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COMMUNICATION

The design and synthesis of novel IBiox N-heterocyclic carbene ligands derived from substituted amino-indanols†

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A synthetic route towards a number of novel IBiox N-heterocyclic carbene (NHC) ligands has been developed. The resulting ligands have restricted flexibility and high steric demand. Preliminary studies have shown these ligands to give high levels of asymmetric induction in the copper-free allylic alkylation of cinnamyl bromide.

The use of N-heterocyclic carbenes (NHCs) in preparative chemistry is now ubiquitous. Indeed, NHCs have a wide range of applications, from enabling ligands for transition metal mediated and main group processes, to highly useful organocatalysts.[1] Numerous studies have concerned the design and preparation of chiral NHCs to mediate stereocontrol in asymmetric reactions.[2,3] Despite this large body of work however, there are few such chiral NHCs that could be termed "privileged" due to a broad applicability to diverse reaction types. Using an alternative "privileged" ligand class, the bisoxazolines, as inspiration, Glorius and co-workers have pioneered the development of NHC ligands derived from oxazolines (IBiox, Fig. 1).[3] Such IBiox ligands have shown particular applicability as ligands in cross-coupling reactions of unactivated partners,[1a,3b] and more recently (for IBiox[(−)-menthyl] **3**) in asymmetric α-arylation reactions,[3c] and asymmetric hydroarylation reactions.[4] When we commenced our work in this area, we were surprised that IBiox ligands derived from an amino-indanol nucleus had not been significantly studied,[5] despite the fact that this unit has proved an extremely successful scaffold on which to build effective chiral NHC organocatalysts.[6] Furthermore, current issues in chiral NHC ligand design include the fact that the elements of chirality are often far from the reactive carbenic C-2 centre, and that chiral N-substituents often are freely rotating, defining a poor chiral space.[7] We felt the structurally rigid "wings" of the aminoindanol unit would provide a well defined chiral space around the C-2 centre. Indeed, key to our design was the use of substituents (R), which project directly into the C-2 centre, defining an effective, C_2-symmetric chiral pocket (see **4**, Fig. 1). We therefore decided to explore the synthesis of a selection of amino-indanol derived IBiox ligands, with a variety of R groups, and explore their use as chiral NHC ligands.

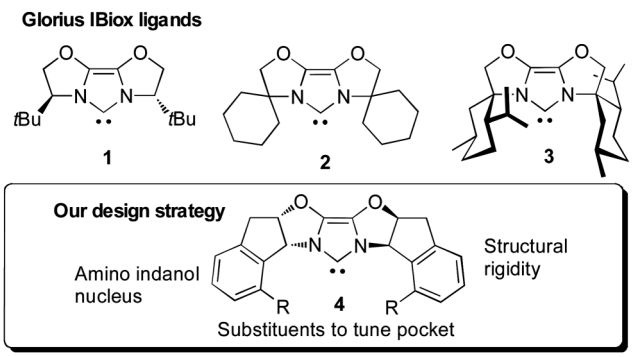
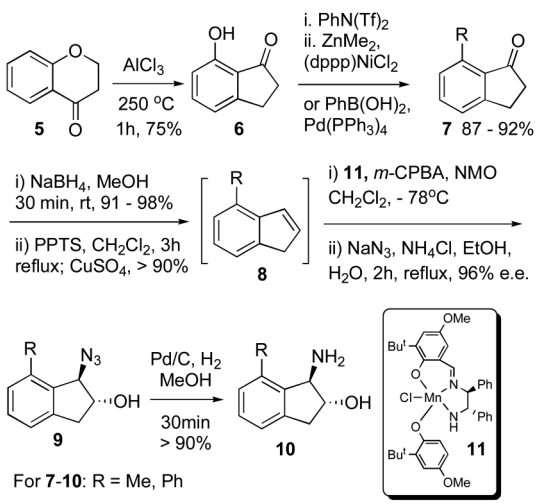


Fig. 1 Examples of IBiox ligands.

Rearrangement of the 4-chromanone (**5**) at high temperature in the presence of $AlCl_3$ afforded hydroxyindanone **6** (Scheme 1).[8] Triflation of **6** afforded the corresponding aryltriflate in excellent yield (99%). This was followed by either the use of dimethylzinc in the presence of a nickel catalyst, or a palladium-mediated cross-coupling reaction with phenylboronic acid to give the methyl



Scheme 1 Synthesis of aminoindanol derivatives (R = Me, Ph).

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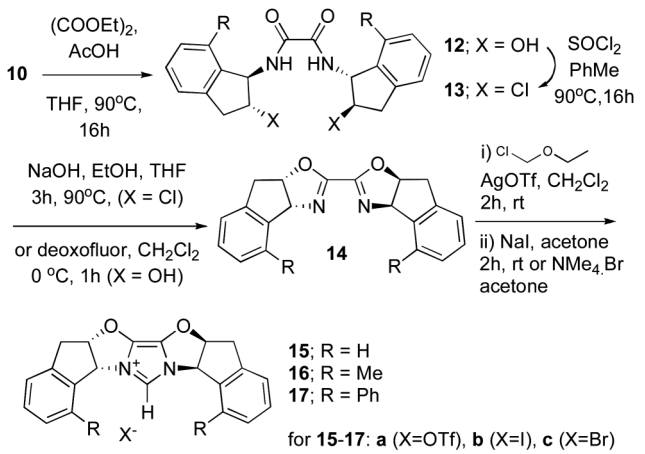
(R = Me) or phenyl (R = Ph) appended indanones **7** respectively. Exposure of the products to $NaBH_4$ afforded the corresponding benzylic alcohols. We found elimination of the resultant alcohol to yield the indene rather problematic, with polymerization of the indene readily occurring under acidic conditions. After an extensive survey of conditions however, two equivalents of pyridinium *p*-toluenesulfonate (PPTS) was found to be optimal. Since removal of the pyridine under reduced pressure resulted in the partial evaporation of the desired product, a modified work-up was employed using a saturated solution of copper sulphate to remove residual pyridine.

The crude indenes obtained were used to prepare the required amino-indanol derivatives **10** *via* epoxide formation and ring opened by sodium azide. The epoxidation reaction was performed with the (salen)Mn catalyst **11** designed by Jacobsen and co-workers to perform enantioselective epoxidation of indene.[9] Attempts at a rapid chromatographic purification of the epoxide failed due to conversion of the indene oxide to 2-indanone. Regioselective opening of the crude epoxide with sodium azide in the presence of ammonium chloride in refluxing aqueous ethanol afforded the *trans*-azido alcohols in a good yield after chromatography (Scheme 1).[10] At this stage the enantiomeric excess was determined by chiral HPLC. Pleasingly, the levels of asymmetric induction (96% e.e.) were comparable to those reported by Jacobsen for the epoxidation of indene. Reduction of the azide group *via* hydrogenation using activated palladium on charcoal was performed to give the desired *trans*-aminoindanols. Further purification on silica gel resulted in some degradation; therefore the crude material was directly used in the next step (Scheme 1).

Condensation of the aminoindanol **10** with diethyl oxalate was performed with a substoichiometric amount of amount of acetic acid to yield **12**. Chlorination of **12** was performed as described by Glorius.[3] Reflux of **12** with 5 equivalents of thionyl chloride afforded the desired products **13** in good yield. Subsequent heating of **13** in the presence of sodium hydroxide gave the cyclized products. This reaction sequence could be telescoped (**9** to **14**) without purification of the intermediates in good yield over the four steps. Alternatively, formation of the bisoxazoline **14** could be achieved in one step from the alcohol **12** using deoxofluor as previously described by Wipf and co-workers to promote the direct cyclization of amino alcohols to oxazoline rings.[11] This method in general proved to be a faster and more reliable strategy (Scheme 2). The bisoxazolines were isolated as single stereoisomers due to the small amount of the *meso* compound being removed during purification.

The final step of our reaction sequence consisted of the cyclization to the desired imidazolium salts. Using the Glorius procedure, chloromethyl pivalate was stirred with silver triflate at ambient temperature for one hour in the dark, followed by transfer of the resultant reagent to a solution of the bisoxazoline **14** in dichloromethane. Unfortunately, there was no formation of the desired imidazolium salt. After 70 h at 40 °C, starting material was still observed along with some decomposition. After some experimentation, we found that degassing and drying the dichloromethane with molecular sieves and performing the reaction in the microwave at 90 °C gave the imidazolium salt in low yield (22%). An exploration of different solvents did not improve this low yield. We hypothesized that the high propensity



Scheme 2 Formation of imidazolium salts **15–17**.

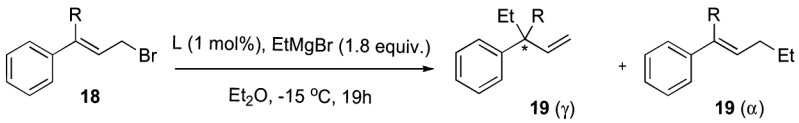
of the pivalate group to leave led to the subsequent undesired side reactions and we therefore sought an alternative electrophile. Hong and co-workers have previously synthesized constrained imidazolium salts with chloromethyl ethylether under ambient temperature in THF.[12] Indeed this was the original reagent used by Arduengo and co-workers in their seminal work.[13] These reported conditions did not yield the desired imidazolium salt in our case. A modified version using one equivalent of chloromethyl ethylether and silver triflate in dichloromethane showed consumption of the starting material after two hours at ambient temperature and the crude NMR showed the desired compound as the main product. Unfortunately, purification by chromatography resulted in partial decomposition. To combat this, the triflate counterion was immediately exchanged for an iodide or a bromide which proved to be more stable to chromatography. To our delight this provided the desired target salts **15–17** (41–61%, Scheme 2). We solved crystal structures for our three novel IBiox precursor imidazolium salts. The crystal structure of **16** is shown in Fig. 2 and **15** and **17** are shown in the ESI.† Of interest, the structure of **17a** was found to contain two crystallographically independent cations in the asymmetric unit (see ESI†). For both of these cations the C-2 proton is encapsulated by the phenyl substituents such that there are a pair of C–H $\cdots\pi$ interactions. For molecule **17a-A** the H $\cdots$ centroid separations are *ca.* 2.59 and 2.80 Å with the H $\cdots\pi$ vectors inclined by *ca.* 89 and 80° to the ring plane respectively, whilst for molecule **17a-B** the H $\cdots$ centroid separations are *ca.* 2.66 and 3.02 Å with the H $\cdots\pi$ vectors inclined by *ca.* 72 and 83° to the ring plane respectively. In support of such C–H $\cdots\pi$ interactions in this compound, the C-2 proton of salt **17** shifts from around 9.8 to 4.71 ppm in the ^{1}H-NMR spectra. With this structural data in hand, we felt it would be interesting to quantify

Table 1 Calculated buried volume (%V_{bur})

Entry	Ligands	%V_{bur}[a]
1	**3**	51.6
2	**4** (R = H)	36.3
3	**4** (R = Me)	50.1
4	**4** (R = Ph)	80.5

[a] The calculations used Samb*V*ca[15] with the following parameters: radius of sphere, 3.5 Å; distance from sphere, 2.1 Å; mesh step, 0.05 Å.

Table 2 Different conditions for asymmetric allylic alkylation reaction



Entry	Ligand precursor	Substrate	Addition rate	Additive	NMR Conv. %	γ[a]	α[a]	% ee[a]
1	**15b**	R = H	Slow	None	>99	1.0	1.1	74
2	**16b**	R = H	Slow	None	>99	1.0	2.8	87
3	**17b**	R = H	Slow	None	23	0	1	/
4	**16c**	R = H	Slow	None	>99	1.0	3.4	86
5	**16c**	R = H	Fast	None	>99	1.0	3.3	86
6	**15b**	R = Me	Slow	None	>99	1.7	1	57
7	**16c**	R = Me	Slow	None	74	1.1	1	56

[a] Determined by GC using a Chiracil-Dex-CB column.

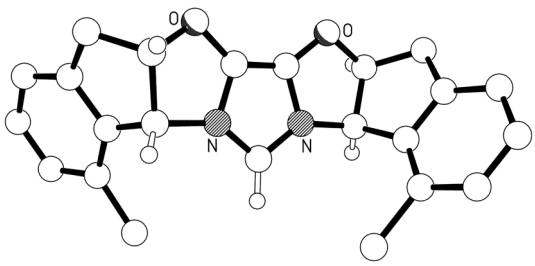


Fig. 2 The molecular structure **16b** (counterion omitted).

the steric demand of our ligands using the buried volume metric (%V_{bur}).[14] The buried volume of the most commonly used NHCs ranges from 35 to 47%. Glorius' sterically demanding chiral NHC ligand **3** (see Fig. 1) was reported to have the largest buried volume ever reported for any monodentate ligand (Table 1, entry 1).[1b,3c] Calculating the buried volume for our ligands[15] gave a value of 36.3 for the unsubstituted ligand, which is comparable to IMes (Table 1, entry 2). The methyl substituted ligand had a %V_{bur} of 50.1 which is comparable to ligand **3** (Table 1, entry 3). %V_{bur} for the phenyl derivative was an incredible 80.5 (Table 1, entry 4), which, to the best of our knowledge is the largest buried volume ever reported for any ligand.

We next sought a suitable reaction to test the applicability of our novel chiral ligands. While there has been much activity on the copper-catalyzed allylic alkylation (CAAA),[12,16–19] in line with pioneering work of Hoveyda and co-workers on activation of Grignard reagents by NHC Lewis bases,[20] Alexakis and Hoveyda have demonstrated that the allylic alkylation could be equally as efficient *without* copper with NHC ligands.[20,21] We felt that such copper-free allylic alkylation would be an interesting case study for our novel IBiox ligands.

Following slow addition of the Grignard reagent to a solution of cinnamyl bromide **18** (R = H) and the ligand at −15 °C, the reaction was stirred for 19 h at −15 °C. The results are shown in Table 2. For reactions employing ligands bearing an unsubstituted indanol unit **4** (R = H) or a methylated unit **4** (R = Me, entries 1 and 2), full conversion to the products was observed. For our phenyl-substituted derivative **4** (R = Ph) however, only low conversion was observed (entry 3). This lack of activity is most likely due to the large steric bulk of this ligand, as demonstrated by the calculated buried volume, hindering coordination to the magnesium species. To our delight, good levels of asymmetric induction were observed. This is, to our knowledge, the highest ee value that has been reported in this reaction from an NHC ligand lacking a further potentially chelating function (OH,[20–22] SO_3H[23]), as used in previous studies. Interestingly, the change of counterion does not have an effect on the selectivity or the enantioselectivity (entries 2, 4 and 5). Finally, the speed of addition of the Grignard reagent had no discernable effect.

To further explore this reaction, another substrate, α-methyl cinnamyl bromide **18** (R = Me) was also surveyed using our ligands. In line with previous studies,[21] a somewhat better γ-selectivity was observed at the cost of some enantioselectivity (entry 1 *vs.* 7). Interestingly, although it significantly increases the %V_{bur}, the additional methyl functionality in ligand **4** (R = Me) appears not to be significantly involved in the selective transition state for this substrate.

Conclusions

We have developed an efficient route to novel amino-indanol derived IBiox NHCs, thus extending this important family of ligands. Our novel ligands have a very large percentage buried volume and are effective in allylic alkylation chemistry. An in depth exploration of their use is currently underway in our laboratories.

Acknowledgements

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