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Straightforward synthesis and catalytic applications of rigid *N*,*O*-type calixarene ligands†

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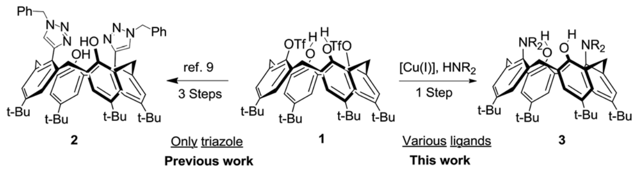
Here, we report a simple one-step access to new rigid *N*,*O*-calixarene ligands which is based on copper-catalyzed amination at the lower rim. We also present the coordination properties of these ligands with some main group and transition metals leading to new complexes with superior catalytic activity, in several organic transformations, compared with calixarene metal complexes reported in the literature.

While transition metal calixarene complexes have been known for several decades,[1–3] their catalytic applications received only sparing attention.[4–6] Unlike the more popular ligand systems that contain a combination of hard and soft heteroatoms, calixarene molecules possess only phenol-based hard donor centers which impair their coordination properties and catalytic behavior. To address this issue, calixarene ligands with softer donors as pendant groups have been prepared and their catalytic activity studied in much detail.[7] However, such design does not capitalize on the rigid core properties of the calixarene scaffold which remain largely unexplored.[8] We earlier reported the first *N*,*O*-type calixarene ligand **2** (Scheme 1, previous work) where two of the phenol groups were replaced with soft triazole rings.[9]

Catalytic activity of its Ti(IV) complex in TMS-CN addition to benzaldehyde was highly superior to the Ti complex of a parent non-modified calixarene. However, the ligand synthesis involved three steps starting from the known 1,3-calixarene bis-triflate **1** and was limited to the 1,2,3-triazole moiety not allowing useful modifications next to the coordination sites. Thus, we were interested in developing more general straightforward synthetic protocols to new *N*,*O*-type calixarene ligands allowing for easy optimizations of their coordination properties for potential catalytic applications. Herein, we present a one-step access to a variety of such ligands **3**, including a chiral one, and preliminary screening of these new ligands in various catalytic transformations (Scheme 1, this work).



Scheme 1 Ligand synthesis *via* coupling reactions at the lower rim.

Although direct Pd-catalyzed amination of aryl triflates with secondary amines is relatively well-developed, all our efforts to carry out such reactions in a calixarene system have been unsuccessful. In general, in our hands, out of many named coupling reactions the originally reported Sonogashira cross-coupling was the only Pd-catalyzed transformation that led to the desired product.[10] Having failed in the direct amination reaction with several Pd catalysts and various reaction conditions, we turned to the copper(I)-catalyzed amination. Copper catalysis was previously successfully employed for calixarene amination with primary amines,[11] however the reported protocol did not work for secondary amines. After screening of several reaction conditions, we found that using isopropanol as a solvent and CuOTf as a catalyst, converted **1** to a series of amine disubstituted calixarene compounds in moderate yields (Table 1). The developed procedure allows convenient access to aromatic (**3a**) and aliphatic (**3b–f**), including chiral (**3f**), ligands. In addition to complete NMR characterization, compounds **3a** and **3b** were also analyzed by X-ray crystallography (Fig. 1). Both compounds exhibit the calixarene cone conformation in the solid state with the nitrogen donors involved in the hydrogen bonding with the phenolic moieties.

With access to new *N*,*O*-type tetradentate ligands in hand, we moved to explore their coordination behavior. As expected, the hard dialkylaniline ligand **3b** readily formed complexes with the main-group metals. For example, the reaction of **3b** with $AlMe_3$ resulted in a new complex **4** which show signals at −0.18 ppm in the ^1H NMR spectrum due to the remaining

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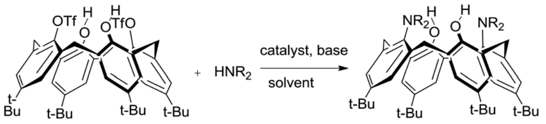
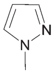
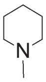
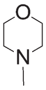
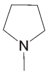
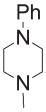
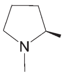
† Electronic supplementary information (ESI) available: Experimental details and spectral data of all the new compounds. CCDC 1427187–1427189 for **3a**, **3b** and **7**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob01987g

Table 1 Catalyst optimization for direct amination of calixarene 1,3-ditriflate **1**[a]



1 **3 a-f**

Entry	Amine	Catalyst	Base	Solvent	Yield[b], %	NR_2
1	Pyrazole	Pd_2dba_3/t-Bu_3P, CuI	DBU	DMF	—	
		Pd_2dba_3/t-Bu_3P, CuI	K_3PO_4	DMF	—	
		$Pd(OAc)_2$/t-Bu_3P	Cs_2CO_3	Toluene	—	
		CuI	K_3PO_4	Toluene	—	
		CuI	K_3PO_4	i-PrOH	29	 **(3a)**[d]
		CuCl	K_3PO_4	i-PrOH	28	**(3a)**[d]
		CuCN	K_3PO_4	i-PrOH	—	
		$(CuOTf)_2C_6H_5CH_3$	K_3PO_4	i-PrOH	58	**(3a)**[d]
		$(CuOTf)_2C_6H_5CH_3$	Na-O^{t}Bu	i-PrOH	—[c]	
		$(CuOTf)_2C_6H_5CH_3$	K_3PO_4	t-BuOH	34	**(3a)**[d]
2	Piperidine	$(CuOTf)_2C_6H_5CH_3$	K_3PO_4	i-PrOH	68	 **(3b)**[d]
3	Morpholine	$(CuOTf)_2C_6H_5CH_3$	K_3PO_4	i-PrOH	57	 **(3c)**[d]
4	Pyrrolidine	$(CuOTf)_2C_6H_5CH_3$	K_3PO_4	i-PrOH	53	 **(3d)**[d]
5	1-Phenyl piperazine	$(CuOTf)_2C_6H_5CH_3$	K_3PO_4	i-PrOH	50	 **(3e)**[d]
6	(R)-2-Methyl pyrrolidine	$(CuOTf)_2C_6H_5CH_3$	K_3PO_4	i-PrOH	46	 **(3f)**[d]

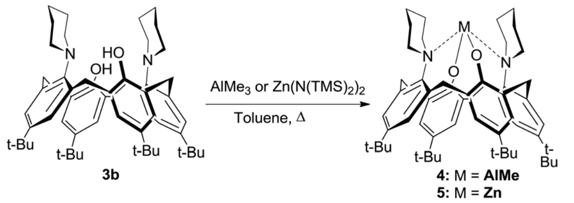
Reaction conditions. [a] 1,3 Bistriflate 1 (0.54 mmol), amine (4 equiv.), catalyst (10 mol%), ethylene glycol (3 equiv.), solvent (15 ml), 80 °C, 12 h. [b] Isolated yield. [c] Free calixarene. [d] Bis-xanthene[10,11] was the other major product.

Al–Me group (Scheme 2). Similarly, with $Zn(N(TMS)_2)_2$, new complex **5** was formed. Catalytic properties of these compounds are presently under investigation.

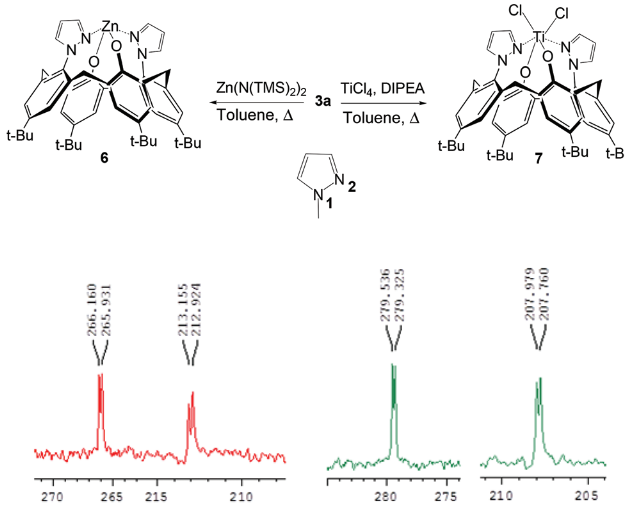
We were particularly interested in the reactivity of ligand **3a** since its pyrazole moiety possesses two different nitrogen donors that can potentially coordinate to a metal center. It was also likely to form stable complexes with transition metals and could be directly compared with **2**. The reaction between **3a** and $Zn(N(TMS)_2)_2$ in hot toluene produced a new complex **6** in 90% yield. Under the same conditions, the reaction between **3a** and $TiCl_4$ gave a new complex **7** in a 75% yield (Scheme 3).

To verify the pyrazole rings coordination mode, we also prepared **3a-N**, the ^{15}N-labeled analogue of **3a**, and studied its complexation with zinc and titanium by ^{15}N NMR spectro-

Fig. 1 ORTEP view (50% probability) of **3a** (left) and **3b** (right). Hydrogen atoms are omitted for clarity.



Scheme 2 Al and Zn complexes of ligand **3b**.



Scheme 3 Zn and Ti complexes of **3a** and their ^{15}N NMR spectra.

scopy. The ^{15}N NMR spectrum of **3a-N** shows two doublets at 298.6 (J_{NN} = 12.3 Hz) and 211.8 ppm. Comparison of these signals with the reported spectrum of *N*-methylpyrazole[13] allows the assigning of N1 and N2 nitrogen atoms in metal complexes of **3a** (Scheme 3). The reaction between **3a-N** and $Zn(N(TMS)_2)_2$ or $TiCl_4$ produced complexes **6-N** and **7-N**, respectively. The ^{15}N NMR spectrum of **6-N** exhibits two doublets at 266.2 ppm (J_{NN} = 9.2 Hz) and 213.1 ppm, while in **7-N** the same signals appear at 279.5 (J_{NN} = 9.2 Hz) and 208.0 ppm (Scheme 3). The substantial changes in the positions of the N2 atom signal compared with the free ligand strongly suggest that this atom is coordinated to the metal center. Final evidence for such coordination mode came from the X-ray structure analysis of **7** which showed **3a** behaving as a tetradentate ligand with the titanium center bound to the N2 atoms of the pyrazole moiety (Fig. 2).

As the structure of **7** is similar to that of the Ti complex of **2** (**2-Ti**), it was interesting to directly compare their catalytic activity in model organic reactions. We earlier reported that, in TMS-CN addition to benzaldehyde, **2-Ti** showed catalytic behavior superior to that of the titanium complex **8** of the 1,3-dimethoxycalixarene ligand. Gratifyingly, **7** was found to be significantly more active as a catalyst than **2-Ti** giving the product in a quantitative yield after 3 h at room temperature (Scheme 4).

Titanium complexes of multidentate ligands have been used extensively for catalytic alkene epoxidation.[14] Silica-grafted Ti calixarene complexes showed high selectivity in cyclohexene epoxidation with organic peroxides, the reactions taking place at 60 °C.[15] In addition, Ti complexes of tetradentate *N*,*O*-type salan ligands were successfully employed in asymmetric epoxidation.[16] Thus, we were interested to explore **7** as a catalyst in alkene epoxidation. We found that with 1 mol% of **7**, the epoxidation of cyclohexene with TBHP in CH_2Cl_2 was complete after 7 h at room temperature (Scheme 5). For comparison, under the same conditions, complex **2-Ti** gave the product in 45% yield, while using the Ti complex[15] **8** of a regular 1,3-dimethoxycalixarene ligand gave 27% yield of cyclohexene oxide.

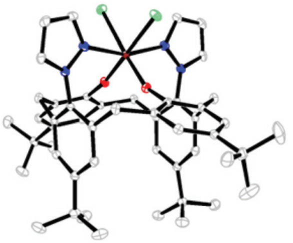
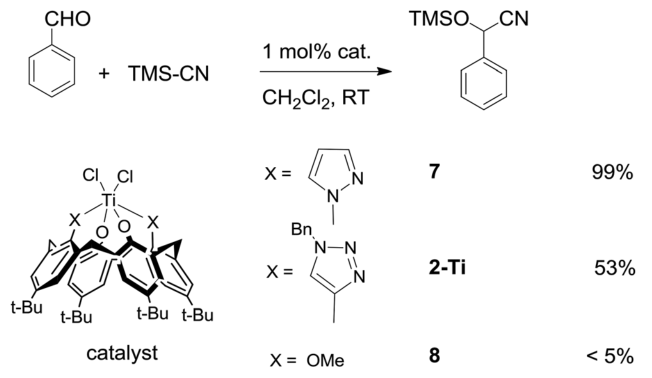


Fig. 2 ORTEP view (50% probability) of the Ti(IV) complex **7**. Hydrogen atoms are omitted for clarity.



Scheme 4 Catalytic cyanosilylation of benzaldehyde.

Scheme 5 Epoxidation of cyclohexene.

Table 2 Alkene polymerization catalyzed by **7**[a]

Entry	Alkene	Time, h	Activity (g mol^{-1} h^{-1})	Stereochemistry[b]
1	1-Hexene (neat)	10	15.3	Atactic
2	Styrene (neat)	3	52.3	Syndiotactic
3	Styrene (toluene)	12	11.2	Syndiotactic

Reaction conditions [a] 7 mg (10 μmol) of **7**, 500 equiv. of MAO (activator), room temperature, 3.39 g (5 mL) of 1-hexene, 1.18 g (2 ml) of styrene, 2 ml of styrene in 10 ml of toluene. [b] Determined by ^{13}C NMR.

Group 4 metal complexes of multidentate *N*,*O*-ligands have received a great deal of recent attention as catalysts for α-olefin polymerization.[17] In this regard, it was important to explore **7** as a catalyst in α-olefin polymerization reactions.[18] While poor activity in 1-hexene polymerization was observed when **7** was activated with $B(C_6F_5)_3$, using methylaluminoxane (MAO) as an activator led to a highly active catalytic system (Table 2, entry 1). At room temperature, a polymer with high molecular weight M_w of 186 kDa and low polydispersity (1.44) was obtained.[12] Similarly, a combination of **7** and MAO, was reactive in the polymerization of styrene both in neat styrene and toluene solution. Syndiotactic polystyrene was obtained in both cases (Table 2, entries 2 and 3).

In conclusion, we developed a one-step synthetic protocol toward new *N*,*O*-type calixarene molecules that rely on copper-catalyzed amination at the lower rim. The new compounds serve as dianionic tetradentate ligands in their main-group and transition metal complexes. A Ti(IV) complex of one such ligand showed superior catalytic activity in TMS-CN addition to benzaldehyde and cyclohexene epoxidation reactions compared with complexes of other calixarene-based ligands. It also behaves as an efficient catalyst for α-olefin polymerization. More studies on the catalytic properties of the new ligands are presently underway.

Author contributions

The manuscript was written through contributions of all authors.

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