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Organocatalytic alkynylation of densely functionalized monofluorinated derivatives: C(sp^3)–C(sp) coupling

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ABSTRACT

Organocatalytic alkynylation of nucleophilic fluorocarbons using hypervalent iodine compounds under cinchona-based catalysis, namely using *O*-allyl *N*-anthracenyl cinchona alkaloid derivative **II**, is described. The reaction gives the final fluoro-propargyl compounds in good to excellent yields (up to 91%) and with moderate to low enantioselectivity (up to 61% ee). The reaction represents the first example of the use of hypervalent iodine compounds for the construction of fluorinated compounds and opens access to the preparation of biologically attractive compounds such as 1,2,3-triazoles.

The ability of fluorine to improve molecular properties has been convincingly demonstrated in a wide range of applications. In many cases, the small and highly electronegative fluorine atom is introduced following a particular rationale, based on our understanding of the effects of fluorination.[1] In the life sciences area, well-known effects include enhancement of metabolic stability, conformational stabilization, and modifications of functional group reactivity, acid/base properties, enhanced binding interactions, and increased CNS penetration or lipophilicity. Importantly, these effects cannot be considered individually as usually a number of properties are influenced simultaneously.[2] For example, fluorination of amines in order to increase their metabolic stability also leads to a decrease in pK_a(H), an increase in their lipophilicity, and may induce strong conformational effects.

For these reasons the development of new methodologies that delivers fluorinated molecules in an enantioselective fashion has experienced a significant growth in recent years.[3] Organocatalysis has emerged as a promising tool for their synthesis.[4] Since the first organocatalytic fluorination was reported, almost simultaneously, by Enders,[5] Barbas,[6] MacMillan,[7] and Jorgensen,[8] much research has been performed in this area. For example Shibata,[9] Rios,[10] Wang,[11] Tan,[12] and Cordova[13] have reported the formal fluoromethylation of enones, enals, and Baylis–Hillman carbonates with excellent results. Our group, fascinated by the use of fluorine building blocks in organocatalysis, has developed the first fluoromalonate addition[14] and first fluoro phenylsulfonyl nitromethane[15] addition to enals catalyzed by secondary amines with excellent results.

The unique properties of alkynes such as sp hybridized carbon atoms and their electronic properties, impart rich reactivity.[16] Moreover, triple bonds have emerged as a useful tool in nanosciences and chemical biology,[17] as a result of the copper-catalyzed cycloadditions of azides to acetylenes (click chemistry). Chiral molecules bearing a triple bond adjacent to a stereogenic carbon atom, have found utility as building blocks in the synthesis of natural products,[18] and as bioactive compounds possessing antiviral properties.[19]

Despite their importance in organic chemistry, there are only a few examples of organocatalytic enantioselective syntheses of chiral propargylic compounds. The majority are based on the use of nucleophilic propargyl compounds. For example, Schreiner reported the alkynylation of aldehydes and ketones under PTC conditions.[20] A few years later, Jørgensen developed the alkynylation of enals using secondary amines as catalysts.[21] The use of electrophilic propargylic compounds has been less studied,[22] and only two examples have been described in an enantioselective fashion. In 2010, Waser reported the addition of β-keto esters to ethynyl-1,2-benziodoxol-3(1*H*)-one (EBX) under PTC conditions,[23] and Jørgensen developed a highly enantioselective addition of β-keto esters to haloalkynes with excellent results.[24]

Based on these previous results and our experience in organocatalysis[14–16,25] and the synthesis of fluorine compounds, we envisioned an easy entry into fluoro-propargyl compounds based on the addition of fluoronitrosulfones[26] and other fluorinated substrates to hypervalent iodine compounds.

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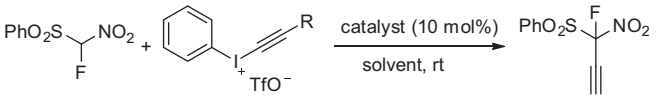
Table 1
Alkynylation of fluoronitrosulfone

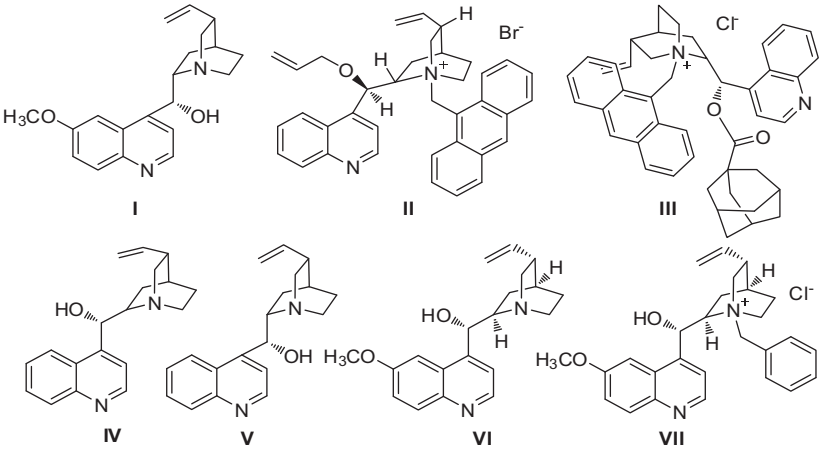


1a 2a, b 3a

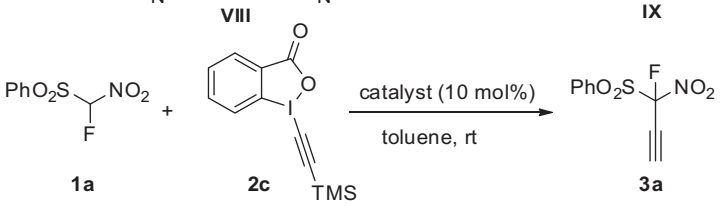
Entry	Solvent	Catalyst	R	Time (h)	Conversion (%)	ee[a] (%)	Yield[b] (%)
1	Toluene	**I**	TMS	16	50	0	42
2	$CHCl_3$	**II**	TMS	16	50	0	38
3	Toluene	**IX**	TMS	24	0	—	—
4	Toluene	**I**	TIPS	24	0	—	—

[a] Determined by chiral HPLC.
[b] Isolated yield.

Table 2
Screening of the catalyst for the alkynylation of fluoronitrosulfone **1a**



I II III IV V VI VII VIII IX



1a 2c 3a

Entry	Catalyst	Time (h)	ee[a] (%)	Yield[b] (%)
1	**I**	16	0	88
2	**II**	16	61	91
3	**III**	16	12	89
4	**IV**	48	0	65
5	**V**	16	3	65
6	**VI**	48	−2	60
7	**VII**	16	−15	75
8	**VIII**	72	−5	25
9	**IX**	48	—	n.d.
10	**II**	16	61	92[c]
11	**II**	22	56	75[d]

Experimental conditions: a mixture of **1a** (0.1 mmol), catalyst (10 mol %), and **2c** (0.2 mmol) in toluene (1 mL) was stirred at rt for the time shown in the table. After full conversion, the crude product was purified by column chromatography.
[a] Determined by Chiral HPLC.
[b] Isolated yield.
[c] 5% Catalyst loading.
[d] 2% Catalyst loading.

When fluoronitrosulfone **1a** was treated with iodonium triflate **2a** in the presence of quinine (10 mol %), the desilylated α-fluoroacetylene **3a** was obtained in 50% conversion, but in an unacceptable yield (42%) (Table 1, entry 1).

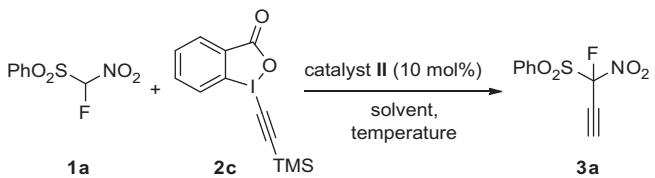
Next, we decided to use the more reactive 1-[(trimethylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TMS-EBX, **2c**), previously reported by Waser et al., as a highly active alkynylation reagent under PTC conditions. The use of TMS-EBX under catalysis with quinine led to the formation of the corresponding product **3a** in high yield (88%). Unfortunately, no enantiocontrol was observed with quinine as the catalyst (Table 2, entry 1).

Subsequently, various organocatalysts (**I**–**IX**) were screened. High efficiency for other quinine-based catalysts (**I**–**III**) was observed, but on the other hand, lower conversions were obtained with other cinchona-based catalysts (**IV**–**VII**) and the Sharpless catalyst (**VIII**). The best results were obtained with the bulky quaternary cinchona-based catalyst **II**; the corresponding α-fluoroacetylene **3a** was obtained in excellent yield (91%) and with satisfactory enantioselectivity (61% ee, entry 2). We studied the dependence of the reaction efficiency on the catalyst loading. Interestingly, no change in terms of the enantioselectivity and conversion was observed when 5 mol % of **II** was used (entry 10). On the other hand, using 2 mol % of the catalyst led to a lower conversion as well as a slight drop in the enantioselectivity (entry 11).

Next, the influence of the solvent and temperature was investigated (Table 3). Using THF as the solvent at room temperature, the reaction reached full conversion in 2 h with excellent yield, but in only poor enantiomeric excess. Interestingly, a decrease in the temperature did not improve the enantioselective induction toward the product (entries 2–4). The best results in terms of efficiency and selectivity were obtained in toluene at room temperature.[27] Other solvents, such as propan-2-ol or dichloromethane were tested, but in spite of the high yields obtained only poor enantioselectivity was observed (entries 5 and 6).

Subsequently we studied the reactions with fluorocarbon nucleophiles **1a–g** (Table 4). Changing the nitro functionality in **3a** to cyano, benzoyl, acetyl, methyl carboxylate, or diethylphosphoryl led to formation of the corresponding α-fluoroacetylenes **3b–g** in good to excellent yields (58–88%), but generally with lower enantioselectivities (Table 4, entries 2–6). For example *O*-allyl *N*-anthracenyl cinchona alkaloid derivative **II** catalyzed the alkynylation reaction between methyl phenylsulfonyl acetate **1e** and 1-[(trimethylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**2c**) to furnish

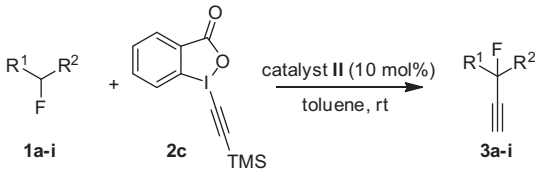
Table 3
Temperature and solvent screening



Entry	Solvent	Temp (°C)	Time (h)	ee[a] (%)	Yield[b] (%)
1	Toluene	20	16	61	91
2	THF	20	2	27	92
3	THF	0	7	26	88
4	THF	−20	16	23	82
5	Propan-2-ol	20	12	12	87
6	CH_2Cl_2	20	12	9	90

Experimental conditions: a mixture of **1a** (0.1 mmol), catalyst II (10 mol %), and **2c** (0.2 mmol) in the selected solvent (1 mL) was stirred at rt for the time shown in the table. After full conversion, the crude product was purified by column chromatography.
[a] Determined by chiral HPLC.
[b] Isolated yield.

Table 4
Substrate scope of the organocatalytic alkynylation



Entry	R^1	R^2	Time (h)	Product	ee[a] (%)	Yield[b] (%)
1	SO_2Ph	NO_2	16	**3a**	61	91
2	SO_2Ph	CN	18	**3b**	30	88
3	SO_2Ph	COPh	16	**3c**	25	83
4	SO_2Ph	COMe	16	**3d**	19	58
5	SO_2Ph	CO_2Me	16	**3e**	37	77
6	SO_2Ph	$PO(OEt)_2$	16	**3f**	0	65
7	SO_2Ph	SO_2Ph	16	**3g**	—	70[c]
8	*p*NO_2Ph	*p*NO_2Ph	24	**3h**	n.d.	n.d.[c]
9	CO_2Et	CO_2Et	24	**3i**	n.d.	n.d.[c]

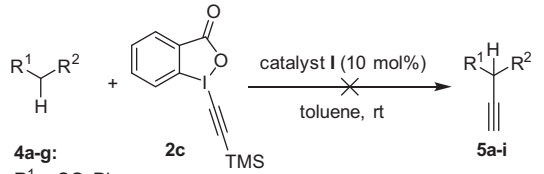
Experimental conditions: a mixture **1a–i** (0.1 mmol), catalyst II (10 mol %), and **2c** (0.2 mmol) in toluene (1 mL) was stirred at rt for the time shown in the table. After full conversion, the crude product was purified by column chromatography.
[a] Determined by chiral HPLC.
[b] Isolated yield.
[c] Performed with I as the catalyst.

the corresponding α-fluoroacetylene **3a** in 77% yield and low enantioselectivity (37% ee). Unfortunately, switching the sulfonyl group for a *p*-nitrophenyl or ester group did not lead to the corresponding alkynylated products (entries 8 and 9). As shown in Scheme 1, using non-fluorinated carbon nucleophiles **4a–i** did not lead to formation of the corresponding acetylene derivatives **5**.

Next, the effect of the silyl group on the alkynyl moiety of the hypervalent iodine species **2** was studied. More bulky and acid-stable silyl groups were found to be unsuitable for this transformation. In the case of sterically demanding silyl groups, such as *tert*-butyldiphenylsilyl and tri-isopropylsilyl, no reaction was observed even after three days (Table 5, entries 3–5). On the other hand, hypervalent iodine species **2** with less bulky silyl moieties, in particular triethylsilyl and trimethyl, afforded the desired products in good to high yields (entries 1 and 2).

The prepared α-fluoroacetylenes **3** can be converted into various structural motifs, for example, via Huisgen cycloaddition, a reaction that has found many applications in life sciences and materials chemistry.[28,29] For example, treatment of nitrophenylsulfonyl α-fluoroacetylene (**3a**) with *p*-bromobenzyl azide in the presence of copper(II) sulfate and sodium ascorbate led to the formation of 1,2,3-triazole derivative **6a** in good yield (55%) with no change in the enantioselectivity (Scheme 2).

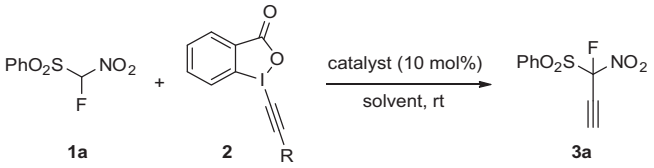
In summary, we have developed an alkynylation of nucleophilic fluorocarbons using hypervalent iodine compounds under cinchona-based catalysis. The reaction affords the products in good



4a-g:
R^1 = SO_2Ph
R^2 = NO_2, CN, COPh, COMe, CO_2Me, $PO(OEt)_2$, SO_2Ph
4h:
R^1 = R^2= *p*NO_2Ph
4i:
R^1 = R^2= CO_2Et

Scheme 1. Reaction of non-fluorinated substrates with hypervalent iodine compound **2c**.

Table 5
Effect of the silyl group on the organocatalytic alkynylation

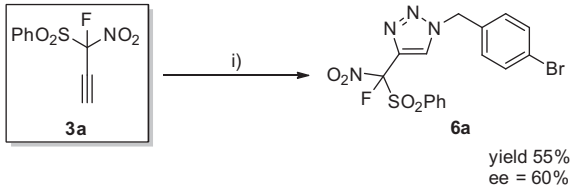


Entry	Solvent	R	Catalyst	Time (h)	ee[a] (%)	Yield[b] (%)
1	Toluene	TMS	**II**	16	61	91
2	Toluene	TES	**II**	120	60	65
3	Toluene	TIPS	**I**	24	—	—
4	THF	TIPS	**I**	24	—	—
5	Toluene	TBDP	**I**	24	—	—

Experimental conditions: a mixture of **1a** (0.1 mmol), catalyst (10 mol %), and **2** (0.2 mmol) in toluene (1 mL) was stirred at rt for the time shown in the table. After full conversion, the crude product was purified by column chromatography.

[a] Determined by chiral HPLC.

[b] Isolated yield.



Scheme 2. An example of the transformation of alkynylated product **3a**. (i) To a stirred solution of **3a** (0.1 mmol) and *p*-bromobenzyl azide (0.12 mmol) in *t*BuOH:H_2O (1:1) (1 mL) was added copper(II) sulfate (0.02 mmol) and sodium ascorbate (0.4 mmol) and the mixture was stirred overnight. After full conversion, the crude product was purified by column chromatography.

yields and low enantioselectivities. Mechanistic studies and synthetic applications of this new methodology, as well as the investigation of new reactions based on this concept, are currently underway in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.023.

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27. To a stirred solution of catalyst (0.1 equiv) in toluene (1 mL) was added sulfone (1.0 equiv) and the alkynyl benziodoxolone reagent (1.5 equiv). The mixture was stirred at rt and the reaction monitored by TLC. After completion of the reaction, the crude was transferred directly to a silica-gel column and eluted with a mixture of hexane and EtOAc (in 3:1 ratio) to afford the alkynylated product **3a**. Compound **3a**: White solid. Yield 91%, 61% ee. The ee was determined by HPLC analysis using a Chiralpak IB column (95/5 heptane/*i*-PrOH, flow rate 1.0 mL/min; λ = 190 nm, R_t major = 14.3 min, R_t minor = 16.0 min); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.01 (d, J = 7.6 Hz, 2H), 7.87–7.84 (m, 1H), 7.69–7.66 (m, 2H), 3.33 (d, J = 5.5 Hz, 1H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 136.76, 131.50 (2C), 130.81, 129.68 (2C), 111.90 (d, J = 333.6 Hz, 1C), 85.97 (d, J = 7.8 Hz), 68.73 (d, J = 34.1 Hz) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ = −111.44 ppm; $[\alpha]_D$ +3.7 (c = 0.6, $CHCl_3$); IR (KBr): ν = 3276, 3069, 2905, 2128, 1586, 1446, 1365, 1314, 1169, 1045, 722, 588 cm^{-1}; HRMS (ESI) m/z [M+Na]$^+$ calcd for $C_9H_6FNO_4SNa$: 265.9889, found: 265.9894.
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