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Design and asymmetric synthesis of chiral diaryliodonium salts

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ABSTRACT

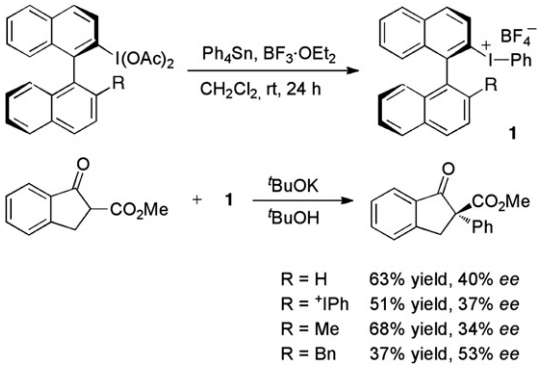
The application of chiral hypervalent iodine reagents in asymmetric synthesis is highly desirable, as the reagents are metal-free, environmentally benign and employed under mild conditions. Three chiral diaryliodonium salts have been designed to provide chemoselectivity and asymmetric induction in asymmetric α-phenylation of carbonyl compounds. The synthetic routes to the selected targets are detailed herein, together with a structural investigation into the diastereoselectivity of the alkylation process.

1. Introduction

Hypervalent iodine compounds have emerged as selective and environmentally benign reagents in many areas of organic synthesis.[1–3] Iodine(III) reagents with two heteroatom ligands are employed in α-oxidations of carbonyl compounds, oxidations of alcohols, carbon–carbon bond formation, and many other transformations.[1–3]

Diaryliodonium salts, also named diaryl-λ^3-iodanes, are iodine (III) reagents with two aryl ligands. They are efficient electrophilic arylation reagents for a number of nucleophiles, including enolates, phenols, and amines.[4] Furthermore, they can be employed in a wide range of cross-coupling reactions under metal-catalyzed or metal-free conditions.[4–6]

Recent progress in hypervalent iodine chemistry has focused on the development of catalytic methodology[7–9] and asymmetric applications using chiral reagents.[10] The first chiral hypervalent iodine compound ever reported, diphenyliodonium tartrate, was published already in 1907.[11] Surprisingly few chiral diaryliodonium salts have since then appeared in the literature.[12] In 1999, Ochiai and co-workers reported the synthesis of 1,1′-binaphthyl-2-yl(phenyl) iodonium salts **1** (Scheme 1).[13] The efficiency of the salts was evaluated in arylations of β-keto esters, and gave α-phenylated products in moderate yields and enantioselectivities.[13] In a similar fashion, Zhdankin and co-workers prepared chiral benziodazole structures, where the *N*-functionalized amide moiety acted as internal anion.[14]



Scheme 1. Asymmetric phenylation with chiral diaryliodonium salts.

Aggarwal and Olofsson used a different strategy to realize enantioselective α-arylation of carbonyl compounds with diaryliodonium salts. Asymmetric induction was obtained by the use of a chiral base, followed by treatment with an achiral diaryliodonium salt. This methodology was applied in an efficient total synthesis of (−)-epibatidine (Scheme 2).[15] Although this arylation protocol is highly enantioselective, it can only be applied to a limited set of cyclic, prochiral substrates.

We have recently performed a theoretical study on the mechanism of α-arylation of carbonyl compounds with diaryliodonium salts, which together with experimental results led to the conclusion that asymmetric induction cannot be achieved by use of chiral anions or chiral PTC.[16] Thus, the design of chiral diaryliodonium

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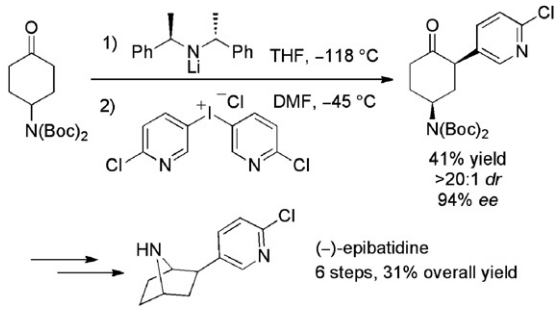


Scheme 2. Asymmetric synthesis of (−)-epibatidine.

salts, where one of the aryl moieties have substituents with stereogenic elements, remains as one of few possibilities to obtain enantioenriched α-arylated carbonyl compounds using hypervalent iodine reagents.

The development of chiral hypervalent iodine(III) compounds with two heteroatom ligands has been more successful.[17] Catalytic reactions involving chiral iodine(III) reagents have also resulted in high enantioselectivities.[18,19] In 2008, Kita and co-workers employed chiral reagent **2**, with a rigid 1,1-spiroindanone backbone, in oxidative spirolactonizations (Fig. 1).[20] Very recently, Ishihara's group reported the use of C_2-symmetric chiral iodane **3** in the same reaction.[21] Both reagents could be formed in situ from the corresponding aryl iodide with a stoichiometric amount of *m*-chloroperbenzoic acid (*m*CPBA).

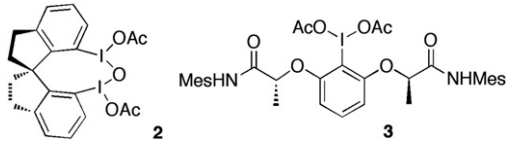


Figure 1. Chiral iodine(III) reagents used in oxidative spirolactonization.

The synthesis of chiral diaryliodonium salts has been an ongoing project in our laboratory for some time. The similarity between Ishihara's chiral iodane **3** and our chiral salts prompted us to report our results in the synthesis of chiral, enantiopure diaryliodonium.

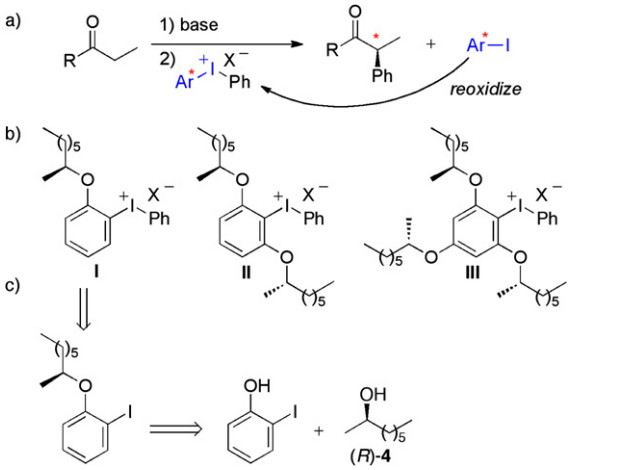
2. Results and discussion

2.1. Design and synthetic strategy

The design of chiral diaryliodonium salts is limited by the often harsh conditions used in the synthetic routes. Therefore, the use of acid- or base-labile substituents should be avoided. The absence of catalytic arylation protocols, where the diaryliodonium salt is formed in situ from the corresponding iodoarene, makes stability issues of the target compounds a difficult problem. The recent success in applications of chiral iodine(III) reagents with two heteroatom ligands has indeed often depended on catalytic formation of the chiral iodine(III) species, thus avoiding stability issues in the isolation.

When unsymmetric diaryliodonium salts are employed in enolate and heteroatom arylations, the aryl groups can often be differentiated. Generally, the more electron-deficient aryl moiety is selectively transferred, although aryl moieties bearing *ortho*-substituents are sometimes transferred despite being more electron-rich (the so-called *ortho*-effect).[22,23]

We envisioned the use of diaryliodonium salts where one of the aryl groups is more electron-rich and has substituents bearing stereocenters. This aryl moiety should behave as a chiral ligand and promote asymmetric induction in the transfer of the other, more electron-deficient, aryl group to the nucleophile (Scheme 3a). The resulting chiral iodoarene could be recovered and reoxidized into the chiral salt to provide good atom economy.

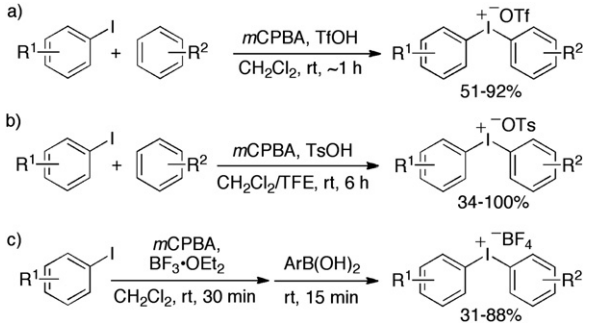


Scheme 3. a) Expected chemoselectivity in the arylation. (b) Target structures. (c) Retrosynthetic analysis.

Three target structures (**I**–**III**) were designed to fulfill these demands, having one, two or three substituents (Scheme 3b). *ortho*-Substituents with stereocenters were selected to deliver asymmetric induction by close proximity to the iodine. Furthermore, the oxygen-based substituents should make the aryl moiety electron-rich enough to give chemoselective phenyl transfer. The steric bulk of the substituents was given careful consideration, as too small substituents were likely to cause little induction, while too large substituents could give rise to undesired chemoselectivity by the *ortho*-effect. The long aliphatic chains were selected to improve the solubility and thus allow arylation reactions in a variety of solvents.

The number of substituents was expected to influence the reactivity, asymmetric induction and chemoselectivity in arylation reactions. In the synthesis of mono- and disubstituted targets **I** and **II**, regioselectivity issues must be controlled, which limits the number of possible synthetic routes. The diaryliodonium salts would be derived from the corresponding substituted iodoarenes, which could be prepared from the iodophenol and enantiomerically pure alcohol (*R*)-**4**, as shown for target **I** (Scheme 3c).

The synthesis of the diaryliodonium salts was envisioned using the methodology recently developed in our laboratory (Scheme 4). Symmetrical and unsymmetrical diaryliodonium triflates can be obtained in high yields and short reaction times employing *m*CPBA and trifluoromethanesulfonic acid (TfOH), as depicted in Scheme 4a.[24,25] The protocol can be extended to the direct formation of diaryliodonium triflates from iodine and arenes.[24–26]



Scheme 4. Some of our one-pot routes to diaryliodonium salts.