lactide^a	91	11 530	1.06	> 0.95
unpurified lactide^b	90	13 000	1.08	> 0.95

^{a} Purified by sublimation prior to use. ^{b} Used as received from (Aldrich) chemical supplier. ^{c} Determined by GPC. ^{d} Determined by homodecoupled ^{1}H NMR.

Table 1. Ring-opening of *rac*-lactide initiated by the Zr species **4** (Conditions: CH$_2$Cl$_2$, [lactide] = 1 M, room temperature).

Scheme 3. Ring-opening of *rac*-lactide initiated by the Zr species **4** under catalytic conditions. Selected examples of the produced polymers.

methylene carbonate and the subsequent ROP of *rac*-lactide to yield well-defined, molecular-weight controlled and highly stereoregular heterotactic materials.

Conclusion

The tridentate NHC *bis*-phenolate ligand appears to be a quite versatile and robust ligand for coordination chemistry and its applications. The synthetic route of the ligand precursors is characterized by its ready synthesis through a three high-yield step procedure and facile purification. The preparation of the corresponding NHC car-

bene metal complexes is straightforward and high yielding. In the case of oxophilic metals, the alcohol elimination pathway involving the direct reaction of the azolium precursor with a metal alkoxide was found to lead to the corresponding complexes in quantitative yield and no further purification may be required.

As envisioned, such a ligand structure is suitable for coordination to a variety of metal centers across the periodic table from group 4 transition metals to group 13 metals, usually giving stable and highly robust compounds.

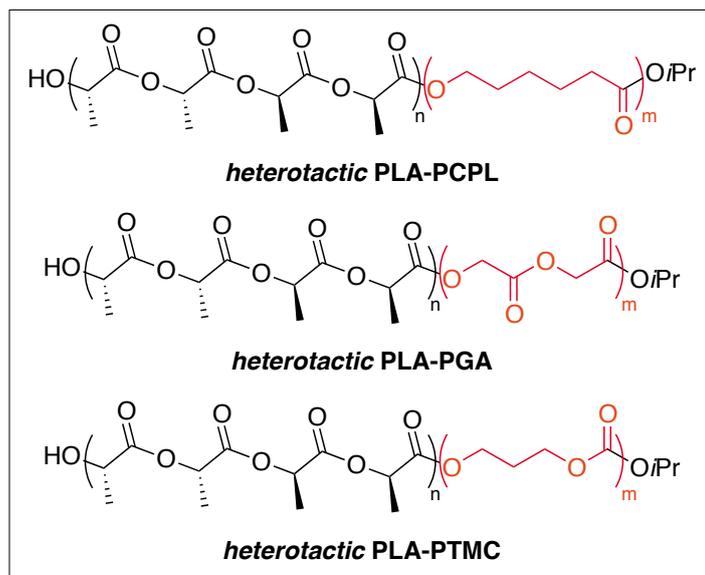The Zr-based NHC complexes efficiently mediate the controlled *stereo-*

Fig. 4. Examples of the molecular structure of block copolymers obtained using NHC-Zr **4** as initiator.

selective ring-opening polymerization of *rac*-lactide to produce highly chain-length controlled and heterotactic PLA at room temperature. Remarkably, these high levels of polymerization control and stereoselectivity are unaltered under catalytic conditions, *i.e.* in the presence of an excess of alcohol acting as a chain transfer agent. These initiators also allowed access to well-defined and highly heterotactic block *bio*-copolymers.

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