A Triazole-Substituted Aryl Iodide with Omnipotent Reactivity in Enantioselective Oxidations**

Ayham H. Abazid and Boris J. Nachtsheim*

Abstract: A widely applicable triazole-substituted chiral aryl iodide is described as catalyst for enantioselective oxidation reactions. The introduction of a substituent in ortho-position to the iodide is key for its high reactivity and selectivity. Besides a robust and modular synthesis, the main advantage of this catalyst is the excellent performance in a plethora of mechanistically diverse enantioselective transformations, such as spirocyclizations, phenol dearomatizations, α-oxygenations, and oxidative rearrangements. DFT-calculations of in situ generated hydroxy(tosyloxy)iodoarene isomers give an initial rational for the observed reactivity.

Hypervalent iodine compounds are versatile oxidants which have been utilized with great success in a plethora of oxidative coupling reactions[1] and in natural product synthesis.[2] In related enantioselective processes, a chiral aryl iodide precursor can be used in catalytic amounts in combination with a terminal co-oxidant to generate a chiral hypervalent iodine compound in situ. This chiral oxidant is subsequently capable of transferring its chirality onto the desired coupling products through diastereotopic transition states in the key oxidative C–X bond forming step.[3]

Since the discovery of the first enantioselective transformation catalyzed by a chiral aryl iodide in 2007 by Wirth and co-workers,[4] more than a dozen highly diverse C1- and C2-symmetric chiral aryl iodides have been developed.[5] Successful catalysts, such as 1–4 (Figure 1), usually show a good reactivity and selectivity in only one distinct class of oxidative transformation. So far there is no omnipotent chiral aryl iodide available that performs well throughout the most important oxidative transformations and hence can be seen as broadly applicable catalyst for iodane-based enantioselective couplings. Our group is heavily interested in the development of N-heterocycle-stabilized iodanes (NHIs) as a new class of stable and at the same time highly reactive hypervalent iodine compounds.[6,7] With the aim to design novel chiral aryl iodides which are robust to synthesize in a modular sequence and show a good performance throughout a diverse range of enantioselective oxidations, we recently developed the novel triazole-substituted aryl iodide 5 (Figure 2) and evaluated its reactivity in the Kita-spirocyclization of 1-naphthols.[8]

Even though this “first-generation” catalyst gave the so far highest enantioselectivities in direct comparison to other C1-symmetric aryl iodides for this reaction, reactivities were low. Well-established C2-symmetric aryl iodides, such as spiroindanides developed by Kita or resorcinol ethers 1 developed by Uyanik and Ishihara, showed significantly higher stereoinduction and yielded the desired chiral lactones in better yields.[9] Due to the promising initial results with catalyst 5 and its highly modular and robust synthesis, we further developed “second-generation” triazole catalysts 6 (Figure 2) bearing a simple ortho-modification at the aryl iodide. We therefore synthesized ortho-Cl, -Me, and -OMe-substituted derivatives 6a–e (Scheme 1). Their synthesis is supported by detailed optimization studies, experimental procedures, analytical data (1H, 13C, and chiral HPLC analysis), and the corresponding spectra, and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201912023.

Figure 1. Best-performing chiral aryl iodide catalysts for enantioselective oxygenations.

Figure 2. Structure of first- and second-generation triazole catalysts.
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ee (Table 1, entry 6). These are the highest enantioselectivities ever observed in this representative model reaction. 6e even outperforms all of the well-established C2-symmetric chiral aryl iodides, such as the C2-symmetric resorcinols 1a and 1b. [10] Surprised by the significantly increased reactivity based on this simple synthetic modification we wanted to evaluate the general applicability of 6e in other, more challenging, oxidative C–O bond forming reactions (Scheme 2). First, we investigated the oxidative dearomatization of 4-substituted phenols to para-quinols. Even with sterically highly demanding aryl iodide catalysts, this reaction gives low enantioselectivities due to the high distance between the phenolate, which is bound to the hypervalent iodine center, and the hydroxylated C4. Even the successful resorcinol-derived aryl iodides 1 give only moderate selectivity of up to 50%. In 2018, Maruoka and co-workers introduced a specially designed C1-symmetric indanol-based aryl iodide 2, which was so far the best performing catalyst for this reaction. [11] We were pleased to find that with 10 mol% 6e, 2-bromo-4-methylphenol 12 could be efficiently dearomatized into the 2-bromo para-quinol 13 in 92% yield and 93% ee, again a novel best mark for this transformation (Scheme 2a).

Having these second-generation catalysts in hand, we investigated their performance in the Kita-spirocyclization of 1-naphthol carboxylic acid 10 (Table 1). In comparison to 5, the ortho-Cl substituted catalyst 6a had a higher reactivity yielding the spirolactone (R)-11 with improved yields after shorter reaction times but with a slightly lower enantioselectivity. Ortho-Me-substituted catalyst 6b was more reactive than 5 and 6a, which correlated with an increased enantioselectivity of 78% ee. The highest reactivity and enantioselectivity was observed with OMe-substituted catalyst 6c giving 11 in 81% yield and 82% ee. We further optimized the reaction conditions and found that a 1:1 mixture of DCM/CHCl₃ and addition of ethanol increased the enantioselectivity of 11 to 99% ee (Table 1, entry 6). These are the highest enantioselectivities ever observed in this representative model reaction. 6e even outperforms all of the well-established C2-symmetric chiral aryl iodides, such as the C2-symmetric resorcinols 1a and 1b. [10] Surprised by the significantly increased reactivity based on this simple synthetic modification we wanted to evaluate the general applicability of 6e in other, more challenging, oxidative C–O bond forming reactions (Scheme 2). First, we investigated the oxidative dearomatization of 4-substituted phenols to para-quinols. Even with sterically highly demanding aryl iodide catalysts, this reaction gives low enantioselectivities due to the high distance between the phenolate, which is bound to the hypervalent iodine center, and the hydroxylated C4. Even the successful resorcinol-derived aryl iodides 1 give only moderate selectivity of up to 50%. In 2018, Maruoka and co-workers introduced a specially designed C1-symmetric indanol-based aryl iodide 2, which was so far the best performing catalyst for this reaction. [11] We were pleased to find that with 10 mol% 6e, 2-bromo-4-methylphenol 12 could be efficiently dearomatized into the 2-bromo para-quinol 13 in 92% yield and 93% ee, again a novel best mark for this transformation (Scheme 2a).

We then investigated the intramolecular α-oxygenation of 5-oxo-5-phenylpentanoic acid 14 to 5-benzoylhydrofuran-2(3H)one 15. Here, the C1-symmetric pseudoephedrine-substituted aryl iodide 3, as developed by Moran, gave the best results so far (47% yield and 51% ee). [12] Again, 6c is a superior catalyst for this transformation and yielded the desired lactone 15 in 88% yield and 81% ee (Scheme 2b). We then tested the performance of 6e in the α-tosylation of propiophenone. This was the first oxygenation to be catalysed by a chiral aryl iodide catalyst as developed by Wirth and co-workers in 2007. [4] However, even after more than a decade of this first enantioselective report, numerous efforts to design efficient chiral aryl iodide catalysts did not result in synthetically adequate enantioselectivities due to hard to control concurring S₉₂-and S₈₂-based reaction pathways. In 2017, Masson and co-workers developed the sulfone-containing aryl iodide 4 as the best performing catalyst for this reaction giving 17 in 67% ee. [13] Again, 6c showed superior results in this transformation. A combination of 10 mol% 6e and mCPBA as co-oxidant resulted in an efficient conversion of propiophenone 16 to 17 in 90% yield and 88% ee (Scheme 2c). Apart from oxygenations, hypervalent iodine compounds can be applied efficiently in enantioselective rearrangements. [14] Very recently, Gong and co-workers developed the oxidative rearrangement of allylic alcohols to β-oxygenated ketones with the lactic-acid-derived catalyst 1c. [15] We utilized this useful reaction as another benchmark for 6c (Scheme 2d). Treatment of the tertiary allyl
alcohol 18 with 10 mol % 6c, Selectfluor as co-oxidant, and benzyl alcohol, resulted in the formation of the rearranged β-oxygenated ketone 19 in 80% yield and 98% ee.

After catalyst 6c showed this superior performance among a variety of mechanistically diverse transformations, we decided to gain a better rational about the underlying structural aspects that cause the high reactivity of 6c, in particular in direct comparison to the first-generation catalyst 5. It was of particular interest, which secondary bonding interactions stabilize the oxidized hydroxy iodobenzene. After initial oxidation, the iodane can be further stabilized either by an oxygen lone pair of the TIPS-protected benzyl alcohol or by N3 of the triazole giving two potential isomers. Both isomers could further react in distinct ligand exchange and oxidation pathways and this competition should result in diminished yields and enantioselectivities. To confirm this finding for 6c and to verify the importance of an N–I interaction for the performance of this catalyst we synthesized the N-methyl triazolium tetrafluoroborate 6d by treatment of 6c with Meerwein salt (Scheme 3a). This catalyst was then used in the Kita-spirolactonization. Here we found that 6d has a diminished reactivity compared to 6c giving the spirolactone in only 32% yield and 61% ee (Scheme 3b).

Even though the N-methylation experiment is a first hint for an intramolecular N–I interaction in the active species of 6c, it does not explain the observed effect of the ortho-substituent. Besides the donor ligand, the angle between the plane of the iodoarene and the I–OH bond is an important structural feature which is heavily influenced by ortho-substituents, as described by Legault and co-workers. Since all attempts to produce suitable crystals for X-ray analysis were not successful, DFT calculations were performed for a deeper structural understanding of the catalyst structure and its reactivity. Energy minima of oxidized [hydroxy(tosyloxy)iodo]arenes 5-OH and 6c-OH were searched by preoptimization with Grimme’s tight-binding method GFN2-xTB and further fine optimized on a PBEh-3c/ma-def2-SVP(O,N)/def2-TZVP(I) level of theory. Single point energies were calculated with the double hybrid PWBP95-D3 functional together with ma-def2-TZVP(O,N)/def2-TZVPP(I) basis sets. Preoptimization with GFN2-xTB resulted in four distinct energy minima for each catalyst (Figure 3). In good agreement with theoretical investigations by Legault et al., initial calculations based on dissociated species with a separated tosylate anion and an

\[ \text{Scheme 3.} \]

\[ \text{a) Synthesis of N-methyl triazole 6d.} \]
\[ \text{b) Evaluation of the performance of 6d in the Kita-spirolactonization.} \]
iodonium cation revealed that the dissociation process is highly endergonic. (Supporting Information, Scheme S1).[22] Therefore, dissociated iodonium complexes were not further considered. Minimized structures of 5-OH are summarized in Figure 3a, minimized structures of 6c-OH are summarized in Figure 3b. For both catalysts two isomers (5/6c-OH-N and 5/6c-OH-O) show a direct stabilization of the hypervalent iodine atom through dative N–I or O–I interactions.
These oxidized isomers are nearly equal in energy for 5-OH, whereas for 6c-OH the N-bound isomer is favored by 3.81 kcal mol\(^{-1}\). In these isomers the tosylate counterion (not shown) is usually bound in an apical position with typical TsO–I bond length of more than 2.6 Å. In the other observed isomers (5/6c-OH-OTs1 and 5/6c-OH-OTs2) the tosylate acts as the key ligand building the linear hypervalent bond in the oxidized state together with the OH group (TsO–I bond length of 2.19–2.25 Å). In 5/6c-OH-OTs1 the hydroxy group is located cis to the triazole ring and is engaged in hydrogen bonding with the N-heterocycle. For 6d this hydrogen bond is not operational and therefore this isomer would be destabilized. Furthermore, the oxidation with mCPBA should be favored through an initial hydrogen bonding between the triazole and the transferred terminal hydroxy group of the peracid.

However, for isomer 5/6c-OH-OTs2, the hydroxy ligand is located trans to the triazole ring and hence no further intramolecular secondary interactions can be observed. For 5-OH the TsO-bound isomers are significantly higher in energy (+1.97 and +5.47 kcal mol\(^{-1}\)) compared to the triazole-bound isomer 5-OH-N. In contrast, the TsO-stabilized isomers of 6c are equal or slightly lower in energy compared to 6c-OH-N. In particular, the relatively high stability of 6c-OH-OTs1 is remarkable due to the high dihedral angle of 93.86 between C(1)/C(6) of the arene ring and the I–O bond. Usually, linear arrangements are preferred in which the arene is in plane with the hypervalent bond. This can be nearly found in 5-OH-O. This isomer has the smallest dihedral angle of 11.00°. A high dihedral angle between the arene ring and the hypervalent bond, defined by Legault and co-workers as “hypervalent twist”\(^{[10]}\) together with the good leaving-group ability of the tosylate ligand as found in 6c-OH-OTs1 are crucial for further ligand exchange reactions with phenolic or enolic oxygens to initiate the discussed enantioselective coupling reactions. We are therefore confident that these calculations give a good initial rational for the high reactivity of catalyst 6c and are an ideal starting point for further catalyst improvements and theoretical investigations concerning the underlying mechanisms of each investigated enantioselective transformation.

In summary, the triazole-substituted aryl iodide 6c is the most versatile chiral aryl iodide catalyst that has been developed so far for enantioselective reactions based on in situ generated hypervalent iodine compounds. This single catalyst shows a remarkable reactivity in the Kita-spirocyclization, the α-tosyloxylolation of propiophenone, oxidative lactonizations, and in the oxidative rearrangement of allyl alcohols. To our knowledge the observed enantioselectivity for every investigated reaction is the highest ever reported and hence this catalyst can be defined as omnipotent. The initial DFT calculations indicate a significant role of the triazole as a stabilizing donor both in a potential N-bound state or as a hydrogen-bond acceptor in a [hydroxy-(tosyloxy)iodo]arene derivative. This forces the geometry of the hypervalent iodine centre into a reactive bent state with an unusual vertical alignment between the hypervalent bond and the arene. In-depth theoretical investigations are now necessary for every investigated reaction to fully explain the observed omnipotence. With this information rational fine tuning of this highly modular catalyst for further enantioselective oxidations will be possible.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric oxidation · chiral hypervalent iodine compounds · organocatalysis · oxidation · stereoselective synthesis

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