Brønsted Acid Catalyzed Friedel–Crafts Alkylation Reactions of Trifluoromethyl-α,β-ynones with Indoles

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Abstract: The successful development of a Brønsted acid catalyzed Friedel–Crafts alkylation reaction between trifluoromethyl-α,β-ynones and indoles has been described. The reaction is catalyzed by benzoic acid (5 mol%), with the indoles adding to the carbonyl carbon of the trifluoromethyl-α,β-ynones producing the corresponding 1,2-addition products as trifluoromethyl propargyl alcohols in high yields. Furthermore, treatment of the product with indoles in the presence of trifluoroacetic acid (10 mol%) afforded trifluoromethyl-functionalized unsymmetrical bis(indolyl)propynes in high yields.

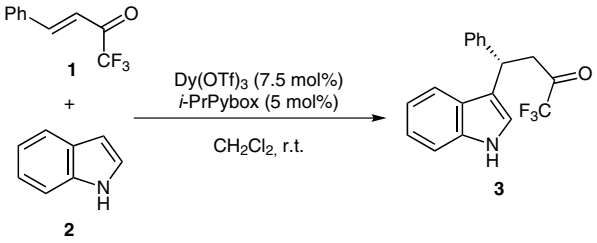
Key words: Brønsted acid, trifluoromethyl-α,β-ynones, indoles, trifluoromethyl propargyl alcohols, bis(indolyl)propynes

Trifluoromethylated compounds are an important class of pharmaceutical and agrochemical materials because of their interesting properties, such as their binding interactions and bioavailability.[1] Trifluoromethylated compounds have been usefully applied to the synthesis of organofluorine compounds, and various methods have been developed for the introduction of the trifluoromethyl moiety into organic compounds and building blocks.[2]

The Friedel–Crafts (FC) alkylation reaction of indoles is an interesting transformation because a number of biologically active indole alkaloid derivatives have been reported in the literature.[3]

Recently, considerable interest has been focused on the FC alkylation reaction of indoles with a variety of different electrophiles.[4] Consequently, several efficient methods have been developed by numerous research groups for the synthesis of organofluorine compounds using the FC alkylation reaction.[5]

In our previous work,[6] we reported the catalytic enantioselective FC alkylation reaction of trifluoromethyl-α,β-enone **1** with indole **2** to yield the corresponding 1,4-adduct **3** (Scheme 1) through a Michael addition reaction. It is worthy of note that the reaction proceeded cleanly and no byproducts were observed. To the best of our knowledge, however, there have been no reports in the literature describing the FC alkylation reaction of indoles with trifluoromethyl-α,β-ynones to yield the corresponding alkylation products. Herein, we describe the successful development of a catalytic FC alkylation reaction between trifluoromethyl-α,β-ynones and indoles, yielding synthetic fluorine-containing indole derivatives.



Scheme 1 The catalytic enantioselective FC alkylation of trifluoromethyl-α,β-enones with indoles

The reaction of trifluoromethyl-α,β-ynone **4**[7a] with indole **2** was chosen as a model reaction system to assess the behavior of ynone **4** in the proposed FC alkylation reaction. Thus, indole **2** was reacted with 1.05 equivalents of ynone **4** in an optimization screen in the presence of several easily available acid catalysts (Table 1).

We initially examined the FC alkylation reaction using $Sc(OTf)_3$ and $Dy(OTf)_3$/(*S,S*)-*i*-PrPybox as a catalyst in dichloromethane (CH_2Cl_2) for 18 hours. Contrary to our expectations, which were based on the successful FC alkylation reaction of indoles with trifluoromethyl-α,β-enones (Scheme 1), this reaction proceeded to give the 1,2-addition product of indole **2** to the carbonyl carbon of ynone **4**, providing the trifluoromethyl propargyl alcohol **5** in low yield, none of the desired product (Table 1, entries 1 and 2) and with no enantioselectivity (Table 1, entry 2).

In contrast, when the proposed FC alkylation was conducted in the presence of a Brønsted acid catalyst, no reaction was observed (Table 1, entries 3–5). In these cases, indole **2** existed in the liquid phase at the reaction temperature and was miscible[8] with the ynone **4**. Interestingly, we found that the reaction proceeded at a much greater rate in the absence of solvent, generating alcohol **5** in higher yields, depending on the catalyst used (Table 1, entries 6–8: 94%, 50%, and 90%, respectively). During the optimization study, benzoic acid performed as an effective catalyst in the absence of solvent for the FC alkylation reaction indole **1** with ynone **4**.

Although 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) also performed well, benzoic acid was selected as the optimum catalyst going forward because it is relatively inexpen-

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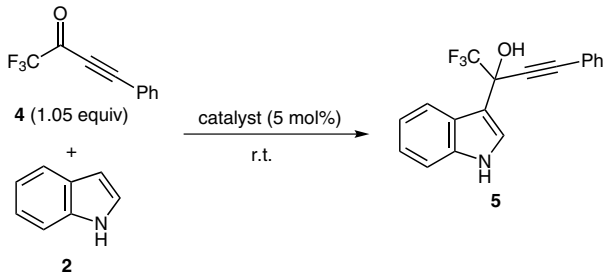
Table 1 Optimization of the Reaction Conditions



Entry	Catalyst	Solvent	Time	Yield of **5** (%)[a]
1	$Sc(OTf)_3$	CH_2Cl_2	18 h	40
2[b]	$Dy(OTf)_3$/(*S*,*S*)-*i*-PrPybox	CH_2Cl_2	18 h	48[d]
3	HFIP[c]	CH_2Cl_2	18 h	n.r.[e]
4	phenol	CH_2Cl_2	18 h	n.r.[e]
5	benzoic acid	CH_2Cl_2	18 h	n.r.[e]
6	HFIP	none	1.5 h	94
7	phenol	none	2 h	50
8	benzoic acid	none	50 min	90

[a] Isolated yield.
[b] The reaction was performed with 7.5 mol% $Dy(OTf)_3$ and 5 mol% (*S*,*S*)-*i*-Pr-Pybox.
[c] HFIP: 1,1,1,3,3,3-hexafluoro-2-propanol.
[d] No enantioselectivity was observed (see Supporting Information).
[e] No reaction.

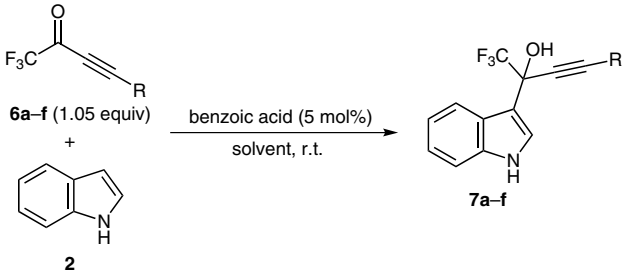
sive, easy to treat, and easily obtained from a commercial source.

To further expand the scope of our new FC alkylation reaction, indole **2** was reacted with 1.05 equivalents of a variety of different ynone derivatives **6a**–**f**[7] under the optimized conditions (Table 2).

Pleasingly, the desired 1,2-addition products **7a**–**f** were successfully formed in high yields in all cases. Trifluoromethyl-α,β-ynone derivatives containing strongly electron-donating substituents at the *para* position of the aromatic ring showed slightly lower levels of reactivity (R = 4-MeC_6H_4, 4-$MeOC_6H_4$; Table 2, entries 1 and 2) relative to ynone **4** likely because of the resulting increase in the electron density at the trifluoromethyl carbonyl carbon. Interestingly, the trifluoromethyl-α,β-ynone derivatives containing electron-withdrawing substituents directly linked to the *para* position of the aromatic ring (e.g., **6c**–**e**) were all solid at room temperature and could therefore not be effectively mixed under the reaction conditions and required the presence of a solvent. Consequently, an extended reaction time was required to obtain the products in good yields.

We continued to investigate the scope and limitations of the optimized FC alkylation reaction by applying the op-

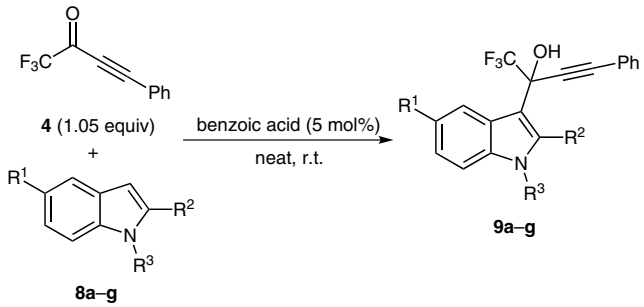
Table 2 The FC Alkylation Reactions of Indole **2** with Trifluoromethyl-α,β-ynone Derivatives **6a**–**f**



Entry	**6**	R	Solvent	Time (min)	**7**	Yield (%)[a]
1	**6a**	4-MeC_6H_4	none	60	**7a**	77
2	**6b**	4-$MeOC_6H_4$	none	150	**7b**	87
3	**6c**	4-ClC_6H_4	CH_2Cl_2	80	**7c**	90
4	**6d**	4-$MeOCOC_6H_4$	CH_2Cl_2	150	**7d**	91
5	**6e**	4-NCC_6H_4	CH_2Cl_2	20	**7e**	93
6	**6f**	*n*-Bu	none	60	**7f**	81

[a] Isolated yield.

Table 3 The FC Alkylation Reactions of Indoles **8a**–**g** with Trifluoromethyl-α,β-ynone **4**



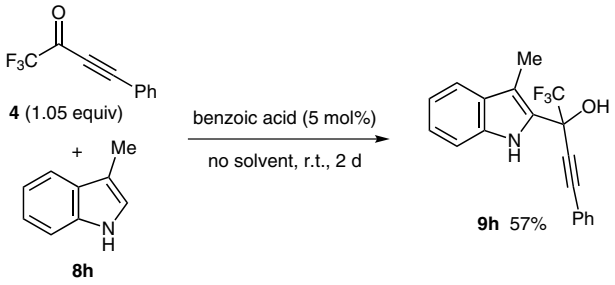
Entry	**8**	R^1	R^2	R^3	Temp	Time (h)	**9**	Yield (%)[a]
1	**8a**	Me	H	H	r.t.	0.25	**9a**	98
2	**8b**	OMe	H	H	r.t.	0.5	**9b**	95
3	**8c**	Br	H	H	r.t.	22	**9c**	96
4	**8d**	CO_2Me	H	H	r.t.	22	**9d**	n.r.[b]
5	**8d**	CO_2Me	H	H	70 °C	24	**9d**	61
6	**8e**	CN	H	H	r.t.	20	**9e**	n.r.[b]
7	**8e**	CN	H	H	70 °C	20	**9e**	complex mixture
8	**8f**	H	Me	H	r.t.	16	**9f**	97
9	**8g**	H	H	Me	r.t.	24	**9g**	89

[a] Isolated yield.
[b] No reaction.

timized reactions conditions to the reaction a variety of different indole derivatives **8a**–**g** with ynone **4** (Table 3).

In the majority of cases, the reactions provided the desired trifluoromethyl propargyl alcohol derivatives **9a**–**g** in good yields, except for 5-cyanoindole (**8e**) in Table 3, entries 6 and 7. In addition, the presence of electron-donating groups at the C-5 position of the indole skeleton (R^1 = Me and MeO; Table 3, entries 1 and 3) appeared to have a beneficial effect on the reaction, resulting in higher yields over a shorter reaction time.

In contrast, substrates containing electron-withdrawing groups (R^1 = Br and CO_2Me; Table 3, entries 3–5) at the C-5 position of the indole skeleton had an adverse impact on the reactivity, resulting in the requirement for extended reactions times and a higher reaction temperature (70 °C) to deliver adequate yields. Unfortunately, however, the use of 5-cyanoindole (**8e**) in the FC alkylation reaction at 70 °C resulted only in a complex mixture instead of the desired product. Furthermore, 2-methylindole (**8f**) and *N*-methylindole (**8g**) both required extended reaction times to obtain the desired 1,2-addition products in good yield (Table 3, entries 8 and 9). The reaction of 3-methylindole (**8h**) with **4** proceed as anticipated to give the 1,2-addition product at the 2-position of the 3-methylindole (Scheme 2).

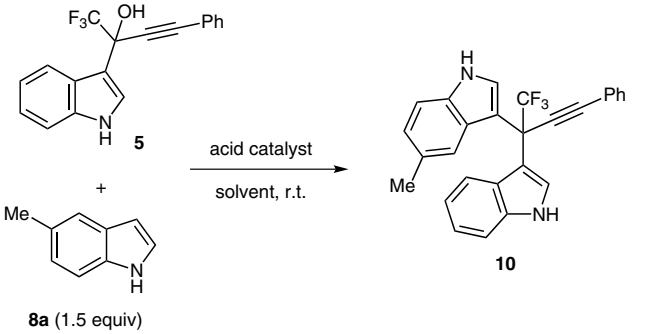


Scheme 2 The reaction of 3-methylindole (**8h**) with trifluoromethyl-α,β-ynone **4**

It is worthy of note that the reaction of carbonyl compounds with indoles in the presence of the acid catalyst afforded the corresponding bis(indolyl) derivatives[9] via a highly resonance-stabilized cation on the indole group.[10] In contrast, the reaction of trifluoromethyl-α,β-ynones with indoles in the presence of the benzoic acid catalyst provided the trifluoromethyl-functionalized propargyl alcohol derivatives. Bis(indolyl)propynes were not obtained in the current study because the trifluoromethyl moiety effectively destabilized the α-carbocation as a consequence of its strong electron-withdrawing nature.[11] It was therefore envisaged that the use of a trifluoroacetic acid catalyst more acidic than benzoic acid would overcome this issue and allow for the synthesis of trifluoromethyl-functionalized unsymmetrical bis(indolyl)propynes. We proceeded to investigate the possibility of achieving this transformation using a standard reaction system.

The reaction of trifluoromethyl propargyl alcohol **5** with 1.5 equivalents of 5-methylindole (**8a**) was chosen as a model reaction system for optimizing the reaction condition using a variety of different acid catalysts (Table 4).

Table 4 Optimization of the Reaction Conditions of **5**[12] with **8a**



Entry	Catalyst (mol%)	Solvent	Time	Yield of **10** (%)[a]
1	PTSA (5)	CH_2Cl_2	7 d	32
2	TFA (5)	CH_2Cl_2	24 h	35
3	TFA (10)	CH_2Cl_2	38 h	74
4	TFA (10)	CH_2Cl_2	24 h	59
5	TFA (10)	DCE	38 h	11
6	TFA (10)	CCl_4	20 h	n.r.[b]
7	TFA (10)	DMF	20 h	n.r.[b]
8	TFA (10)	$CHCl_3$	18 h	98

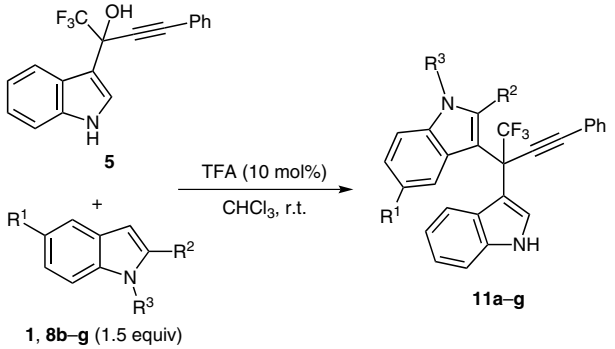
[a] Isolated yield.
[b] n.r. = no reaction.

Initially, alcohol **5** was reacted with 5-methylindole (**8a**) in the presence of *p*-toluenesulfonic acid (PTSA) (5 mol%) in CH_2Cl_2 at ambient temperature for seven days, affording the unsymmetrical bis(indolyl)propyne **10**[13] in low yield (Table 4, entry1) together with many other unidentified compounds. It is worthy of note that many unidentified compounds were generated when sulfonic acids were used as the catalyst. This was attributed to the strong acidity of the catalysts which may have led to the decomposition of the starting materials and the product **10**, giving rise to the observed lower yields. We then turned our attention to the acidity of catalyst and selected trifluoroacetic acid (TFA, 5 mol%). When TFA was used as the catalyst in the reaction, only the desired bis(indolyl)propyne **10** and residual starting materials could be detected in the product mixture (Table 4, entry 2). We proceeded to increase the amount of TFA to 10 mol% and found that the yield of the bis(indolyl)propyne **10** increased to 98% when the solvent was also changed to $CHCl_3$ and the reaction was conducted at ambient temperature for 18 hours (Table 4, entry 8).

With the optimized conditions in hand for the synthesis of a trifluoromethyl-functionalized unsymmetrical bis(indolyl)propyne, we proceeded to further evaluate the scope

of the reaction and examined the performance of a variety of other indole derivatives **1** and **8b**–**g** in the reaction with trifluoromethyl propargyl alcohol **5** in $CHCl_3$ in the presence of TFA (10 mol%) at ambient temperature (Table 5).

Table 5 Synthesis of the Trifluoromethyl-Functionalized Unsymmetrical Bis(indolyl)propynes **11a**–**g**



Entry	**1** or **8**	R^1	R^2	R^3	Time	**11**	Yield (%)[a]
1	**1**	H	H	H	18 h	**11a**	82
2	**8b**	OMe	H	H	18 h	**11b**	95
3	**8c**	Br	H	H	22 h	**11c**	98
4	**8d**	CO_2Me	H	H	5 d	**11d**	84
5	**8e**	CN	H	H	5 d	**11e**	91
6	**8f**	H	Me	H	16 h	**11f**	97
7	**8g**	H	H	Me	24 h	**11g**	79

[a] Isolated yield.

In all cases, the reactions provided the desired corresponding trifluoromethyl-functionalized unsymmetrical bis(indolyl)propynes **11a**–**g**. Furthermore, the electronics of the indole system did not appear to have a significant impact on the yield of the reaction, with indole derivatives bearing either electron-donating or electron-withdrawing groups providing the corresponding products in good yield. Electron-withdrawing substituents at the C-5 position of the indole skeleton, however, had an adverse impact on the rate of the reaction, with extended reaction times being required to deliver high yields (Table 5, entries 4 and 5).

In summary, we have demonstrated that benzoic acid can efficiently facilitate the FC reaction between trifluoromethyl-α,β-ynones and indoles. The FC reaction occurred via a 1,2-addition of the 3-position of the indole to the carbonyl carbon of a trifluoromethyl-functionalized propargyl alcohol in high yields. Furthermore, we also achieved a novel facile synthesis of trifluoromethyl-functionalized unsymmetrical bis(indolyl)propynes using TFA as a catalyst. We effectively demonstrated the impact of different acid catalysts on the stability of the α-carbocation and how this effected the selective synthesis of trifluoromethyl-functionalized propargyl alcohols and unsymmetrical bis(indolyl)propynes. We then proceeded to successfully manipulate this understanding to allow for the selective synthesis of trifluoromethyl-functionalized unsymmetrical bis(indolyl)propynes. The current methodologies are particularly well suited for the introduction of trifluoromethyl moieties and indole skeletons because they are facile procedures which provide high yields of the desired products. Furthermore, these structural classes enjoy significant application in the fields of biochemical, biomedical, and pharmaceutical research, and it is envisaged that the current methodologies will be of significant use to researchers in these areas.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **General Procedure for the Synthesis of Propargyl Alcohols**

The reaction was performed in a 3 mL V-vial equipped with Teflon-coated magnetic stirrer bar and screw cap. The V-vial was charged with indole (0.5 mmol), trifluoromethyl-α,β-ynone (1.05 equiv, 0.525 mmol), and CH_2Cl_2 (0.5 mL; as needed), then was stirred for 10 min. Then benzoic acid (5 mol%, 25 μmol, 3 mg) was added in one portion. After completion of reaction as indicated by TLC, the mixture was purified by silica gel chromatography directly.

1,1,1-Trifluoro-2-(1*H*-indol-3-yl)-4-phenylbut-3-yn-2-ol (5)

Purification by silica gel chromatography ($CHCl_3$–MeOH, 29:1) gave white solid (mp 134–136 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.11 (s, 1 H), 7.20 (ddd, *J* = 7.5, 7.0, 1.2 Hz, 1 H), 7.25 (ddd, *J* = 7.5, 7.0, 1.2 Hz, 1 H), 7.23–7.24 (m, 4 H), 7.52–7.56 (m, 3 H), 8.02 (d, *J* = 8.0 Hz, 1 H), 8.29 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 71.01 (q, *J* = 34.3 Hz), 84.50, 87.12, 111.41, 111.51, 120.54, 121.04, 121.13, 122.66, 123.94 (q, *J* = 285.5 Hz), 124.80, 128.20, 129.39, 132.03, 136.53. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –71.6. IR (KBr): 3425, 3360, 2240 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{18}H_{12}F_3NO$: 319.1184; found: 319.1208. Anal. Calcd for $C_{18}H_{12}F_3NO$: C, 68.57; H, 3.84; N, 4.44. Found: C, 68.87; H, 3.91; N, 4.50.

(13) **General Procedure for the Synthesis of Unsymmetrical Bis(indolyl) Propynes**

To a solution of trifluoromethyl propargyl alcohol derivative **5** (0.5 mmol) in $CHCl_3$ (2 mL) were added indoles (1.5 equiv, 0.75 mmol) and TFA (10 mol%, 50 μmol, 6 mg) at r.t. The reaction mixture was stirred until the disappearance of trifluoromethyl propargyl alcohol derivatives as observed by TLC. The reaction mixture was quenched with an aq sat. $NaHCO_3$ solution (2 mL), and the organic layer was separated. The aqueous layer was extracted 3 times with $CHCl_3$. The combined organic layer was dried with anhyd Na_2SO_4 and then evaporated. The residue was purified by column chromatography.

5-Methyl-3-[1,1,1-trifluoro-2-(1*H*-indol-3-yl)-4-phenylbut-3-yn-2-yl]-1*H*-indole (10)

Purification by silica gel chromatography ($CHCl_3$) gave a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 1 H), 6.97–7.04 (m, 2 H), 7.13–7.19 (m, 1 H), 7.19–7.21 (m, 1 H), 7.21–7.24 (m, 2 H), 7.26–7.31 (m, 3 H), 7.35 (d, *J* = 8.1 Hz, 1 H), 7.45–7.49 (m, 2 H), 7.56 (s, 1 H), 7.75 (d, *J* = 8.1 Hz, 1 H), 8.00 (s, 1 H), 8.09 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.56, 46.52 (q, *J* = 31.0 Hz), 85.14, 86.23, 110.91, 111.14, 111.24, 111.85, 119.70, 120.85, 121.29, 122.09, 122.53, 123.82, 124.33, 124.46, 125.87, 126.07, 126.15 (q, *J* = 284.6 Hz), 128.22, 128.47, 128.88, 131.74, 134.77, 136.45. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –71.54. IR (KBr): 3413, 2235 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{27}H_{18}F_3N_2$: 427.1422; found: 427.1419.

