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Communication

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Regio- and Stereoselective Cyanotriflation of Alkynes Using Aryl(cyano)iodonium Triflates

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Supporting Information Placeholder

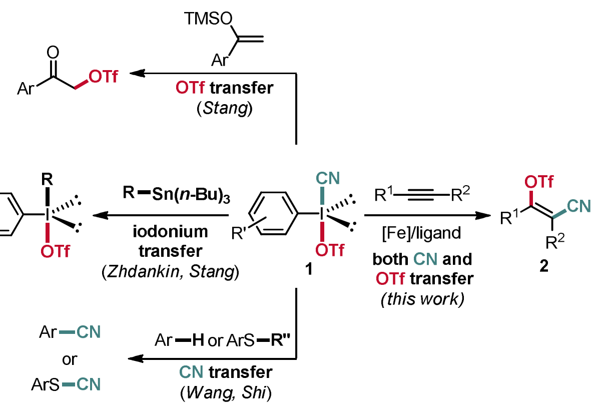
ABSTRACT: A novel, mild, and versatile approach for regioselective *syn*-addition of both the CN group and the OTf group of aryl(cyano)iodonium triflates to alkynes is described. The reaction uses Fe-catalysis and can be conducted in gram-scale. Products of the vicinal cyanotriflation can be stereospecifically readily further functionalized, rendering the method highly valuable.

The acrylonitrile structural motif is highly versatile in organic synthesis. Acrylonitriles occur as building blocks in natural product synthesis, in pharmaceutical industry, and in materials science. Therefore, the development of practical methods for their synthesis is of importance.[1] A direct approach towards acrylonitriles is the transition metal catalyzed alkyne hydrocyanation.[2] Even more valuable are stereoselective alkyne cyanations with concomitant C-C and C-X-bond formation. Along these lines, Pd-, Ni-, and Lewis acid catalyzed carbocyanations[3] and heterocyanations[4] of alkynes have been reported. The latter reactions use X-CN-type reagents where X is Me_3Si, R_2B, Bu_3Sn, Me_3Ge, RS, ArO, or Br.[4] The Br, R_2B and Bu_3Sn-products are particularly interesting since they can be further chemically transformed by cross coupling reactions.

Vinyl triflates have been recognized as reliable precursors for vinyl-organometallic intermediates in cross coupling reactions.[5] They are generally prepared by trapping of in situ generated enolates with triflating reagents.[6] Alternatively, Lepore described the $Zn(OTf)_2$ catalyzed alkyne triflation to vinyl triflates with trimethylsilyl trifluoromethanesulfonate and little water.[7a] Cu-catalyzed *cis* aryl- and vinyl-triflation of alkynes has been successfully established by the Gaunt group.[7b] Akita and Koike recently disclosed the preparation of trifluoromethylated vinyl triflates via *trans* addition of both the CF_3 and the OTf group to alkynes via photoredox catalysis.[7c]

Aryl(cyano)iodonium triflates of type **1**, first introduced by Zhdankin and Stang, were shown to react with silyl enol ethers to afford α-trifluoromethylsulfonyl ketones (Scheme 1).[8a] ArI(CN)OTf (**1**) has been also applied as an iodonium transfer reagent in the reaction with aryl or alkynyl tributyltin compounds to give the corresponding iodonium salts.[8b] Reagents of type **1** also act as efficient electrophilic cyanation reagents. Along these lines, Wang and coworkers developed the direct electrophilic cyanation[9] of various aromatic compounds[8c] and the preparation of thiocyanates through electrophilic cyanation of thioethers was published by the Shi group.[8d] Hence, existing reports on the use of reagents **1** reveal that they react either as electrophilic iodonium, triflate or cyano transfer reagents. However, reactions with **1** where both the cyano and the triflate moiety are transferred are currently unknown. Since both functionalities are valuable, such transformations would be highly useful. Herein, we disclose a practical method for highly stereo- and regioselective *syn* alkyne cyanotriflation with an aryl(cyano)iodonium triflate under Fe-catalysis.

Scheme 1. Iodonium, triflate, and cyano transfers with aryl(cyano)iodonium triflates

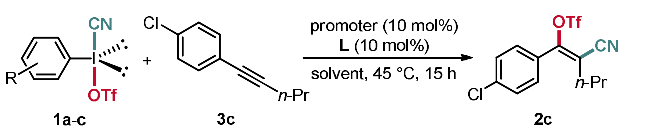


Based on previous reports on single electron transfer (SET) reduction of I(III)-reagents,[10] we assumed that an aryl(cyano)iodonium triflate **1** can react via SET reduction to the corresponding aryl(cyano)iodanyl radical and the triflate anion.[8c] α-Fragmentation of the cyano radical in such an iodanyl radical is not likely due to the high energy of the CN-radical. For the same reason, aryl radical fragmentation should be a high energy pathway.[11] Therefore, the iodanyl radical might be long enough lived to undergo radical addition to an alkyne which might eventually lead to cyanotriflation products of type **2**.

To proof our hypothesis we tested the cyanotriflation of alkyne **3c** with various I(III)-reagents **1a**-**c** under different conditions (Table 1, Figure 1). Careful optimization revealed that cyanotriflation works and that reaction of model compound **3c** is best conducted at 45 °C with 3,5-di(trifluoromethyl)-phenyl(cyano)iodonium triflate (**1a**) (2.2 equiv) as the triflate and cyanide source, $Fe(OAc)_2$ in combination with phenanthroline (**L1**) as the catalyst,[12] and 1,2-

dichloroethane as the solvent (Table 1, entry 1). Product **2c** was isolated in 81% yield with excellent *cis*-selectivity and complete regioselectivity. Without $Fe(OAc)_2$ and 1,10-phenanthroline only a trace amount of **2c** was formed (entry 2). Yield dropped to 36% without phenanthroline indicating the importance of the ligand (entry 3). Therefore, other ligands **L2**-**L5** were tested. However, in all cases a significant loss in yield was noted (entries 4-7).

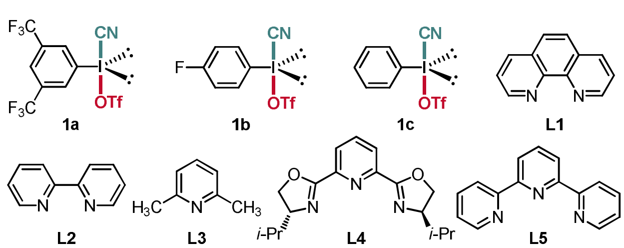
Table 1. Reaction optimization



entry[a]	promoter	ligand	1	solvent	yield (%)[b]
1	**$Fe(OAc)_2$**	**L1**	**1a**	**DCE**	**78, 81[c] (72:1)**
2	none	none	1a	DCE	trace (NA)
3	$Fe(OAc)_2$	none	1a	DCE	36 (26:1)
4	$Fe(OAc)_2$	**L2**	1a	DCE	51 (61:1)
5	$Fe(OAc)_2$	**L3**	1a	DCE	20 (24:1)
6	$Fe(OAc)_2$	**L4**	1a	DCE	24 (18:1)
7	$Fe(OAc)_2$	**L5**	1a	DCE	31 (23:1)
8	$Fe(OAc)_2$	**L1**	1b	DCE	22 (22:1)
9	$Fe(OAc)_2$	**L1**	1c	DCE	40 (54:1)
10	$Fe(OAc)_2$	**L1**	1a	DCM	63 (42:1)
11	$Fe(OAc)_2$	**L1**	1a	MeCN	trace (NA)
12	$Fe(OAc)_2$	**L1**	1a	DCE	64[d] (91:1)
13	$Fe(OTf)_2$	**L1**	1a	DCE	23 (4:1)
14	$FeCl_2$	**L1**	1a	DCE	49 (15:1)
15	$FeCl_3$	**L1**	1a	DCE	55 (21:1)
16	CuCl	none	1a	DCE	trace (NA)
17	$BF_3{\cdot}Et_2O$	none	1a	DCE	trace (NA)
18	HOTf	none	1a	DCE	trace (NA)
19	$AlCl_3$	none	1a	DCE	12 (2:1)
20	TBAI	none	1a	DCE	32 (9:1)

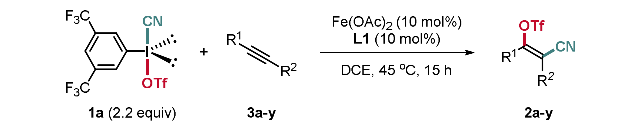
[a]Reaction condition: **3c** (0.20 mmol, 1.0 equiv), reagent **1** (0.44 mmol, 2.2 equiv), promoter (0.02 mmol, 10 mol%), ligand (0.02 mmol, 10 mol%), solvent (1 mL), 45 °C, 15 h. [b]Yield determined by ^{19}F NMR analysis using $PhCF_3$ as an internal standard; isomer ratio in parentheses determined by GC-MS analysis on the crude product; NA, not applicable; [c]Isolated yield; [d]Conducted at room temperature.

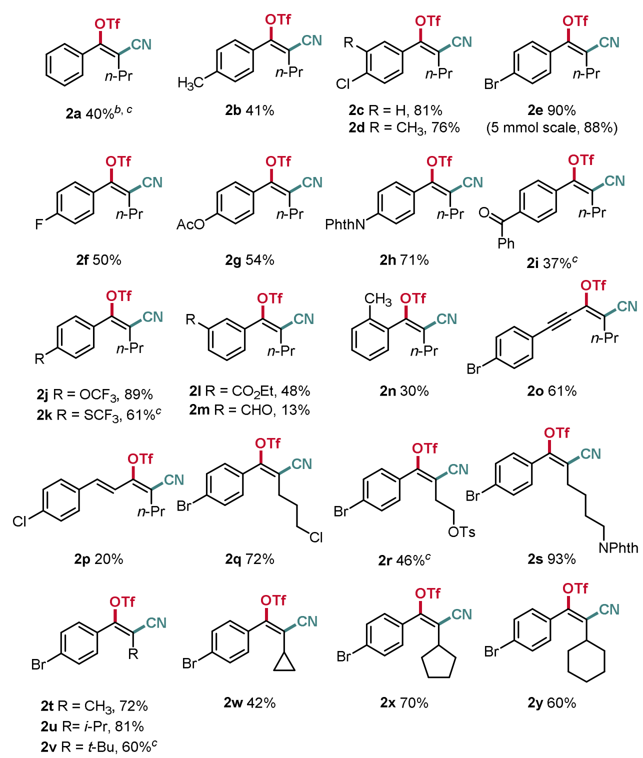
Figure 1. Reagents and ligands tested



The electronic nature of the R substituent of the iodine reagent played an important role: **1b** and **1c** provided worse results (entries 8-9). A lower yield was achieved in DCM (entry 10) and reaction did not work in acetonitrile (entry 11). A slightly lower yield (64%) but highest selectivity was obtained at room temperature (entry 12). $Fe(OTf)_2$, $FeCl_2$, and $FeCl_3$ provided worse results (entries 13-15) and only traces of **2c** were formed by replacing $Fe(OAc)_2$ with CuCl (entry 16). Cyanotriflation with $BF_3{\cdot}Et_2O$ or HOTf failed and $AlCl_3$ showed a very low yield (entries 17-19). **3c** was smoothly converted into **2c** in the presence of tetrabutylammonium iodide (TBAI), albeit in a moderate yield (entry 20).

Table 2. Substrate scope of the regio- and stereoselective cyanotriflation reaction[a,b]

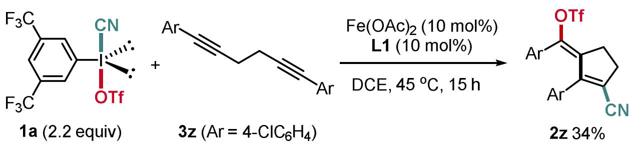




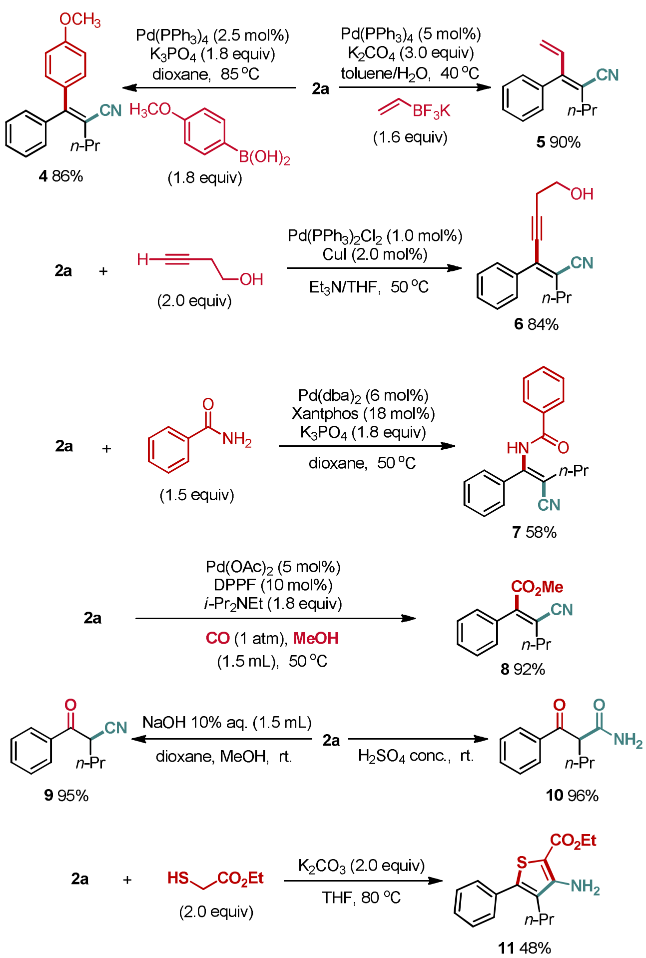
[a]Reaction condition: **3** (0.20 mmol, 1.0 equiv), **1a** (0.44 mmol, 2.2 equiv), $Fe(OAc)_2$ (0.02 mmol, 10 mol%), ligand **L1** (0.02 mmol, 10 mol%), solvent (1 mL), 45 °C, 15 h. [b]Isolated yield. [c]After 15 h, renewed $Fe(OAc)_2$ (0.02 mmol, 10 mol%), ligand **L1** (0.02 mmol, 10 mol%), and **1a** (0.44 mmol, 2.2 equiv) addition and continued stirring for another 15 h.

Having identified optimized conditions, we next tested the scope and limitations of the novel transformation (Table 2). 1-Aryl-1-pentynes bearing either electron-withdrawing or -donating substituents at the para position of the aryl group were smoothly converted in moderate to high yield with excellent regio- and stereoselectivity[13] to the acrylonitriles **2a**-**i**. Gram scale synthesis of **2e** was achieved in 88% yield demonstrating the practicability of the transformation. The trifluoromethyloxy (**2j**) and the trifluoromethylthiyl substituent (**2k**), which are popular in pharmaceuticals and in agrochemicals, are compatible with the cyanotriflation. Lower yields were obtained by cyanotriflation of alkynes bearing meta- and ortho-substituents (**2l**-**n**). We were delighted to find that the 1,3-diyne **3o** could be selectively cyanotriflated (**2o**). A significantly lower yield was obtained for the transformation of a 1,3-enyne (**2p**). Primary alkylchlorides, alkyltosylates and alkylphthalimides were tolerated (**2q**-**s**). Not surprisingly, reaction worked well on a methyl substituted alkyne (**2t**). Remarkably, also with bulky *i*-Pr (**2u**) and *t*-Bu (**2v**) substituted arylalkynes, moderate to good yields were achieved. Aryl alkynes bearing a cyclopropyl, a cyclopentyl, and a cyclohexyl group could also be converted to the targeted tetrasubstituted alkenes **2w**-**y**. Whereas for **2x** and **2y** good yields were obtained, the cylopropyl alkyne reacted in moderate yield to **2w**. Unfortunately, bisarylalkynes and bisalkylalkynes did not react under optimized conditions to the corresponding cyanotriflated products and phenylacetylene provided the cyanotriflation product in very low yield (<5%, not isolated) as checked by GC-MS-analysis.

Scheme 2. Cyanotriflation of diyne 3z



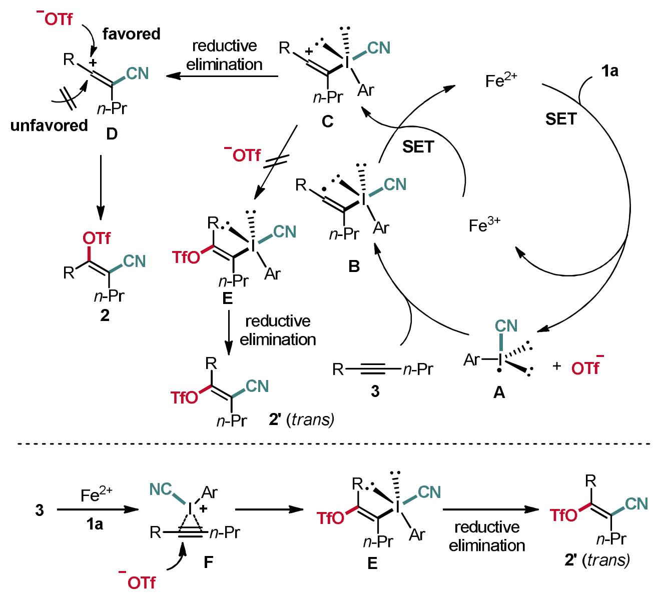
Scheme 3. Follow-up chemistry



We also investigated the transformation of the 1,5 diyne **3z** under standard conditions as a potential substrate for a cascade comprising a cyanotriflation with concomitant cyclization. Pleasingly, reaction of **3z** with **1a** provided cyclopentene **2z** through a cyanation-cyclization-triflation sequence in moderate yield and complete selectivity (Scheme 2). To demonstrate the synthetic value of the method, we investigated follow-up chemistry using cyanotriflated product **2a** as a substrate (Scheme 3). The vinyl triflate **2a** efficiently engaged in a series of stereospecific palladium catalyzed cross coupling reactions, including Suzuki couplings (**4**, **5**), a Sonogashira reaction (**6**), and a Buchwald-Hartwig amidation (**7**). Notably, during amidation complete isomerization of the double bond to give the thermodynamically more stable isomer **7** occurred. Moreover, Pd-catalyzed methoxycarbonylation of **2a** gave **8** as a single isomer. Hydrolysis of **2a** provided the *α*-cyano ketone **9** (basic conditions) and the *β*-keto amide **10** (acidic conditions) in high yields. Moreover, the synthetic utility of **2a** was demonstrated by preparation of bioactive tetrasubstituted thiophene **11** upon treatment with ethyl thioglycolate under basic conditions.

A possible mechanism for the cyanotriflation is depicted in Scheme 4. Iodanyl radical **A**, generated through SET reduction of **1a** by the Fe(II)-complex, adds to alkyne **3** to give *α*-styryl-type iodonium radical **B**. Oxidation of radical **B** by the intermediately generated Fe(III)-complex leads to *π*-stabilized vinylic cation **C**, thereby regenerating the Fe(II)-complex. Reductive elimination at the I(III) center affords cation **D** which gets trapped by the triflate anion to provide the observed *cis*-product **2**. Trapping occurs from the less hindered site of the vinyl cation *syn* to the small CN group. Since the nature of the ligand influences *cis*/*trans*-selectivity, the triflate is likely transferred from an LFe(III)OTf-complex.

Scheme 4. Suggested Mechanism for the alkyne cyanotriflation



Trapping of the cation **C** prior to reductive elimination via **E** is not likely, since it should give the *trans*-product **2'**. The successful cascade (see **2x**, Scheme 2) supports a radical mechanism.[14] A pathway involving electrophilic iodonium activation of the triple bond (see **F**) with the Fe-complex acting as a Lewis acid is not very likely, since we did not obtain *trans*-product **2'** as the major product that would form in the cationic route via **E**. This is in agreement with the failed experiments using typical Lewis acids as catalysts.

In summary, we have described the first method for direct vicinal alkyne cyanotriflation. Reactions occur under mild conditions with complete regioselectivity, excellent stereoselectivity and a wide range of functional groups are tolerated. The tetrasubstituted alkenes obtained are valuable building blocks as shown by a series of follow-up reactions.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all compounds are provided in the SI. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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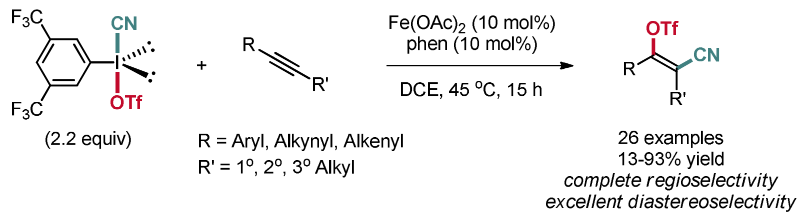
(13) Since *trans*-isomers are not in hand, we cannot unambiguously determine the selectivity by GC analysis on the crude product. After chromatography on silica gel, we always obtained only the *cis*-isomer and the *trans*-congener could not be identified. Therefore, selectivity in all cases must be very high. Yields given correspond to the isolated *cis*-compound.

(14) In the presence of TEMPO cyanotriflation did not occur. Unfortunately, we could not isolate any TEMPO-trapped intermediate (see SI).

TOC graphic


F3C
CN
OTf
F3C
(2.2 equiv)
+
R
R'
R = Aryl, Alkynyl, Alkenyl
R' = 1°, 2°, 3° Alkyl
Fe(OAc)2 (10 mol%)
phen (10 mol%)
DCE, 45 °C, 15 h
OTf
CN
R
R'
26 examples
13-93% yield
complete regioselectivity
excellent diastereoselectivity