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C−H Triflation of BINOL Derivatives Using DIH and TfOH

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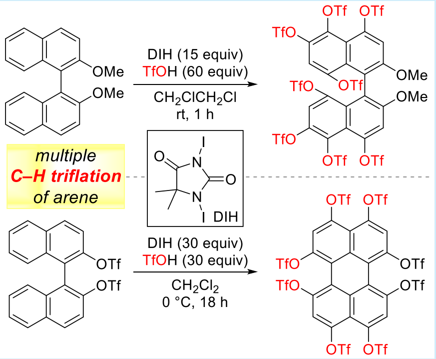
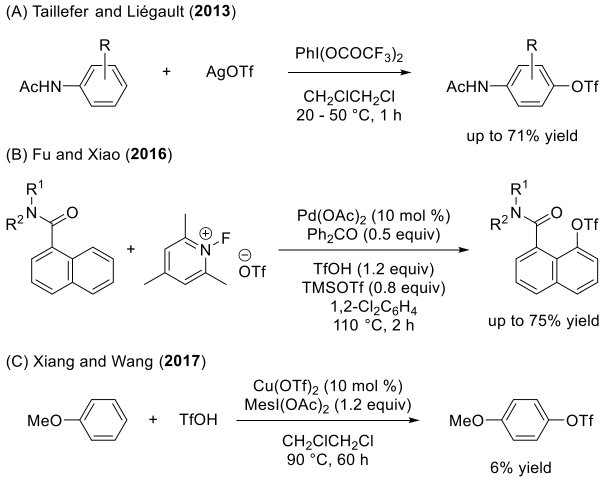
Supporting Information

ABSTRACT: C−H trifluoromethanesulfonyloxylation (triflation) of 1,1′-bi-2-naphthol (BINOL) derivatives has been established under mild conditions using 1,3-diiodo-5,5-dimethylhydantoin (DIH) and trifluoromethanesulfonic acid (TfOH). Up to eight TfO groups can be introduced in a single operation. The resulting highly oxidized BINOL derivatives can be successfully converted to 8,8′-dihydroxy BINOL and bisnaphthoquinone compounds. Mechanistic studies suggested that C−H triflation occurs in the form of an aromatic substitution reaction via the in situ formation of a radical cation.



As the trifluoromethanesulfonate (triflate, TfO−) group is a good leaving group, aryl triflates have been recognized as practical coupling precursors in transition metal-catalyzed cross-coupling reactions.[1] Also, since the trifluoromethyl group increases the lipophilicity of compounds, in addition to its synthetic utilities, the introduction of a triflate group is valuable for exploring new types of bioactive compounds.[2] Classically, aryl triflates can be easily synthesized from phenol derivatives using trifluoromethanesulfonylation reagents such as trifluoromethanesulfonic anhydride (Tf_2O) and bis(trifluoromethanesulfonyl)imide salts. However, several steps are required to introduce a triflate group into an unsubstituted aromatic C−H bond, and the substitution site of the triflate group depends on the position of a preinstalled hydroxy group on the aromatic ring. One solution to this problem is to directly functionalize a C−H bond to realize a step-economy process. To date, direct trifluoromethanesulfonyloxylation (triflation) of aromatic C−H bonds has only been reported three times in the literature (Scheme 1). In 2013, Taillefer and Liégault demonstrated oxidative C−H triflation of acetanilides with silver triflate mediated by hypervalent iodine (Scheme 1A).[3] In 2016, Fu and Xiao achieved palladium-catalyzed C−H triflation of naphthyl amides and naphthyl ketones (Scheme 1B).[4] In 2017, Xiang and Wang reported the copper-catalyzed synthesis of aryl triflates from diaryliodonium triflates through reductive elimination. In their reports, although the C−H triflation of anisole was also attempted, the desired product was obtained in only 6% yield (Scheme 1C).[5] All of the reported examples required the use of hypervalent iodine or a precious transition metal catalyst. Therefore, the development of the direct triflation of aromatic C−H bonds still remains a challenge.[5,6]

Scheme 1. Reported Examples for C−H Triflation



Axially chiral 1,1′-bi-2-naphthol (BINOL) derivatives are important chiral reagents due to their high utility as auxiliaries, ligands, and organocatalysts.[7] Because of the versatile applications of BINOL derivatives, the development of a protocol for modifying the BINOL skeleton to allow the fine-tuning of its electronic nature and steric effects is strongly desired. To date, we have reported the scandium triflate

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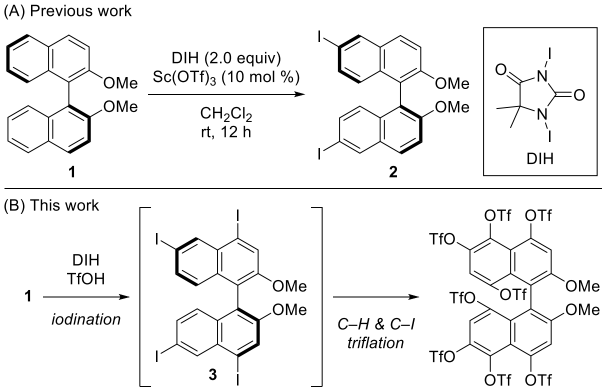
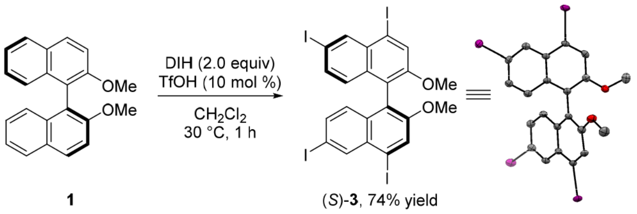
($Sc(OTf)_3$) as a Lewis acid with 1,3-diiodo-5,5-dimethylhydantoin to furnish 6,6′-diiodo BINOL derivative **2** (Scheme 2A).[8] During our continuous research on the functionalization of aromatic compounds, we investigated an activator for iodinating reagents. This time, we report the multiple iodination and C−H triflation of BINOL derivatives using a combination of 1,3-diiodo-5,5-dimethylhydantoin (DIH) and trifluoromethanesulfonic acid (TfOH) as a strong Brønsted acid (Scheme 2B). The present functionalization provides a variety of iodo or triflate BINOL derivatives, which can be converted to highly functionalized BINOL and bisnaphthoquinone derivatives.

Scheme 2. (A) Our Previous Work and (B) This Work



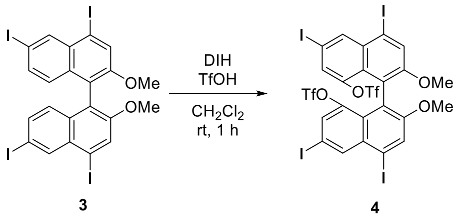
Initially, Brønsted acids were screened as a stronger activator for the iodinating reagent instead of Lewis acids (Table S1 in the Supporting Information). Among the Brønsted acids tested, 10 mol % of TfOH with DIH (2.0 equiv) smoothly promoted the iodination of BINOL derivative **1** to afford 4,4′,6,6′-tetraiodo-BINOL **3** in 74% yield (Scheme 3). Using $Sc(OTf)_3$ as a catalyst in the iodination reaction, **3** was not obtained. Interestingly, when an excess amount of TfOH was used, it was found that the C−H triflation of BINOL occurred in addition to iodination.

Scheme 3. Multiple Iodination of (*S*)-1 Mediated by TfOH[a]



[a] X-ray structure of (*S*)-**3** with ellipsoids at 50% probability (H atoms have been omitted for clarity).

Table 1. C−H Triflation of BINOL Derivative[a]

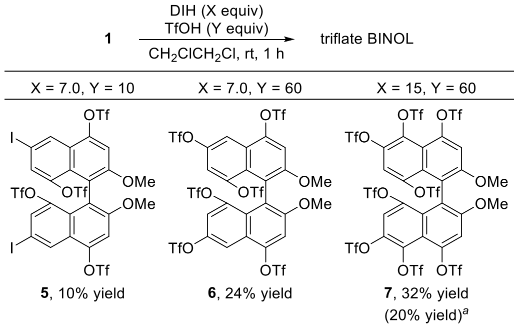


entry	DIH (equiv)	TfOH (equiv)	NMR yield (%)
1	2	4	18
2	3	5	29 (21[b])
3	3	10	12
4[c]	6	5	9
5[d]	6	5	no reaction

[a] Reaction conditions: **3** (0.10 mmol), CH_2Cl_2 (5.0 mL), rt, 1 h. [b] Isolated yield. [c] NIS instead of DIH [d] I_2 instead of DIH.

The discovery of this aromatic C−H triflation encouraged us to investigate the reaction conditions using **3** as a starting material with DIH and TfOH in Table 1. When **3** was reacted with DIH (2.0 equiv) and TfOH (4.0 equiv) in CH_2Cl_2 at 30 °C, 8,8′-ditriflate BINOL **4** was obtained in 18% yield (entry 1). Owing to it being substituted at the 8,8′ positions, 8,8′-subsituted BINOL has attractive characteristics for affecting the dihedral angle. It is noteworthy that the direct functionalization of the 8,8′ positions of BINOL derivatives has not yet been reported. Increasing the amount of both DIH and TfOH resulted in an improvement in the isolated yield of **4** to 21% (entry 2). A further excess of TfOH (10 equiv) did not give better results (entry 3). The use of other iodine reagents such as *N*-iodosuccinimide (NIS) and iodine (I_2) led to low yield and no reaction, respectively (entries 4 and 5). To confirm whether a racemization of BINOL derivatives occurs under the present conditions, **4** was converted to an 8,8′-diol compound by hydrolysis (see the Supporting Information). As a result, complete racemization took place during the C−H triflation, probably due to the use of TfOH, strong Brønsted acid.[9] In the course of the screening of the amounts of DIH and TfOH required for aromatic C−H triflation, unprecedented multiple triflation reactions were discovered (Scheme 4). Treatment of **1** with DIH (7.0 equiv) and TfOH (10 equiv) provided tetratriflate BINOL **5** in 10% yield. Furthermore, hexatriflate product **6** and octatriflate product **7** using further excess amounts of DIH and TfOH were formed in 24% and 32% yields, respectively. The synthesis of **7** using 1.0 mmol of **1** comparably proceeded to give the product in 20% yield. To the best of our knowledge, this is the first report on multiple oxidation reactions of BINOL derivatives by triflation. Each reaction convergently afforded the corresponding triflate product along with an unidentified byproduct that exhibited broad peaks in the ^1H NMR spectrum of the product, which was probably a mixture of polymerized starting materials and triflate compounds.[9] Moreover, there was also competition between the C−C bond cleavage at the 1,1′ position and the deiodination pathway, resulting in the formation of byproducts (see the Supporting Information).

Scheme 4. Synthesis of Multi-triflate BINOL



[a] Yield in parentheses on 1.0 mmol (**1**) scale.

By employing DIH (30 equiv) and TfOH (60 equiv) in reaction with **1**, the formation of other multitriflated compounds **8** and **9** was identified.[10] On the basis of these results, a possible reaction pathway from **1** to **7** is shown in Figure 1. Octatriflate BINOL **7** was converted from **1** via a total of 12 transformations, including multiple iodination and triflation, in which each step proceeded in 91% yield to finally give **7** in 32% yield, in a one-pot process with a single operation. The structures of octatriflate product **7** and diiodohexatriflate BINOL **8** were determined by X-ray crystallographic analysis.

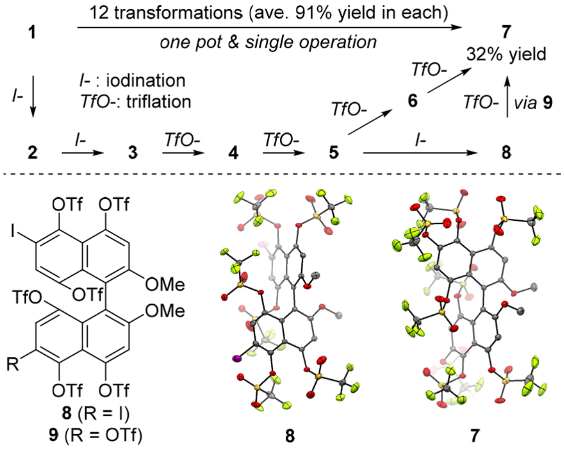
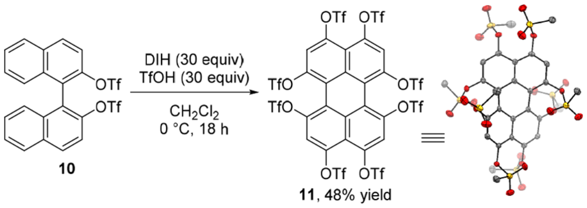


Figure 1. Possible reaction pathway and X-ray structure of **7** and **8** with ellipsoids at 50% probability. H atoms have been omitted for clarity.

We next attempted to employ trifluoromethanesulfonyl ester **10** as a replacement for methyl ether **1** under the triflation conditions.[10] Surprisingly, the addition of DIH (30 equiv) and TfOH (30 equiv) to **10** in CH_2Cl_2 at 0 °C furnished perylene derivative **11** in 48% yield (Scheme 5).[11] While structure **11** was clarified by X-ray crystallographic analysis, the reaction mechanism and pathway remain unclear at present.[12]

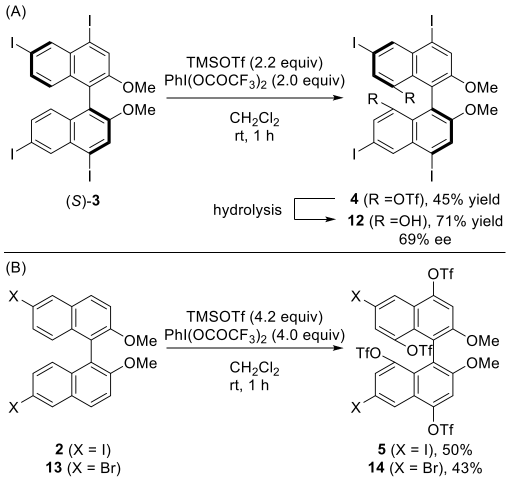
Scheme 5. Synthesis of Octatriflate perylene 11[a]



[a] X-ray structure of **11** with ellipsoids at 50% probability (H and F atoms have been omitted for clarity).

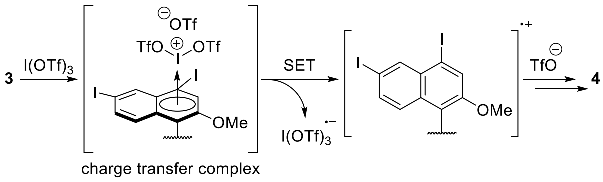
To gain insight into the reaction mechanism, control experiments were carried out (Scheme 6). When optically pure (*S*)-**3** was subjected to reaction conditions using 2.2 equiv of trimethylsilyl trifluoromethanesulfonate (TMSOTf) with 2.0 equiv of (bis(trifluoroacetoxy)iodo)benzene ($PhI(OCOCF_3)_2$) as a hypervalent iodine reagent, the 8,8′-ditriflate compound **4** was successfully obtained in 45% yield (Scheme 6A). This result suggests that a hypervalent iodine species might be generated in situ by the mixing of an excess amount of DIH and TfOH. With TMSOTf and $PhI(OCOCF_3)_2$, the racemization, which was checked by the hydrolysis of **4** to **12**, did not completely proceed (**12**, 69% ee). The use of a combination of TMSOTf and $PhI(OCOCF_3)_2$ also resulted in the multiple triflation of **2** to furnish tetratriflated **5** in 50% yield (Scheme 6B). Because of the reaction of dibromo BINOL **13** with TMSOTf and $PhI(OCOCF_3)_2$ to give the corresponding product **14**, the possibility of the generation of hypervalent iodine derived from the iodinated starting material was ruled out. Considering that the use of an excess amount of TMSOTf and $PhI(OCOCF_3)_2$ did not generate any octatriflate compound **7**, a more active hypervalent iodine species, probably $I(OTf)_3$, should be generated from the disproportionation of TfOI.[13]

Scheme 6. Mechanistic Studies



In the C–H triflation step, $I(OTf)_3$ oxidized **3** via single electron transfer (SET) to afford a radical cation intermediate, which was captured by nucleophilic attack of the trifluorometanesulfonate anion (Scheme 7).

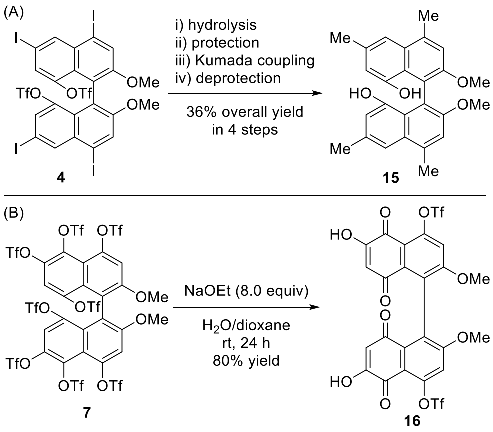
Scheme 7. Plausible Reaction Mechanism for C–H Triflation



While functionalization of aromatic compounds by oxidative nucleophilic substitution using hypervalent iodine reagents was pioneered by Kita's group,[14] there have been no reports on C–H triflation. Moreover, it is noteworthy that this is the first example of the direct use I(III) species in situ generated from the disproportionation of I(I) reagents, while functionalization of aromatic compounds was done by oxidative nucleophilic substitution.

Because the resulting triflate products could potentially be transformed into novel chiral ligands and naturally occurring compounds bearing a polyphenol structure, the derivatization of the obtained products was demonstrated (Scheme 8). Ditriflate product **4** was converted to new type of chiral ligand **15** in good yield via four steps including hydrolysis of the TfO groups, protection of the hydroxy groups at the 8,8′ positions, transition metal-catalyzed coupling, and deprotection of the TBS groups (Scheme 8A). Hydrolysis by sodium ethoxide of **7**

Scheme 8. Synthetic Transformations[a]



[a](i) NaOEt (8.0 equiv), dioxane/H_2O, rt, 12 h, 80% yield. (ii) TBSCl (4.4 equiv), *n*-BuLi (2.2 equiv), THF, 0 °C to rt, 2 h, 71% yield. (iii) MeMgBr (6.0 equiv), $NiCl_2$(dppf) (20 mol %), Et_2O, reflux, 12 h, 96% yield. (iv) TBAF (2.4 equiv), pyridine (2.4 equiv), THF, rt, 12 h, 74% yield.

yielded bisnaphthoquinone derivative **16** in 80% yield (Scheme 8B). The resulting **16** is a key precursor for natural products, which has been successfully synthesized by Kozlowsky's group.[15]

In summary, we have achieved multiple iodination and novel direct triflation of BINOL derivatives. A series of multiple triflated BINOL derivatives was successfully synthesized by control of equivalent amounts of DIH and TfOH. The developed method can be used to introduce up to eight TfO groups in a single operation to afford a highly oxidized compound. The mixing of DIH and TfOH generates hypervalent iodine species $I(OTf)_3$ through disproportionation of TfOI to promote triflation of aromatic C−H bonds. The resulting triflate compounds are expected to be valuable intermediate for the synthesis of chiral ligands and natural products.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02358.

> Experimental procedures, characterization for new compounds including copies of NMR spectra, X-ray crystallographic data for **3** (CCDC 1905896), for **7** (CCDC 1905894), for **8** (CCDC 1905893), and for **11** (CCDC 1905895) (PDF)

Accession Codes

CCDC 1905893−1905896 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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