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IBiox[(−)-menthyl]: A Sterically Demanding Chiral NHC Ligand

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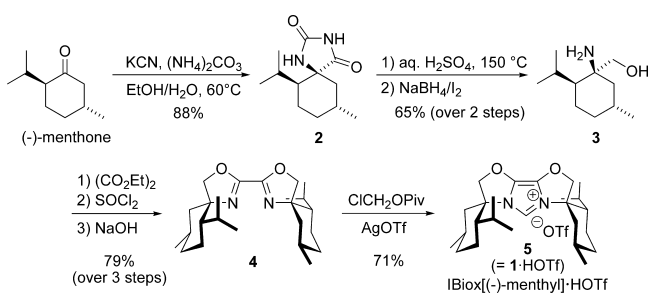
In recent years, N-heterocyclic carbenes (NHCs)[1] have become an important class of ligands for transition-metal catalysis.[2] The reactivity and attractiveness of metal−NHC complexes in catalysis can be attributed to three main properties: very strong σ-donor character of the NHC ligands, high stability of the metal−NHC bond and thus of the complexes themselves, and finally, their large steric demand.[2] The latter feature favors the formation of low-coordinate metal complexes,[3,4] which is key to the catalysis of challenging transformations such as cross-coupling reactions of non-activated aryl chlorides.[5] Herein we report on the synthesis of a most sterically demanding, monodentate, *and* chiral NHC ligand, IBiox[(−)-menthyl] (**1**), and its successful application in palladium-catalyzed asymmetric α-arylation of amides.

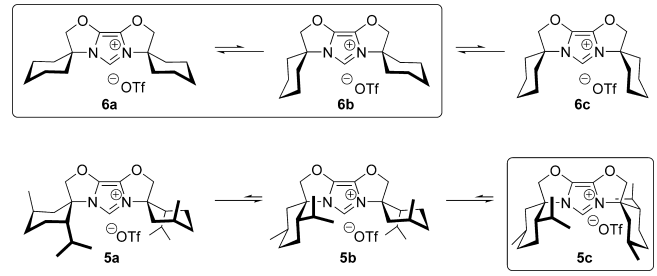
Commercially available, enantiopure (−)-menthone was found to be an ideal starting point for the synthesis of the imidazolium salt and NHC precursor **1**·HOTf (**5** in Scheme 1). Starting with a Bucherer reaction, (−)-menthone was converted to the corresponding hydantoin **2**, providing a single diastereomer after recrystallization.[6] Its challenging hydrolysis was accomplished under vigorous conditions using aqueous sulfuric acid at 150 °C, and this was followed by reduction to the amino alcohol **3**. Through an established protocol,[7] this amino alcohol was smoothly converted to bioxazoline **4** (Scheme 1). The final imidazolium salt formation was realized with the reagent formed by mixing AgOTf and chloromethyl pivalate in CH_2Cl_2.[8]

The IBiox[(−)-menthyl] ligand **1** is structurally related to the cyclohexyl-substituted ligand precursor **6**. The usefulness of **6** in palladium-catalyzed cross-couplings of sterically hindered substrates has been demonstrated.[7b−e] Because of the chair flip of the cyclohexyl rings, this ligand system is structurally dynamic. It has been shown that the least sterically demanding conformations (**6a** and **6b**) prevail (Scheme 2).[9] In (−)-menthyl-derived **5**, however, the additional alkyl substituents on the cyclohexyl rings shift the equilibrium toward the most sterically demanding conformation, **5c**. NMR studies at −80 °C and room temperature showed only one set of signals.[10] Single-crystal structural analysis of **5**[10] unequivocally confirmed conformation **5c**, clearly demonstrating the enhanced steric demand of the novel ligand compared to **6** (Scheme 2).

Scheme 1. Synthesis of the (−)-Menthone-Derived IBiox Salt **5**



Scheme 2. Conformational Equilibria of Ligand Precursors **5** and **6**



The free carbene **1** was cleanly formed by in situ deprotonation in THF-d_8 using NaO*t*Bu as a base. A characteristic signal at δ 194.6 in the ^{13}C NMR spectrum was indicative of the carbene carbon. Most importantly, we succeeded in the formation and crystal structure analysis of **7**, a AgBr complex of **1** (Figure 1).[10] This unequivocally demonstrates the ability of **1** to act as a ligand as well as its extraordinary steric demand, not only as a ligand precursor but also as a ligand.

In order to allow a quantification of the steric demand, the *buried volume*[11] was calculated. Whereas **6a** exhibits a buried volume comparable to IMes, that of **6b** is similar to those of the most sterically demanding monodentate ligands SItBu and SIAd.[11e] However, this steric demand is significantly exceeded by that of IBiox[(−)-(menthyl)], which has a buried volume of ∼50% (Table 1, entries 3 and 4). To the best of our knowledge, this represents by far the largest buried volume ever reported for any monodentate ligand.

The first asymmetric, palladium-catalyzed intramolecular α-arylation of amides for the synthesis of α,α-disubstituted oxindoles **9**

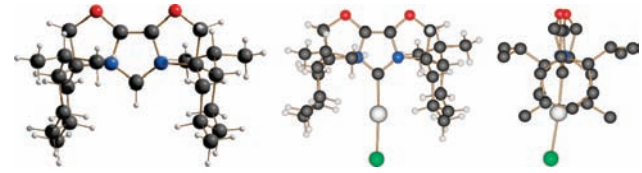


Figure 1. Crystal structures of the imidazolium triflate **5** and the AgBr complex **7** (front and side views) in the ball-and-stick representation (the triflate anion of **5** and hydrogen atoms in the side view of **7** have been omitted for clarity). Selected bond lengths (Å) and angles (deg) for **7**: Ag−Br, 2.4426(6); Ag−C1, 2.098(4); Ag···H5AA, 2.66; Ag···H5BB, 2.79; Ag···H7A, 2.46; Ag···H7B, 2.38; Br−Ag−C1, 175.3(1); N1A−C1−N1B, 101.7(3).

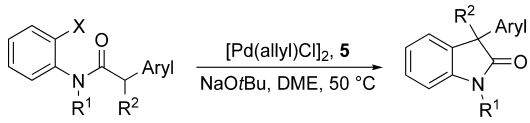
Table 1. Calculated Buried Volumes[a]

entry	ligand	buried volume (%)
1	conformation **6a**	31.1
2	conformation **6b**	39.3
3	IBiox[(−)-(menthyl) (**1**) in **5**	51.6
4	IBiox[(−)-(menthyl) (**1**) in **7**	47.8

[a] The calculations used Samb*V*ca[11e,f] with the following parameters: radius of sphere, 3.5 Å; distance from sphere, 2.1 Å; mesh step, 0.05 Å.

10.1021/ja901018g CCC: $40.75

Table 2. Intramolecular α-Arylation[a]



8 9

entry	X	R^1	R^2	aryl	yield (%)[b]	ee (%)[c]
1	Cl	Me	Me	Ph	91	84
2	Br	Me	Me	Ph	91	81
3	Cl	Bn	Et	Ph	99	85
4	Br	Bn	Et	Ph	94	87
5[d]	Cl	Me	Me	*o*-tol	89	95
6	Cl	Me	Me	*o*-anisyl	82	95
7	Cl	Me	Me	1-naphthyl	99	96
8	Br	Me	Me	1-naphthyl	89	95
9	Cl	Bn	Me	1-naphthyl	86	97
10[e]	Cl	Bn	Me	1-naphthyl	91	92
11	Br	Bn	Me	1-naphthyl	95	97
12[f]	Cl	Bn	Bn	1-naphthyl	83	92
13[f,g]	Cl	Bn	Bn	*o*-anisyl	80	92[h]

[a] Reaction conditions: 0.3 mmol scale, NaO*t*Bu (0.45 mmol), $[Pd(allyl)Cl]_2$ (2.5 mol %), **5** (5 mol %), DME (3 mL), 50 °C, 12−16 h. [b] Isolated yield. [c] Determined by HPLC. [d] 80 °C. [e] 100 °C, 30 min. [f] 90 °C. [g] 24 h. [h] At 80 °C, product **9** was obtained in 37% yield with 99% ee.

was reported by Hartwig et al.[12,13] Although many chiral phosphine and NHC ligands were screened, only moderate enantioselectivities were obtained. Recently, through the use of several novel ortho-substituted α-alkylbenzylamine-derived imidazolylidene ligands, much higher ee's (up to 94%) were reported by Kündig and co-workers[14] with aryl bromides as substrates.[15]

In order to improve these results, we investigated the application of IBiox[(−)-menthyl] in the palladium-catalyzed intramolecular α-arylation of aryl bromides and chlorides **8**. By screening of different reaction conditions, we found the palladium source $[Pd(allyl)Cl]_2$, the base NaO*t*Bu, and the solvent DME to be optimal. For the first time, ligand **1** allows the conversion of the generally less reactive aryl *chlorides* (**8** with X = Cl)[5] under mild reaction conditions in high yields and with high levels of enantioselectivity (Table 2, entries 1, 3, 5−7, 9, 10). Independent of the substitution pattern of the substrates, good to excellent yields were obtained in all cases. Remarkably, in the case of sterically more demanding substrates, IBiox[(−)-menthyl] generally led to the formation of the corresponding oxindoles with increased ee's. Higher ee's were obtained with synthetically more versatile N-benzyl-substituted substrates than with the N-methyl-substituted substrates (entries 8, 11). The highest ee's (92−99%) were obtained with substrates bearing ortho-substituted arenes at the α-position of the amide (entries 5−13). Remarkably, these results are complementary to the ones obtained by Kündig, who obtained lower ee's for more hindered substrates.[14a]

When the reaction temperature was raised from 50 to 100 °C, the reaction time was significantly reduced to only 30 min (entry 10). This allowed one of the most sterically demanding substrates in our study to be converted into the corresponding oxindole in good yield and with a remarkably high ee of 92% (entry 10). This finding is another indication of the high level of rigidity of the novel IBiox ligand **1**, even at higher temperatures.[10] This enables the conversion of less reactive substrates at higher temperature without significant loss of enantioselectivity (entry 5).

In conclusion, we have synthesized a (−)-menthone-derived and exceedingly sterically demanding C_2-symmetric NHC ligand, IBiox[(−)-menthyl] (**1**). The ability to use aryl chloride substrates and to obtain high levels of enantioselectivity (up to 99%) in intramolecular palladium-catalyzed α-arylations reveals the unique reactivity and selectivity of this ligand system. The investigation of other challenging applications of metal complexes of **1** and the syntheses of related NHCs are ongoing.

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Supporting Information Available: Experimental procedures, full spectroscopic data for all new compounds, and crystallographic data for **5** and **7** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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