ORGANIC
LETTERS

2013
Vol. 15, No. 7
1764–1767

Oxidative *para*-Triflation of Acetanilides

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Received March 6, 2013

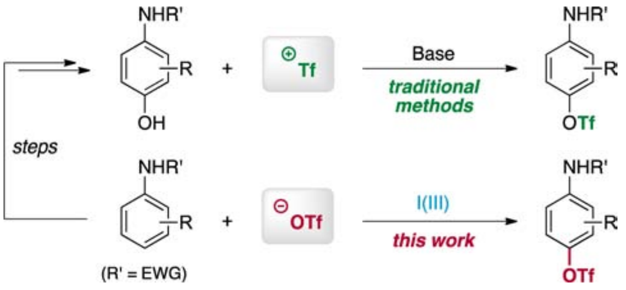
ABSTRACT

Direct triflation of acetanilide derivatives with silver triflate has been accomplished under mild iodine(III)-mediated oxidative conditions. The reaction shows excellent regioselectivity for the *para* position and tolerates a range of *ortho* and *meta* substituents on the aromatic ring. This method is also compatible with the preparation of arylnonaflates in synthetically useful yields.

Aryltriflates (or aryltrifluoromethanesulfonates) constitute a family of very versatile reagents that can notably be used as electrophilic coupling partners in transition metal-catalyzed cross-coupling reactions.[1] They offer an alternative to other (pseudo)halide derivatives, while differing not only by their synthetic accessibility but also by their reactivity,[1a,2,3] which can sometimes be essential for their successful transformation into more elaborated products.[4] Moreover, aryltriflates bearing a trimethylsilyl group at the *ortho* position are the most convenient aryne precursors.[5] Also, a recent study has shown that the aryltriflate moiety has the ability to improve the biological activity of some medicinal compounds.[6]

The preparation of aryltriflates almost exclusively relies on the use of phenols and a source of electrophilic triflate, typically the highly moisture sensitive triflic anhydride, or for better selectivity, practical but expensive *N*-phenyltriflimide (Scheme 1).[2,7] Furthermore, the preparation of highly substituted substrates can sometimes be seriously challenging, due to the lengthy/difficult access to the starting phenol derivatives.

Scheme 1. Synthesis of *para*-Amido Aryltriflates using Electrophilic and Nucleophilic Triflate Sources



Oxidative aromatic *umpolung* reactions represent a class of very useful processes, which have notably been exploited

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(1) (a) For reviews on transition metal-catalyzed coupling reactions involving aryltriflates, see: (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046–2067. (b) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1470. (c) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004.

(2) For reviews on the preparation and applications of aryltriflates, see: (a) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85–126. (b) Ritter, K. *Synthesis* **1993**, 735–762.

(3) Aryltriflates have been shown to react preferentially over bromides and chlorides in palladium-catalyzed cross-coupling reactions, see: (a) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001–13007. However, this trend seems to be inverted when using boronic acids as coupling partners; see: (b) Espino, G.; Kurbangalieva, A.; Brown, J. M. *Chem. Commun.* **2007**, 1742–1744 and references therein.

(4) For a representative example where only aryltriflates (as opposed to other aryl (pseudo)halides) are efficient coupling partners, see: Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661–1664.

(5) Due to its mild reaction conditions, Kobayashi's method for the generation of aryne intermediates from *o*-(trimethysilyl)aryltriflates is the most attractive to date. For recent reviews, see: (a) Bhunia, A.; Yetra, A. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140–3152. (b) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550–3577. (c) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191–218.

(6) Moriconi, A.; Bigogno, C.; Bianchini, G.; Caligiuri, A.; Resconi, A.; Dondio, M. G.; D'Anniballe, G.; Allegretti, M. *ACS Med. Chem. Lett.* **2011**, *2*, 768–773.

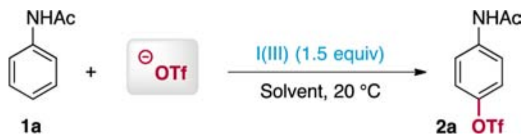
10.1021/ol400604e

in the area of phenol dearomatization.[8] Toward this goal, hypervalent iodine reagents have emerged as the reagents of choice due to their ease of handling, their low toxicity and their commercial availability.[8b,9] These strategies also provide interesting opportunities for the nucleophilic functionalization, with subsequent rearomatization, of electron-rich arenes. In this context, the use of aniline derivatives has remained scarce.[10,11]

Herein we describe the iodine(III)-mediated *para*-functionalization of acetanilides employing *triflates as nucleophiles* (Scheme 1). Under mild reaction conditions, the use of easy-to-handle reagents allows a direct access to a range of functionalized aryltriflates in moderate to good yields. As well, this method has been extended to the preparation of arylnonaflates.

This reactivity was initially discovered during our studies on the development of copper-catalyzed anilide functionalization reactions. Under conditions employing acetanilide **1a**, 10 mol % of Cu(OTf)$_2$ and 1.5 equiv of PhI(OAc)$_2$ (DIB) in CHCl$_3$ at 60 °C, trace amounts of aryltriflate **2a** were isolated (Table 1, entry 1). Based on this intriguing result, a reaction employing an excess of copper(II) triflate at room temperature for 4 h was attempted. Product **2a** was obtained in a moderate, but promising, yield of 54% (Table 1, entry 2). Several parameters were then evaluated in order to optimize the reaction conditions, including the triflate source, the iodine(III) oxidant, the nitrogen-protecting group and the solvent. A general trend first emerged in which combinations of either DIB in CHCl$_3$ or PhI(OCOCF$_3$)$_2$ (BTI) in dichloroethane gave the best results. The triflate source was found to play a crucial role for the desired reactivity. Whereas Cu(OTf)$_2$, Zn(OTf)$_2$, Fe(OTf)$_2$ and Ce(OTf)$_3$ offered moderate yields (and low reproducibility in some cases), CuOTf (as its toluene complex form), NaOTf and KOTf were found to be much less efficient (Table 1, entries 2–5 vs entries 6–8). Finally, aryltriflate **2a** was obtained in 66% isolated yield from acetanilide **1a** and AgOTf (1.2 equiv) in the presence of BTI in DCE at 20 °C over 1 h (Table 1, entry 10).[12] Running the reaction with a Lewis acid as an additive (Table 1, entry 11)[13] or in fluorinated solvents, such as hexafluoro-*iso*-propanol (Table 1, entry 12)[10a,c,e] did not improve the yields.

Table 1. Optimization of Reaction Conditions[a]



entry	triflate	(x equiv)	I(III)	solvent	time (h)	yield[b]
1[d]	Cu(OTf)$_2$	(0.1 equiv)	PhI(OAc)$_2$	CHCl$_3$	24	7% (4%)[c]
2	Cu(OTf)$_2$	(2.0 equiv)	PhI(OAc)$_2$	CHCl$_3$	4	54%
3	Zn(OTf)$_2$	(2.0 equiv)	PhI(OAc)$_2$	CHCl$_3$	4	49%
4	Fe(OTf)$_2$	(2.0 equiv)	PhI(OAc)$_2$	CHCl$_3$	4	45%
5	Ce(OTf)$_3$	(2.0 equiv)	PhI(OCOCF$_3$)$_2$	DCE	4	52%
6	CuOTf[f]	(2.0 equiv)	PhI(OAc)$_2$	CHCl$_3$	1	11%
7	NaOTf	(1.2 equiv)	PhI(OCOCF$_3$)$_2$	DCE	1	7%
8	KOTf	(1.2 equiv)	PhI(OCOCF$_3$)$_2$	DCE	1	4%
9	AgOTf	(2.0 equiv)	PhI(OAc)$_2$	CHCl$_3$	1	60% (58%)[c]
10	AgOTf	(1.2 equiv)	PhI(OCOCF$_3$)$_2$	DCE	1	70% (66%)[c]
11[e]	AgOTf	(1.2 equiv)	PhI(OCOCF$_3$)$_2$	DCE	1	26%
12	AgOTf	(1.2 equiv)	PhI(OCOCF$_3$)$_2$	HFIP	1	trace

[a] Reactions performed on 0.25 mmol scale. [b] Determined by ^{19}F NMR analysis of the crude reaction mixture, in methanol-d$_4$, using 4,4′-difluorobenzophenone as an internal standard. [c] Isolated yield. [d] Reaction performed at 60 °C. [e] BF$_3$·OEt$_2$ (1.2 equiv) was used as an additive. [f] (CuOTf)$_2$·toluene complex.

The scope of the iodine(III)-mediated oxidative *para*-triflation was next investigated with diversely substituted acetanilides (Scheme 2). Aryltriflates bearing halides **2b**–**e** and **2k**–**n**, trifluoromethyl **2f** and carbonyl-derived functional groups **2g**, **2m** and **2n**, at the *ortho* or *meta* position, were prepared in yields ranging from 45% for **2f** to 84% for **2e**. A small increase in temperature (from 20 to 50 °C) was sometimes necessary to obtain complete conversions, probably due to electronic/steric factors. Valuable amido-substituted aryne precursor[5] **2o** could be isolated in a modest 41% yield, which remains synthetically useful when compared to lengthy traditional methods for its preparation (typically 5–6 steps from commercially available *o*-halophenol).[14] The presence of electron-neutral or -donating alkyl or methoxy groups on the aromatic ring proved to be more challenging, owing to the formation of unidentified oxidative byproducts. Indeed, 3-methyl and 2-methyl aryltriflates **2h** and **2p** were obtained in 28 and 26% yield, respectively. Running the reaction at −20 °C or with slow addition of anilide **1h** still led to full consumption of the starting material but was not more

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(7) For representative examples of electrophilic triflation of phenol derivatives, see: (a) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299–6302. (b) Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron* **2000**, *56*, 3077–3119. (c) Frantz, D. E.; Weaver, D. G.; Carey, J. P.; Kress, M. H.; Dolling, U. H. *Org. Lett.* **2002**, *4*, 4717–4718. (d) Bengtson, A.; Hallberg, A.; Larhed, M. *Org. Lett.* **2002**, *4*, 1231–1233.

(8) For reviews on oxidative dearomatization reactions, see: (a) Quideau, S.; Pouységu, L.; Deffieux, D. *Synlett* **2008**, *66*, 467–495. (b) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235–2261. (c) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068–4093.

(9) For reviews on hypervalent iodine chemistry, see; (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299–5358. (b) Zhdankin, V. V. *ARKIVOC* **2009**, 1–62.

(10) For iodine(III)-mediated nucleophilic aromatic functionalization of anilide derivatives, see: (a) Itoh, N.; Sakamoto, T.; Miyazawa, E.; Kikugawa, Y. *J. Org. Chem.* **2002**, *67*, 7424–7428. (b) Karade, N. N.; Tiwari, G. B.; Huple, D. B.; Siddiqui, T. A. J. *J. Chem. Res.* **2006**, 366–368. (c) Jean, A.; Cantat, J.; Bérard, D.; Bouchu, D.; Canesi, S. *Org. Lett.* **2007**, *9*, 2553–2556. (d) Liu, H.; Wang, X.; Gu, Y. *Org. Biomol. Chem.* **2011**, *9*, 1614–1620. (e) Samanta, R.; Lategahn, J.; Antonchick, A. P. *Chem. Commun.* **2012**, *48*, 3194–3196. (f) Jacquemot, G.; Ménard, M.-A.; L'Homme, C.; Canesi, S. *Chem. Sci.* **2013**, *4*, 1287–1292.

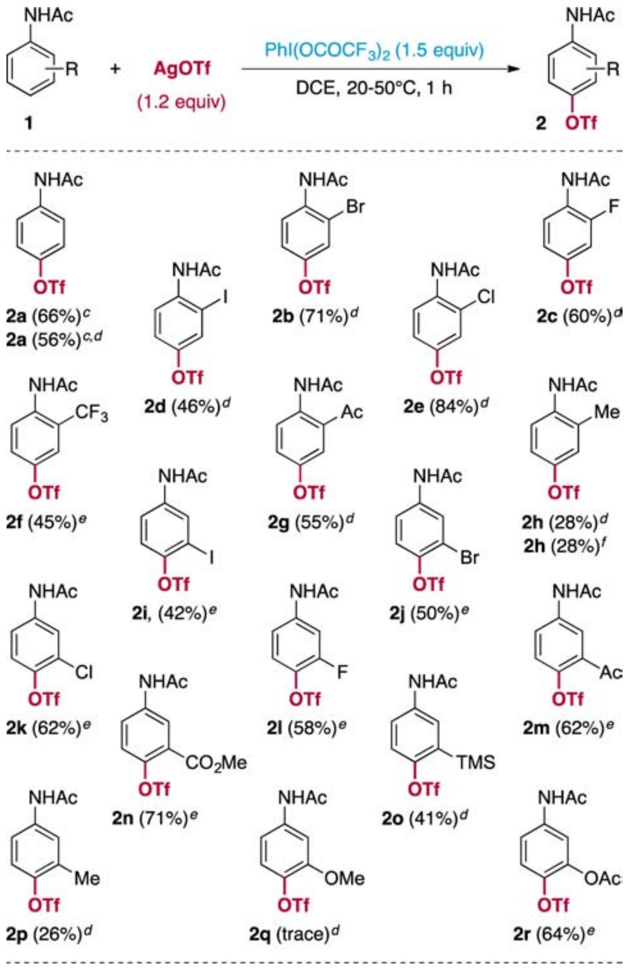
(11) During the preparation of this manuscript, the *para*-fluorination of *N*-pivaloyl anilines was also reported; see: Tian, T.; Zhong, W.-H.; Meng, S.; Meng, X.-B.; Li, Z.-J. *J. Org. Chem.* **2013**, *78*, 728–732.

(12) AgOTf and BTI are affordable and easy-to-handle solids that can be stored in a desiccator and weighed to air without precaution.

(13) It has been proposed that BF$_3$·OEt$_2$ can activate BTI by means of coordination to the trifluoroacetoxy ligand; see: Dohi, T.; Ito, M.; Morimoto, K.; Iwata, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 1301–1304. See also reference 10d.

(14) Brown, N.; Luo, D.; Velde, D. V.; Yang, S.; Brassfield, A.; Buszek, K. R. *Tetrahedron Lett.* **2009**, *50*, 63–65.

Scheme 2. Oxidative *para*-Triflation of Acetanilides[a,b]

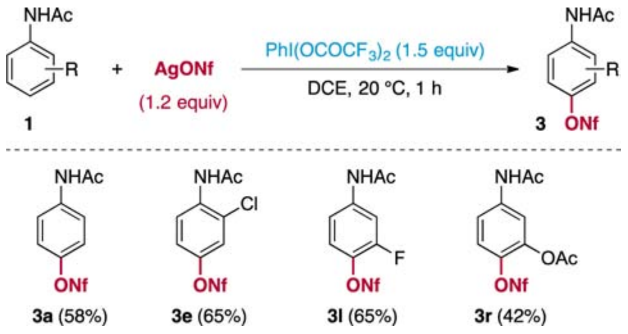


[a] Reactions performed on 0.5 mmol scale. [b] Isolated yield. [c] Reaction performed on 5 mmol scale. [d] 20 °C. [e] 50 °C. [f] −20 °C.

successful. Following the same trend, product **2q** was only detected in trace amounts. Nevertheless, replacing the methyl group on the oxygen atom by an acetyl entirely restored the reactivity, providing aryltriflate **2r** in 64% yield. Of note, a reaction on a larger scale (5 mmol) was realized and led to product **2a** in 56% yield.

All aryltriflates described in Scheme 2 were found to be bench stable and could be purified by standard silica gel chromatography. However, product stability can sometimes be more problematic under harsher, basic conditions, sometimes required in further functionalization reactions such as transition metal-catalyzed coupling reactions.[1] This aspect can conveniently be circumvented with the use of analogous arylnonaflates, less prone to "O−SO$_2$" cleavage.[15,16] Fortunately, easily prepared and bench-stable AgONf[17] also showed good activity under our optimized conditions and allowed us to synthesize arylnonaflates **3a**, **3e**, **3l** and **3r** in moderate to good yields (Scheme 3).

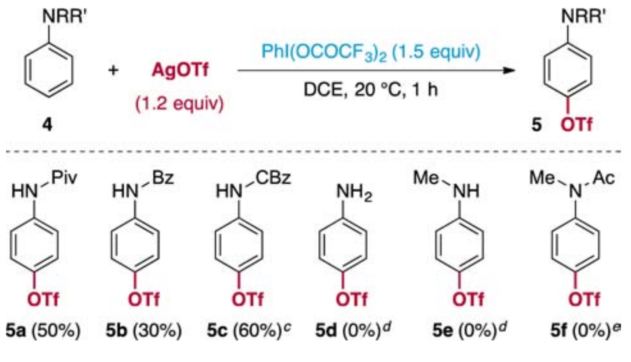
Scheme 3. Oxidative *para*-Nonaflation of Acetanilides[a,b]



[a] Reactions performed on 0.5 mmol scale. [b] Isolated yield.

Although acetanilide starting materials **1** were found to give the best results under the reaction conditions, other *N*-protected anilines were also tested. Gratifyingly, aryltriflates **5a**−**c**, with *N*-pivaloyl, -benzoyl and -benzyloxycarbonyl groups could be prepared, albeit in lower yields (30−60%) than with the corresponding *N*-acetyl derivative **2a** (Scheme 4). Importantly, a lone electron-withdrawing substituent on the nitrogen atom is required. Indeed, aniline **4d** and *N*-methyl aniline **4e** led to complete decomposition, while *N*-methyl-*N*-acetyl aniline **4f** was found to be unreactive under the reaction conditions.

Scheme 4. Oxidative *para*-Triflation of *N*-Substituted Anilines[a,b]



[a] Reactions performed on 0.5 mmol scale. [b] Isolated yield. [c] Conditions from Table 1 Entry 4 were used (DIB in CHCl$_3$). [d] Complete decomposition of the starting material. [e] No reaction.

From a mechanistic point of view, several scenarios can be envisaged and preliminary experiments have been

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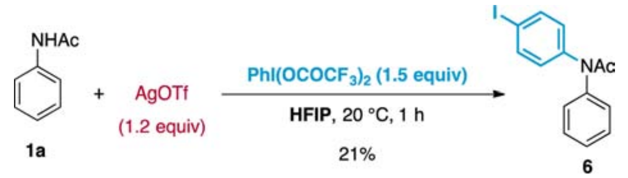
(15) For a review on the use of nonaflates in transition metal-catalyzed couplings, see: Högermeier, J.; Reissig, H.-U. *Adv. Synth. Catal.* **2009**, *351*, 2747–2763.

(16) For recent applications of arylnonaflates, see: (a) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 12898–12899. (b) Monzon, G.; Knochel, P. *Synlett* **2010**, 304–308. (c) Barluenga, J.; Florentino, L.; Aznar, F.; Valdés, C. *Org. Lett.* **2011**, *13*, 510–513. (d) Ikawa, T.; Nishiyama, T.; Nosaki, T.; Takagi, A.; Akai, S. *Org. Lett.* **2011**, *13*, 1730–1733. (e) Shekhar, S.; Dunn, T. B.; Kotecki, B. J.; Montavon, D. K.; Cullen, S. C. *J. Org. Chem.* **2011**, *76*, 4552–4563. (f) Manabe, K.; Kimura, T. *Org. Lett.* **2013**, *15*, 374–377.

(17) Hashmi, A. S.; Hengst, T.; Lothschütz, C.; Rominger, F. *Adv. Synth. Catal.* **2010**, *352*, 1315–1337.

performed to gain some insight. First, a radical pathway can most likely be ruled out since running the reaction in the presence of radical scavengers, such as TEMPO or 1,1-diphenylethylene, only resulted in slightly decreased product yields.[18] As highlighted (Table 1, entry 12), the use of hexafluoro-*iso*-propanol (HFIP) as the reaction solvent has a dramatic effect on the reaction outcome. Not only does it inhibit the formation of the desired aryltriflate product, but it also favors the generation of diarylamide byproduct **6**, isolated in 21% yield (Scheme 5).[10a,e] Additionally, under optimized reaction conditions, no *para*-amidophenol byproduct (arising from a potential competitive nucleophilic attack of a trifluoroacetate moiety in the reaction media) could be detected, in contrast to some other similar processes.[10,11]

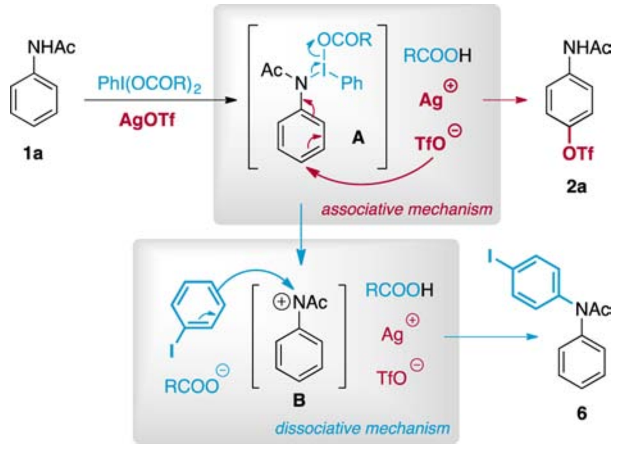
Scheme 5. Isolation of Diarylamide Byproduct **6**



On the basis of the above remarks and literature precedent,[8b,9,10] we propose the following mechanism (Scheme 6). Intermediate **A** is first generated by reaction of anilide **1a** with the electrophilic iodine(III) center. Next, nucleophilic attack of the triflate ion occurs on the most sterically accessible, electrophilic position, with concomitant departure of iodobenzene and the (trifluoro)acetate counterion. This associative bimolecular process, normally favored in poorly polarizable solvents (such as $CHCl_3$ and DCE),[19] would subsequently be followed by a deprotonation/rearomatization step and produce aryltriflate **2a**.[20] Alternatively, HFIP would promote a dissociative pathway in which free iodobenzene would react with the highly electrophilic nitrenium species **B** and generate diarylamide **6**.

The role of the metallic counterion is not clearly understood at this stage. However, the differences in solubility of the various triflate salts reported in Table 1 cannot account for the yield discrepancies. Indeed, a rapid survey showed that their solubilities are in the 1−6 mg.mL^{-1} range (in $CHCl_3$ or DCE), with NaOTf and KOTf being the least and the most soluble, respectively.[21] Finally, the high reactivity of silver triflate over alkaline triflates could potentially be rationalized with the HSAB theory. Ag^+ may "soften" the TfO^- anion, therefore faciliting its interaction with the soft anilide electrophile.[22] As well, hard Na^+ or K^+ and TfO^- ions would be poorly dissociated in the reaction media. Experimentally, we found that the addition of $AgNO_3$ or crown ethers to reactions conducted with NaOTf or KOTf partially reestablished the reactivity (13 and 19% with $AgNO_3$, and 45 and 40% with 15-C-5 and 18-C-6, respectively).

Scheme 6. Proposed Associative and Dissociative Mechanisms



In summary, we have developed an original and practical protocol for the iodine(III)-mediated oxidative *para*-triflation of acetanilides under mild reaction conditions, providing a range of substituted aryltriflates in moderate to good yields and excellent regioselectivity. Replacement of easy-to-handle AgOTf by AgONf as the nucleophile extended the method to the synthesis of several arylnonaflates. Preliminary mechanistic studies suggest that an associative pathway is probably operative. Further extensions of this methodology are currently under investigation.

Acknowledgment. We thank the CNRS, ENSCM and MENRT for a PhD grant (A.P.). Drs. Sophie Rousseaux, Baptiste Lecachey and Eric Leclerc are also kindly acknowledged for insightful discussions and critical reading of this manuscript.

Supporting Information Available. Experimental procedures, characterization data and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) (a) Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996–6005. (b) Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 8605–8608.

(19) For a similar observation, see: Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3787–3790.

(20) A ligand-coupling mechanism, involving a (4-amido-cyclohexadienyl)(phenyl)-λ^3-iodanyl triflate intermediate, can also not be excluded. In such a process, the Ag^+ cation would facilitate the reductive elimination step. However, the use of freshly prepared $PhI(OTf)_2$ proved to be unsuccessful. We thank a reviewer for pointing out this mechanistic pathway.

(21) See Supporting Information for details.

(22) The role of Ag^+ as a soft counterion was recently demonstrated in the trifluoromethylation-iodination of arynes; see: Zeng, Y.; Zhang, L.; Zhao, Y.; Ni, C.; Zhao, J.; Hu, J. *J. Am. Chem. Soc.* **2013**, *135*, 2955–2958.

The authors declare no competing financial interest.