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Giant N-heterocyclic carbene-containing macrocycles for cobalt-catalysed hydroboration of alkynes

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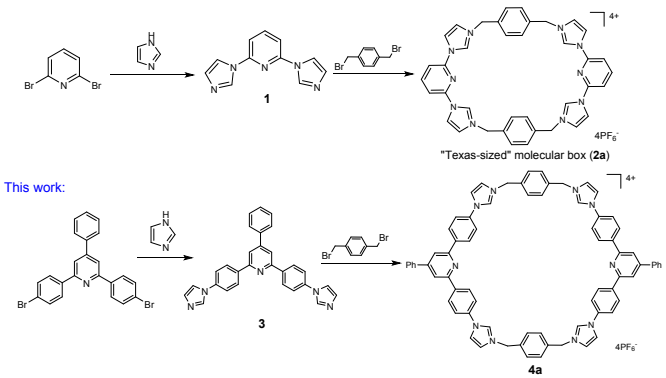
Giant N-heterocyclic carbene-containing organic macrocycles larger than "Texas-sized" molecular boxes have been synthesized and structurally characterized. The new macrocyles were employed for the Co-NHC promoted *syn*-selective hydroboration of alkynes with good stereo- and regioselectivity.

Organic macrocyclic structures have received considerable attention over the past decades, owing to their attractive properties in biological systems, supramolecular host-guest recognition and sensing, metal coordination chemistry and functional materials.[1-6] However, the design and synthesis of valuable macrocyclic molecules have been a challenging task as requirements exist for both functional chemical behaviors and facile structural modification for tunable properties.[7-9] In 2010, the Sessler group reported the synthesis of a class of new tetracationic imidazolium-based macrocycles, the so-called "Texas-sized" molecular boxes (TxSBs).[10,11] These macrocycles are structurally related to the known tetracationic cyclobis(paraquat-*p*-phenylene) ($CBPQT^{4+}$) that was also known as the "blue box" developed by Stoddart earlier.[12] However, unlike the rigid "blue box" macrocycles, the TxSBs are conformationally flexible with a larger central cavity that brings richer chemistry as macrocyclic hosts towards anionic recognition and self-assembly. The fundamental aspects as well as versatile applications of the TxSB family in supramolecular and materials chemistry have been well documented in a recent review.[13]

Intrigued by the fascinating chemistry the TxSBs displayed,[14] we were interested to investigate whether larger macrocycles could be synthesized utilizing methods similar to that for TxSBs synthesis. Typically, the synthesis of TxSBs involves an effective four-component cyclization of 2,6-bis(1H-imidazol-1-yl)pyridine (**1**, Scheme 1) and various bis-(bromomethyl)-substituted arenes. Although several different linking spacers to bridge molecule **1** have been explored following the observation of TxSB **2a** by the Sessler and Gong groups,[13] to our surprise, no examples attempting to replace the key linker molecule **1** have been reported in nearly a decade since the first publication of TxSBs.

An important structural feature of TxSBs is that there exist four N-heterocyclic carbene (NHC) units within the macrocycle, which may bring particular interest for metal complexation and catalysis, considering that NHC ligands have found extensive applications as versatile ligands for transition metal catalysis.[15] The NHC-ligating property has been overlooked for TxSBs, although their applications in supramolecular and materials chemistry have been explored.[13] Among known metal-NHC catalysts, Co-NHC complexes have attracted great attention as they displayed remarkable potential in (transfer) hydrogenation,[16] hydrosilylation[17] and many cross-coupling reactions.[15] However, NHC complexes of cobalt were rarely studied for hydroboration catalysis of alkenes that provide valuable boronate esters as key precursors for C-C coupling reactions,[18] and to the best of our knowledge they are unknown for alkyne hydroboration, while other cobalt catalysts have been reported for this reaction.[19]



Scheme 1. The synthesis of known "Texas-sized" molecular box and the greater macrocycle in this work.

We have recently reported the facile synthesis of a bis(1H-imidazol-1-yl)-derived ligand (**3**, Scheme 1).[20] **3** can be viewed as an elongated version of **1** without changing the directionality of imidazole-N donors. We envisioned that using **3** a similar cyclization reaction to that for TxSBs would work. Therefore, we present here our approach to an imidazolium-based tetracationic macrocycles (**4**) greater than TxSBs. We also report for the first time the application of such NHC-based macrocycles in cobalt-catalysed stereo- and regioselective hydroboration of alkynes.

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† Footnotes relating to the title and/or authors should appear here.
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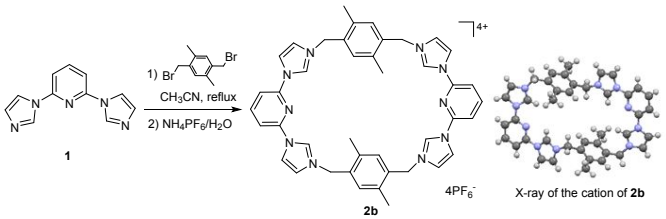
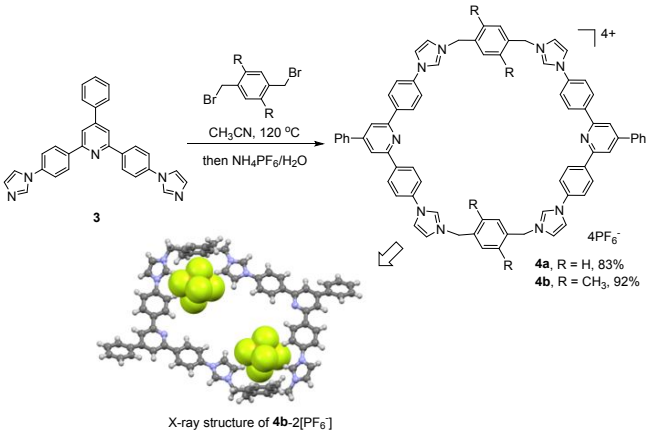
To facilitate the success of synthesizing the newly designed macrocycles (**4**), we first revisited the reaction conditions for the synthesis of TxSBs, yet by replacing the linking agent with a bulkier spacer, 1,4-bis(bromomethyl)-2,5-dimethylbenzene. Thus, the latter was reacted with equimolar **1** under refluxing conditions in acetonitrile for 48 h, according to the reported method for the synthesis of **2a**.[10] We were able to isolate pure **2b** after anionic exchange with NH_4PF_6 and recrystallization in 26% yield (Scheme 2). Compared to the 58% isolated yield for **2a** reported in the literature, the relatively low yield for **2b** could be attributed to the larger steric hindrance of the linking agent. **2b** was characterized by FT-IR, ^{1}H and ^{13}C NMR and high-resolution mass spectra (HR-MS). HR-MS of **2b** displayed peak envelops at m/z 1289.2031 and 1121.2511, corresponding to the species $[M + Na]^+$ and $[M – PF_6]^+$, respectively, which matched with those calculated. The solid-state structure of **2b** was demonstrated by X-ray crystallographic analysis. X-ray diffraction analysis confirmed that **2b** crystallizes in the triclinic space group *P*-1 (Scheme 1). Unlike **2a**, where three polymorphic crystals were isolated and showed distinct conformations of the macrocycle, *i.e.* "boat", "partial chair" and complete "chair" conformers (Fig. S2, see ESI). However, in the case of **2b**, only one kind of crystals were observed as inferred by careful examination of the bulk crystalline sample. **2b** adopts exclusively a "chair" conformation (Fig. S2). This indicates that molecules of **2b** are much less flexible than **2a**, owing to the presence of a sterically hindered space agent. Apparently extra methyl groups prevent the formation of a "boat" conformation.



Scheme 2. The synthesis of **2b**.

While attempts to synthesize the proposed larger macrocycles **4a** and **4b** by applying the same conditions as for **2b** were unsuccessful and the reactions led to complicated mixtures, we modified the reaction conditions by elevating the temperature to 120 °C in sealed tubes and pleasingly both **4a** and **4b** were isolated in high yields (83% and 92%, respectively) after anion exchange (Scheme 3). Both **4a** and **4b** were characterized by FT-IR, NMR spectroscopies and HR-MS (see ESI), consistent with their macrocyclic structures as proposed. Single crystals of **4b** were obtained by slow diffusion of diethyl ether to a dilute CH_3CN solution and its molecular structure was confirmed by X-ray crystallography (Scheme 3). Like **2b**, **4b** also crystallises in the triclinic space group *P*-1 and it adopts a C_2-cymmetry in the unit cell. The conformation of **4b** in the solid state could be described as distorted "partial chair", similar to one of those found for **2a**, yet it is more flattened. Two of the PF_6^- counterions sit closely at the ring with C-H···F hydrogen bonding. The macrocyclic structure thus adopts a nano-scale inner cavity with a dimension of approximately 0.9 × 1.4 nm (Fig. S3, ESI).

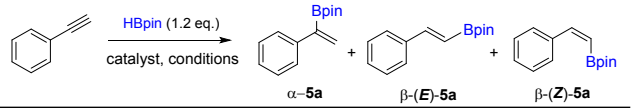
With the new macrocyclic NHC ligands in hand, we examined their role in cobalt catalysed hydroboration of alkynes. Initially, we chose phenylacetylene as a model substrate and the combination of NHC ligands with $CoCl_2$ and an activator as a catalyst. The results of



Scheme 3. The synthetic procedure for **4a** and **4b**, and the X-ray structure of **4b** (only two of the PF_6^- counterions are shown as space-filling representation).

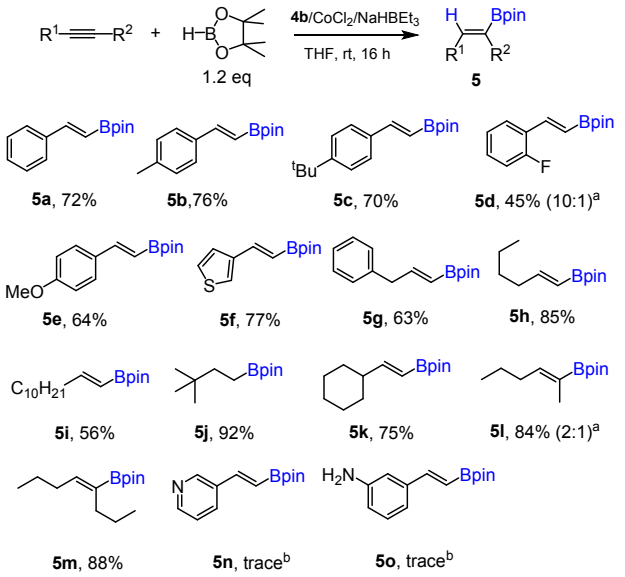
catalyst screening are summarized in Table 1. First, we tested the catalytic performance of **2b** (0.1 mol%) in the presence of 4.0 eq. $CoCl_2$ (four NHC units per ligand) and lithium triethylborohydride ($LiHBEt_3$, 1 mol%) in THF at room temperature. It shows the selective formation of alkenylboronate ester β-(*E*)-**5a** as the major product with 21% GC yield (entry 1). Pleasingly, when the larger macrocycles **4a** and **4b** were employed under the same conditions, the yield was improved to 60 and 65%, respectively (entries 2 and 3), with slightly

Table 1. Reactivity test for **1**-catalysed hydroboration of phenylacetylene with HBpin.[a]



Entry	ligand	Co salt	Additive	Yield of β-(*E*)-**5a**(%)[b]	Selectivity[c]
1	**2b**	$CoCl_2$	$LiHBEt_3$	21	1:90:5
2	**4a**	$CoCl_2$	$LiHBEt_3$	60	6:93:1
3	**4b**	$CoCl_2$	$LiHBEt_3$	65	5:94:1
4	**4b**	$CoCl_2$	-	2	N.D.
5	-	$CoCl_2$	$LiHBEt_3$	<5	N.D.
6	**4b**	$CoCl_2$	$NaHBEt_3$	83	4:95:1
7	**4b**	$CoCl_2$	$KHBEt_3$	66	4:95:1
8	**4b**	$CoCl_2$	KO^tBu	35	21:58:21
9	**4b**	$CoCl_2$	NaO^tBu	28	11:88:1
10	**4b**	$CoCl_2$	$LiNTf_2$	<5	N.D.
11	**4b**	$CoBr_2$	$NaHBEt_3$	74	1:98:1
12	**4b**	$Co(BF_4)_2$	$NaHBEt_3$	60	5:94:1
13	**4b**	$Co(acac)_2$	$NaHBEt_3$	65	7:92:1
14	**4b**	$Co(acac)_2$	$LiHBEt_3$	71	4:95:1
15	**4b**	$Co(BF_4)_2$	$LiHBEt_3$	75	6:93:1
16	**4b**	$Co(BF_4)_2$	$KHBEt_3$	70	3:96:1
17[d]	**4b**	$CoCl_2$	$NaHBEt_3$	42	3:96:1
18[e]	**4b**	$CoCl_2$	$NaHBEt_3$	76	4:95:1

[a] Conditions: phenylacetylene (1.0 mmol), pinacolborane (1.2 mmol), ligand (0.1 mol%), Co salt (0.4 mol%), additive (1 mol%) and THF (0.5 mL), rt, N_2, 16 h, N.D.: not detected. [b]Determined by GC analysis with hexamethylbenzene as an internal standard. [c]Ratio of α-**5a** : β-(*E*)-**5a** : β-(*Z*)-**5a** determined by GC analysis. [d]0.1 mol% $CoCl_2$ was used. [e]0.3 mol% $CoCl_2$ was used. $LiNTf_2$: lithium bis(trifluoromethane)sulfonimidate.



Scheme 4. The substrate scope of cobalt-catalyzed alkyne hydroboration with pinacolborane. Conditions: alkyne (1.0 mmol), HBpin (1.2 mmol), **4b** (0.1 mol%), $CoCl_2$ (0.4 mol%), $NaHBEt_3$ (1 mol%) and THF (0.5 mL), rt, N_2, 16 h, isolated yields. [a]Ratio of two *E*-regioisomers. [b]Determined by GC analysis.

better selectivity for β-(*E*)-**5a**. The different catalytic activity between **2b** and **4b** (or **4a**) can be tentatively attributed to their distinct coordination modes and the cavity sizes. While **2b** features typical CNC chelating coordination to cobalt, **4a** and **4b** have multiple monodentate-NHC sites in a larger macrocycle. Control experiments indicate both the NHC ligands and base activator were required to achieve the reactivity (entries 4 and 5). Next, we aimed to further improve the yield and/or selectivity by altering the activator or cobalt salt. It was found that the use of sodium triethylborohydride ($NaHBEt_3$) increased the yield to 83%, while maintaining the high stereo- and regioselectivity (95%, entry 6). Other cobalt salts such as $CoBr_2$, $Co(BF_4)_2$ and $Co(acac)_2$ gave slightly lower yields while the selectivity all remain at a high level (entries 11-16). Changing the Co/ligand ratio to 1:1 or 3:1 led to lower yields of β-(*E*)-**5a** with the same selectivity (entries 17 and 18).

Thus, the combination of **4b**, $CoCl_2$ and $NaHBEt_3$ was chosen as optimised conditions for the reactions of various alkynes with HBpin in the next step and the results are summarized in Scheme 4. In general, (heterocyclic) aromatic alkynes were suitable substrates for the *syn*-selective hydroboration affording *trans*-alkenylborate esters in appreciable yields after purification by column chromatography (**5a**-**f**), except that in the case of 2-fluorophenylacetylene, a moderate yield of the product **5d** was obtained, while contaminated with ~10% regioisomer (α-**5d**). In addition, both benzyl-substituted and aliphatic terminal alkynes proceeded smoothly with the isolation of desired products with 56-92% yields (**5g**-**k**). To this end, the present catalyst system was found to be effective for the hydroboration of internal alkynes, whereas in the case of the unsymmetric alkyne (2-hexyne) the level of regioselectivity was relatively lower (~67% for **5l**), which has been found previously in vanadium-catalysed alkyne hydroboration.[21] Finally, the limitation of substrates was also disclosed for 3-ethynylpyridine and 3-aminophenylacetylene, presumably owing to strong coordination of active cobalt center with N-donors that deactivates the catalyst (Scheme 4).

While a mechanism under operation for the regio- and stereoselective hydroboration is currently unclear without understanding the actual coordination mode of cobalt with the NHC-based macrocycle, we envision that an NHC-supporting cobalt hydride species could be the active catalyst responsible for *syn*-addition to terminal alkynes in an *anti*-Markovnikov manner that has been proposed for relevant cobalt-catalysed hydroboration of alkynes.[19d,22,23]

Conclusions

In summary, we report here the synthesis of NHC-containing macrocycles larger than the well-known "Texas-sized" molecular boxes and the crystal structure of one of the molecules. We have utilized the ability of the NHC-based macrocycles towards metal coordination and in-situ formed cobalt catalysts for the hydroboration of alkynes leading to stereo- and regioselective synthesis of boronate esters. A range of substrates including terminal and internal alkynes were effectively converted to the β-(*E*)-selective products with moderate to high yields. This represents the first example of the catalytic applications of TxSB derivatives and Co-NHC promoted hydroboration of alkynes. We are currently in progress of identifying the structures of the actual catalysts and reactive intermediates for a detailed mechanistic investigation.

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Conflicts of interest

There are no conflicts of interest to declare

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