Preprint Title	Reaction of indoles with aromatic fluoromethyl ketones: An efficient synthesis of trifluoromethyl-indolyl-phenylethanols using K_2CO_3/ nBu$_4$PBr in water
Authors	Thanigaimalai Pillaiyar, Masoud Sedaghati and Gregor Schnakenburg
Publication Date	12 Feb 2020
Article Type	Full Research Paper
Supporting Information File 1	BJOC_triF_indole_SI.pdf; 7.8 MB
ORCID® iDs	Thanigaimalai Pillaiyar - https://orcid.org/0000-0001-5575-8896

Reaction of indoles with aromatic fluoromethyl ketones: An efficient synthesis of trifluoromethyl-indolyl-phenylethanols using K_2CO_3/*n*Bu_4PBr in water

Thanigaimalai Pillaiyar,*[a] Masoud Sedaghati,[a] Gregor Schnakenburg[b]

[a]PharmaCenter Bonn, Pharmaceutical Institute, Department of Pharmaceutical and Medicinal Chemistry, University of Bonn, An der Immenburg 4, D-53121 Bonn, Germany.

[b]Institute of Inorganic Chemistry, University of Bonn, Gerhard-Domagk-Str. 1, D-53121 Bonn, Germany.

Corresponding author: *Dr. Thanigaimalai Pillaiyar; E-mail: thanigai@uni-bonn.de

Abstract

A new, mild and efficient protocol for the synthesis of trifluoromethyl-indolyl-phenylethanols by the reaction of indoles with a variety of aromatic fluoromethyl ketones in the presence of K_2CO_3 (15 mol%) and *n*Bu_4PBr (15 mol%) in water. The desired products were obtained in good to excellent yields without requiring the column chromatography purification. The reusability of the catalytic system and large-scale synthesis of indolyl-phenylethanols, which would further transform into biological active indole-derived compounds, are further advantages of this protocol.

Keywords

Indole, Friedel-Crafts reaction, C-C-bond formation, C3-funtionalization of indole, indole-3-carbinol, diindolylmethane, recyclability and large-scale synthesis.

Introduction

(1*H*-Indol-3-yl)methanols have emerged as versatile pre-electrophiles for C-C functionalization at the position 3 of indoles[1]. Friedel-Crafts alkylation of (1*H*-indol-3-yl)methanols with indoles has proven to be a powerful strategy for the preparation of biologically important 3,3′-diindolylmethanes (DIMs)[2]. Additionally, (1*H*-indol-3-yl)methanols have been used as key precursors for the construction of complex indole derivatives that would be useful in pharmaceuticals as drugs and agrochemicals[2,3]. The simple (1*H*-indol-3-yl)methanol, a breakdown product of the glucobrassicin, which can be found in cruciferous vegetables[4], has a wide range of biomedical applications as an anticancer,[5] antioxidant, and anti-atherogenic agent [6].

The organofluorine compounds have attracted much attention due to their potential biological applications in medicinal and agricultural sciences. Introducing fluoro groups into organic molecules can dramatically influence their physiochemical and biological properties in comparison with non-fluorinated analogs. Many pharmaceuticals and agrochemicals developed in recent decades have either a fluorine atom or a trifluoromethyl group [7]. Given this, the development of a method for the incorporation of fluorine or trifluoromethyl group into organic molecules remains a great challenge in the research field. Introducing trifluoromethyl group into indole derivatives has envisioned in drug-design. For example, trifluoromethyl substituted (1*H*-indol-3-yl)methanol derivatives were reported for their promising HIV-1 inhibitory activities [8].

Trifluoromethyl substituted (1*H*-indol-3-yl)methanol derivatives can be synthesized by a Friedel-Crafts hydroxyalkylation reaction of indoles with trifluoromethyl ketones in the presence of either Lewis/Bronsted acid catalysts. Bandini et al. reported the trifluoromethyl hydroxyalkylation of indoles catalyzed by an organic base 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (TMG), also known as Barton's base, in excellent yields (Figure 1A) [9].

Recently, Liu and co-workers reported this reaction in the presence of cesium carbonate in acetonitrile (Figure 1B) [10]. Dinuclear zinc [11], cinchonidine catalysts [3b], and solvent-free conditions[12] have also utilized for this reaction. The base-catalyzed reaction has a benefit because it may avoid the formation of diindolylmethane and biindoles as by-products [13].

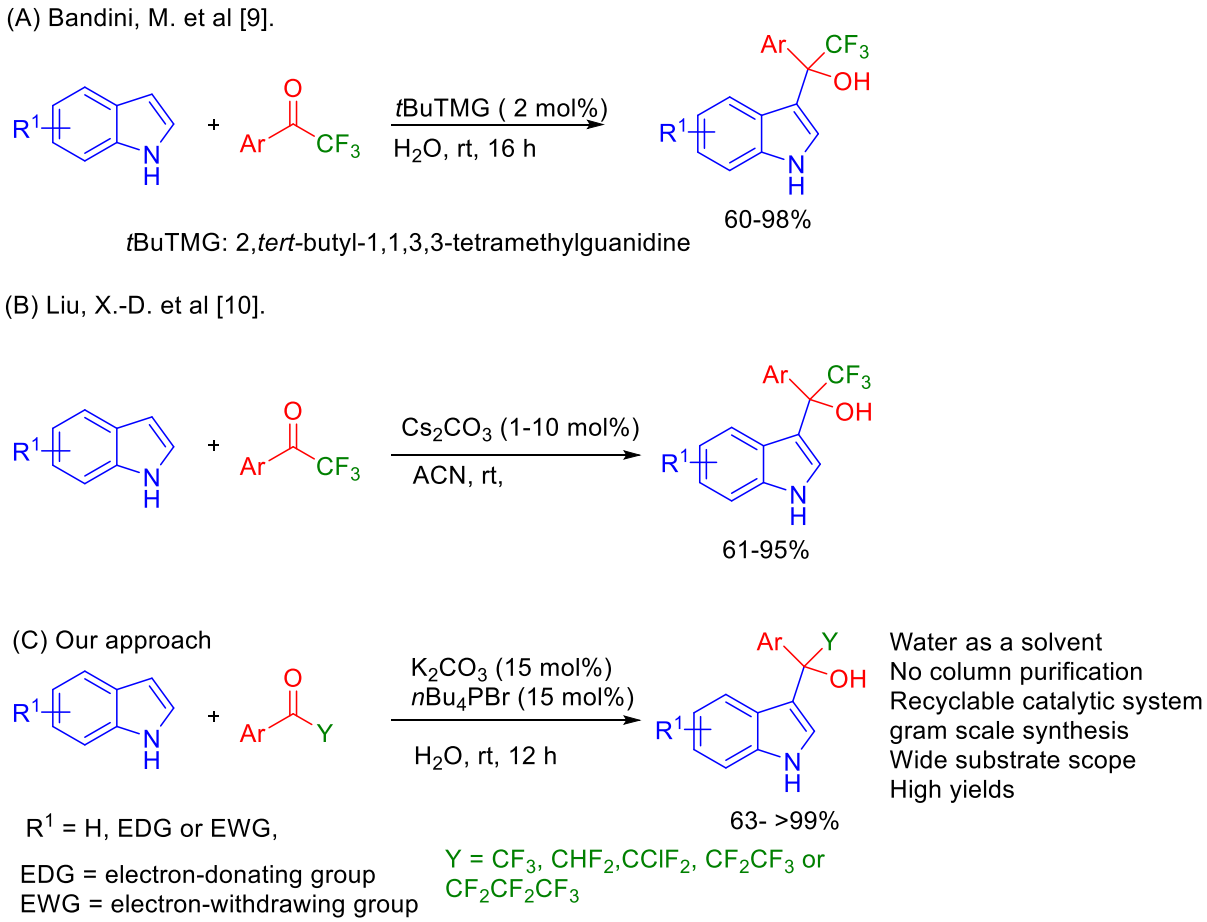


Figure 1. Synthetic approaches toward hydroxyalkylation of indole

Although these methods were useful, they have limitations and drawbacks, which are the use of organic solvents [9], difficulty in recyclability of the catalyst[9,10], generation of a large volume of waste liquids for the compound separation and column chromatographic purification [9,10], and moderate substrate scope of the reaction. Thus, finding an alternative method with broad substrate scope, functional group tolerance, and simple purification technique is highly desired.

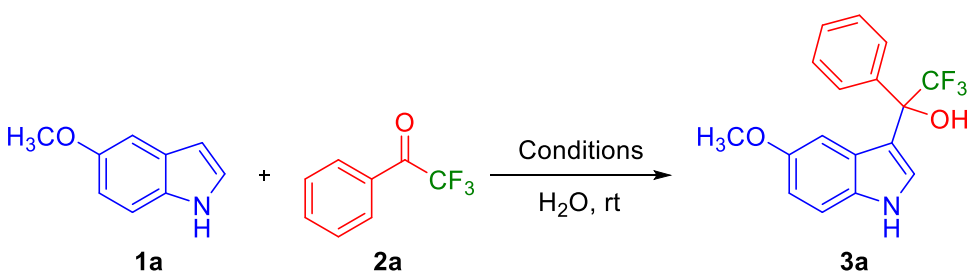
In our continuous effort of synthesizing indole derivatives [14], herein, we report an efficient synthesis of multiple halogens-substituted (1*H*-indol-3-yl)methanol derivatives in the presence of potassium carbonate and tetrabutylphophonium bromide, which mediate the reaction in water through the formation of interface between organic and aqueous phases. The advantageous of this reaction include high yields, no column chromatography, broad substrate scope, multi-scale synthesis, and recyclable of the catalyst (Figure 1C).

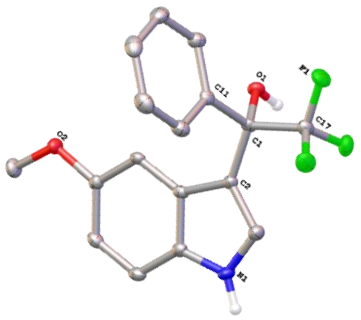
Results and discussion

The optimization studies were carried out with model substrates 5-methoxyindole (**1a**, 3.4 mmol) and 2,2,2-trifluoroacetophenone (**2a**, 3.70 mmol) in water (5 mL) (see for results in Table 1). Using water as a solvent has an advantage that the formation of product **3a** would not be soluble, which makes purification easier through a simple filtration. In a first attempt, the reaction did not initiate at all without any base or catalyst (entry 1). Next, we investigated the reaction in the presence of 20 mol% of base such as NaOH (entry 2) or KOH (entry 3). However, no product was formed (entries 2 and 3), which can be seen that the reactant **2a** was separated from the water. This makes us add quaternary salts into the reaction, which could make the interface between organic and aqueous phases. Very interestingly, the combination of 20 mol% of tetrabutylammonium bromide (TBAB) and NaOH (20 mol%) yielded the desired product, 2,2,2-tritrifluoro-1-(1*H*-indol-3-yl)-ethan-1-ol (**3a**) in 93% yield (entry 4). The product **3a** was isolated by filtration and confirmed by NMR and X-ray crystallography analysis (CCDC-1973322, see supporting information for detailed crystallographic data). It is noteworthy to mention that the formation of the product was even increased in the presence of tetrabutylphosphonium bromide (TBPB) to 96% (entry 5). On the other hand, the reaction did not initiate only with the TBPB (entry 6). It indicates that quaternary salts mediate the reaction in the presence of a base through the formation of the interface between organic and aqueous phases.

As a next step, different bases were investigated by using TBPB. In the presence of KOH and the Cs_2CO_3, the formation product was reduced to 91% (entry 7) and 81% (entry 9), respectively, while it was increased to 97% (entry 8) in the presence of K_2CO_3. The reaction in the presence of tripotassium phosphate base (entry 10; 89%), dipotassium phosphate base (entry 11; 70%) or sodium triphosphate (entry 12; 76%) did not improve the yield. These results suggest that K_2CO_3 can be the best catalyst for the reaction among other bases investigated.

Table 1. Optimization of reaction conditions for the preparation of 2,2,2-tritrifluoro-1-(1*H*-indol-3-yl)-ethan-1-ol (**3a**)[a]





Entry	Base (mol%)	Catalyst (mol%)	Time (h)	Yield (%)[b]
1	-	-	24	0
2	NaOH (20)	-	24	0
3	KOH (20)	-	24	0
4	NaOH (20)	TBAB (20)	15	93
5	NaOH (20)	TBPB (20)	15	96
6	-	TBPB (20)	24	0
7	KOH (20)	TBPB (20)	15	91
8	K_2CO_3 (20)	TBPB (20)	12	97
9	CS_2CO_3 (20)	TBPB (20)	15	81
10	K_3PO_4 (20)	TBPB (20)	15	89
11	K_2HPO_4 (20)	TBPB (20)	15	70
12	$Na_5P_3O_{10}$ (20)	TBPB (20)	15	76
13	K_2CO_3 (20)	TBAC (20)	15	72
14	K_2CO_3 (20)	TBAF (20)	15	61
15	**K_2CO_3 (15)**	**TBPB (15)**	**12**	**>99 (94)** [c]
16	K_2CO_3 (10)	TBPB (10)	18	90
17	K_2CO_3 (5)	TBPB (5)	24	69

[a]Reaction conditions: **1a** (500 mg, 3.4 mmol) and **2a** (524 µL, 3.70 mmol) were used in H_2O (5 mL) at room temperature. [b] Isolated yields. [c]Obtained yield in tap water.

To find the best catalytic system, other quaternary salts were invested in the reaction. When tetrabutylammonium chloride (TBAC) or tetrabutylammonium fluoride (TBAF) was employed in the presence of K_2CO_3, the formation of the product was reduced to 72% (entry 13) and 61% (entry 14), respectively. These results suggest that the combination of K_2CO_3/TBPB could be the best catalytic system for this reaction.

Next, the amount of catalytic system K_2CO_3/TBPB was reduced from 20 mol% to 15% to see if there any change in the yield. As indicated in entry 15, the product **3a** isolated in >99% without losing its efficiency. However, further reduction to 10 mol% or 5 mol% slowed the reaction rate, and only 90% (entry 16) or 69% (entry 17) of **3a** was isolated. These results suggest that the combination of K_2CO_3 (15 mol%)/*n*Bu_4PBr (15 mol%) could be a suitable and efficient catalytic system for this reaction.

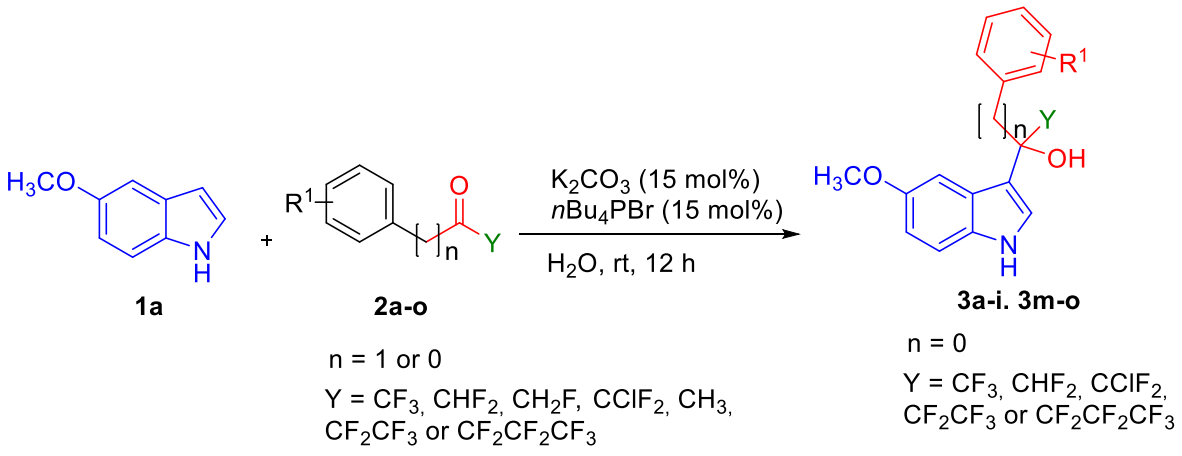
Having the optimized conditions, the substrate scope of the reaction was explored. At first, different trifluoromethyl ketones were investigated, and the results are summarized in Table 2. Trifluoroacetophenones having halogen substituent at the para position of the phenyl ring such as *p*-F (**2b**), *p*-Cl (**2c**), and *p*-Br (**2d**) provided the corresponding tritrifluoro-1-(1*H*-indol-3-yl)-ethan-1-ols **3b**, **3c**, and **3d** in 97, 92 and 89% yields, respectively. Similarly, trifluoroacetophenones having *p*-methyl (**2e**) and *p*-methoxy (**2f**) group of the phenyl ring resulted in **3e**, and **3f** with excellent yields 98 and 93%, respectively. These results suggest that the electronic properties of the substituent on the phenyl ring of the trifluoroacetophenones did not significantly influence the yield of the reaction.

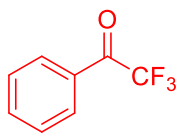
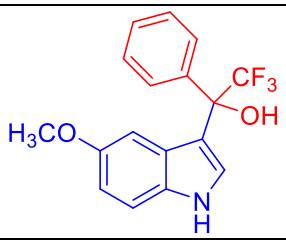
The trifluoromethyl ketones having electron-rich heteroaromatics such as 2-(trifluoroacetyl)furan (**2g**) and 2-(trifluoroacetyl)thiophene (**2h**) gave desired products **3g** (95%) and **3h** (97%) in excellent yields.

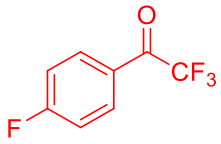
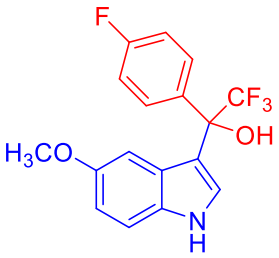
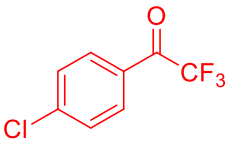
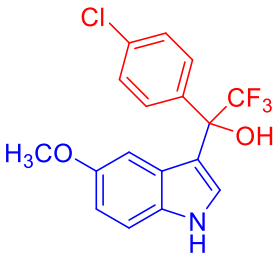
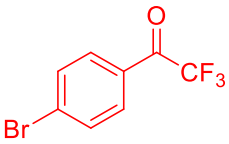
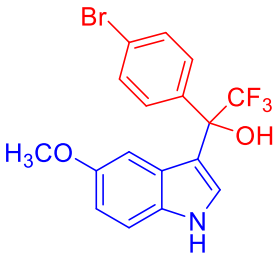
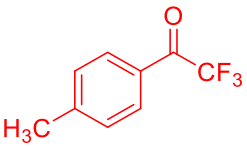
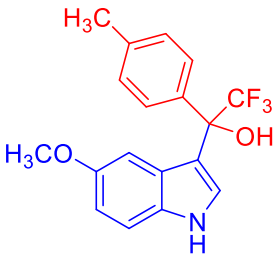
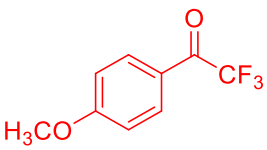
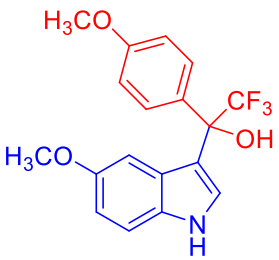
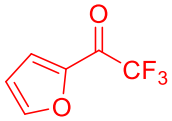
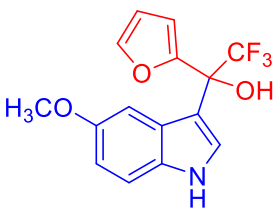
Next, the role of fluorine in the reactants was explored by subjecting the reaction of 2,2-difluoro-1-phenylethan-1-one (**2i**) with **1a**. The desired product **3i** was obtained in 63% yield. However, no product was formed when the reaction was carried out with 2-fluoro-1-phenylethan-1-one (**2j**) or acetophenone (**2k**). The reason could be due to either reducing the electrophilicity of ketone or the presence of enolizable protons in α-position to the keto group in basic medium. Supporting this hypothesis, the reaction of **1a** with 1,1,1-trifluoro-3-phenyl-2-propanone (**2l**), which has a 3-methylene group also did not proceed at all.

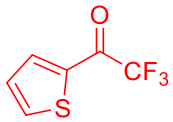
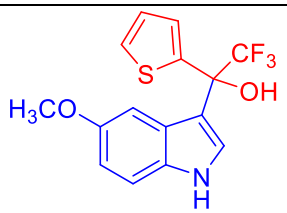
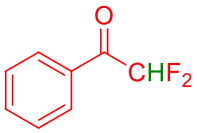
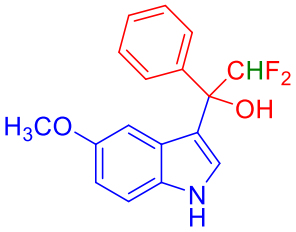
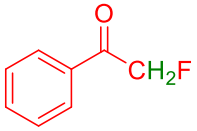
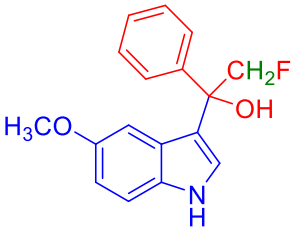
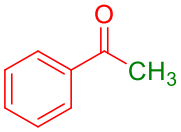
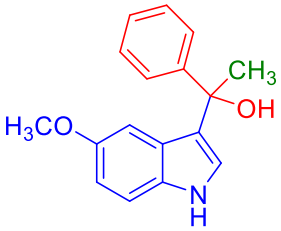
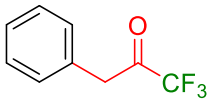
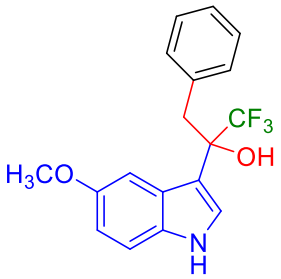
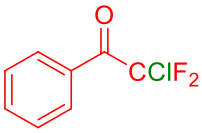
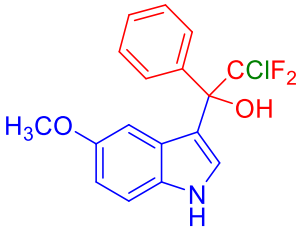
The scope of ketones was further extended with mixed halogens-substituted, pentafluoro or heptafluoro ketones such as 2-chloro-2,2-difluoro-1-phenylethan-1-one (**2m**), 2,2,3,3,3-pentafluoro-1-phenylpropan-1-one (**2n**) and 2,2,3,3,4,4,4-heptafluoro-1-phenylbutan-1-one (**2o**). All these reactions were provided the corresponding products (**3m**: 94%, **3n**: 93%, **3o**: 90%) in excellent yields without losing their efficiencies.

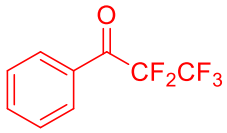
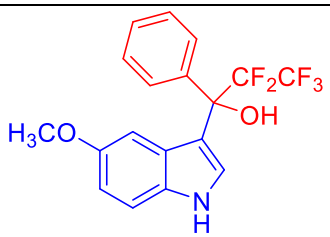
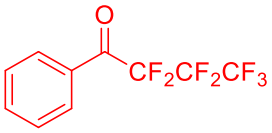
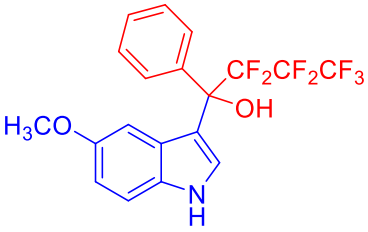
Table 2. Substrate scope of the reaction with ketones[a]



Ketones	Multi-halogens substituted hydroxylakylated indoles	M.p. (°C) (reported m.p.)	Purity (%)[b]	Yield (%)[c] (reported yield)
 **2a**		135-136 (135)[9]	99	>99% (98)

3a [9]				
 **2b**	 **3b**	115-116	98	97%
 **2c**	 **3c**	153-154	99	92
 **2d**	 **3d**	172-173	97	89
 **2e**	 **3e**	130-131	99	98
 **2f**	 **3f**	151-152	98	93
 **2g**	 **3g**	158-159	99	97

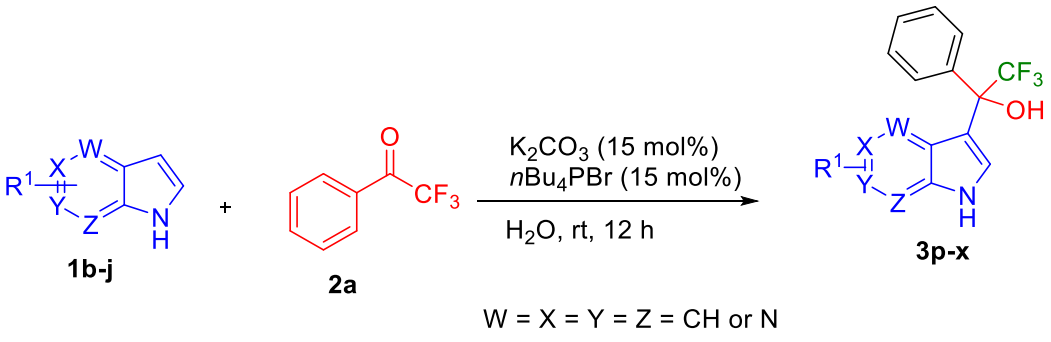
 **2h**	 **3h**	148-149	97	98
 **2i**	 **3i**	185-186	96	63
 **2j**	 **3j**	-	-	0
 **2k**	 **3k**	-	-	0
 **2l**	 **3l**	-	-	0
 **2m**	 **3m**	158-159	98	94

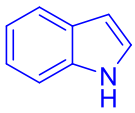
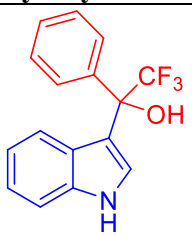
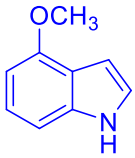
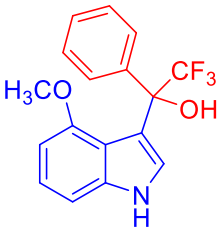
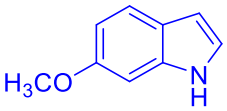
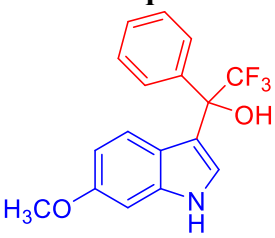
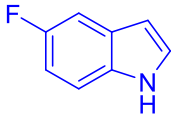
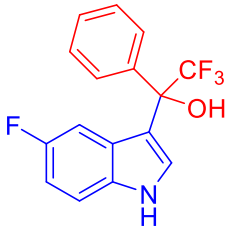
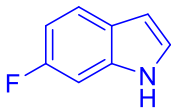
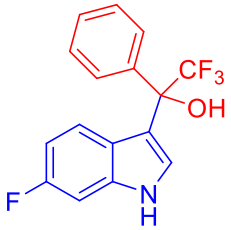
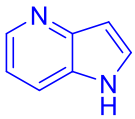
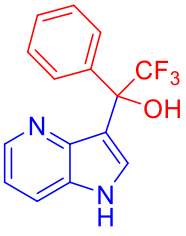
 **2n**	 **3n**	168-169	97	93
 **2o**	 **3o**	161-163	97	90

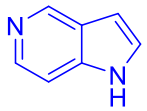
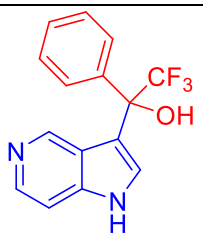
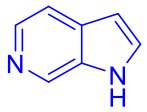
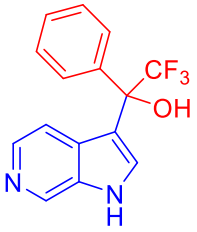
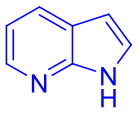
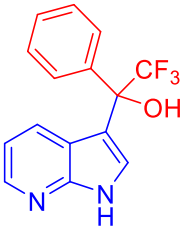
[a]Reaction and conditions: **1** (3.4 mmol) and **2** (3.75 mmol) in water (5 mL). [b]Purity was determined by HPLC coupled to a UV diode array detector (DAD) at 220−400 nm. [c] Isolated yields.

Next, the scope of substituted indoles was studied with trifluoromethyl ketone **2a**, and the results are shown in Table 3. In the case of a simple indole (**1b**), the corresponding product **3q** was isolated in 96% yield. Indoles bearing electron-donating group (i.e., methoxy, **1c-d**) and electron-withdrawing groups (i.e., F, **1e-f**) at the different positions of indoles were well tolerated and delivered the desired fluorinated indol-3-yl-1-phenylethnols (**3r-t**) in excellent yields in the range from 79-96%. The reaction of **3a** with different azaindoles (4-. 5-, 6-, and 7-azaindoles, **1h-j**) provided corresponding products in the range from 91-98% (**3u-x**).

Table 3. Substrate scope of the reaction with indoles[a]

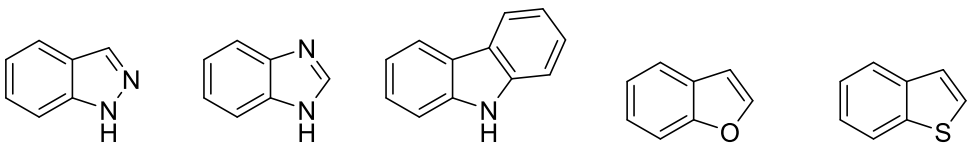


Indoles	Trifluoromethly substituted hydroxylakylated indoles	M.p. (°C) (reported M.p.)	Purity (%)[b]	Yield (%)[c] (reported yield)
 **1b**	 **3p**	122-124 (75)[10]	98	96 (95)
 **1c**	 **3q**	160-161	99	79
 **1d**	 **3r**	192-193	97	90
 **1e**	 **3s**	112-113	99	94 (98)
 **1f**	 **3t**	90-91 90	99	96 98
 **1g**	 **3u**	165-166	98	91

 **1h**	 **3v**	227-228	97	92
 **1i**	 **3w**	239-240	99	97
 **1j**	 **3x**	185-186 185[9]	97	90 (86)

[a]Reaction and conditions: **1** (3.4 mmol) and **2** (3.75 mmol) in water (5 mL). [b]Purity was determined by HPLC coupled to a UV diode array detector (DAD) at 220−400 nm. [c] Isolated yields.

We applied the developed protocol to reactions of other heterocyclic systems such as indazole (**4**), benzimidazole (**5**), carbazole (**6**), benzofuran (**7**), and benzothiophene (**8**) with a ketone **2a** (Figure 2). However, no desired products are formed.

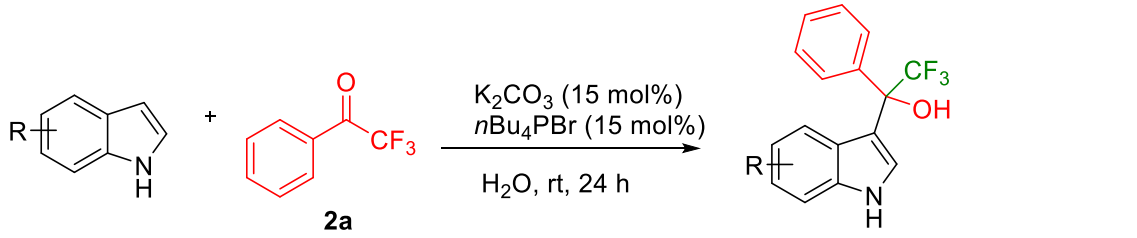


4 **5** **6** **7** **8**

Figure 2. Structures of heterocycles that did not react with ketone **2a**.

As a next step, this protocol is employed in the large scale preparation of 2,2,2-trifluoro-1-(1*H*-indol-3-yl)-1-phenylethan-1-ols. We performed gram scale reactions of 5-methoxyindole

(**1a**, 6.8 mmol) with 2,2,2-trifluoroacetophenone (**2a**, 7.5 mmol) or of indole (**1b**, 8.5 mmol) with **2a** (9.4 mol) (Scheme 1). In both reactions, the desired products are achieved in excellent yields (**3a**: 2.14 g, 98%; **3b**: 2.39 g, 96%) without losing its efficiency.

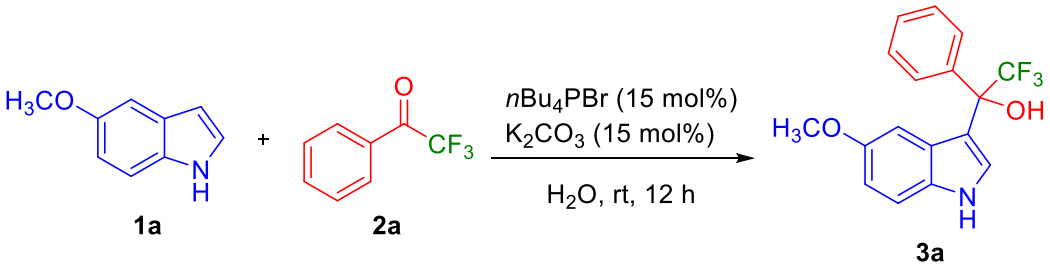


1a: R = 5-OCH_3 (1.0 g,)
1b: R = -H (1.0 g)

3a: R = 5-OCH_3 (2.14 g, 98%)
3q: R = -H (2.39 g, 96%)

Scheme 1. Gram-scale synthesis of 2,2,2-trifluoro-1-(1*H*-indol-3-yl)-1-phenylethan-1-ols (**3a** and **3q**)

The recyclability of the catalytic system *n*Bu_4PBr/K_2CO_3 of this protocol was investigated in the preparation of **3a** using **1a** (3.40 mmol), **2a** (3.70 mmol), K_2CO_3 (0.5 mmol) and *n*Bu_4PBr (0.5 mmol) in distilled water (5 mL) at room temperature for 12 h (Figure 3). The product **3a** was filtered after completion of the reaction. The resulting filtrate was recovered, washed with ethyl acetate to remove if there are any organic impurities, and reused it for the next cycle. This procedure was followed for each cycle. Interestingly the catalytic system was efficient to produce the product **3a** in excellent to good yields up to 4 cycles (99-84%). In fifth cycle, the yield of **3a** was reduced to 67%. This could be due to the dilution of catalytic system in each cycle.



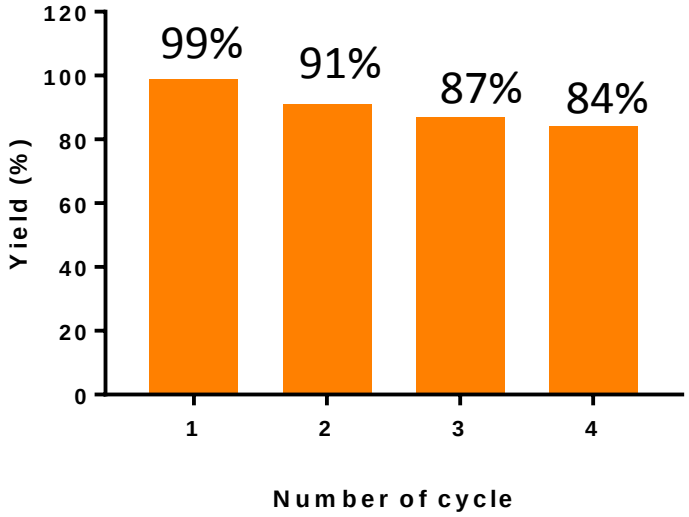
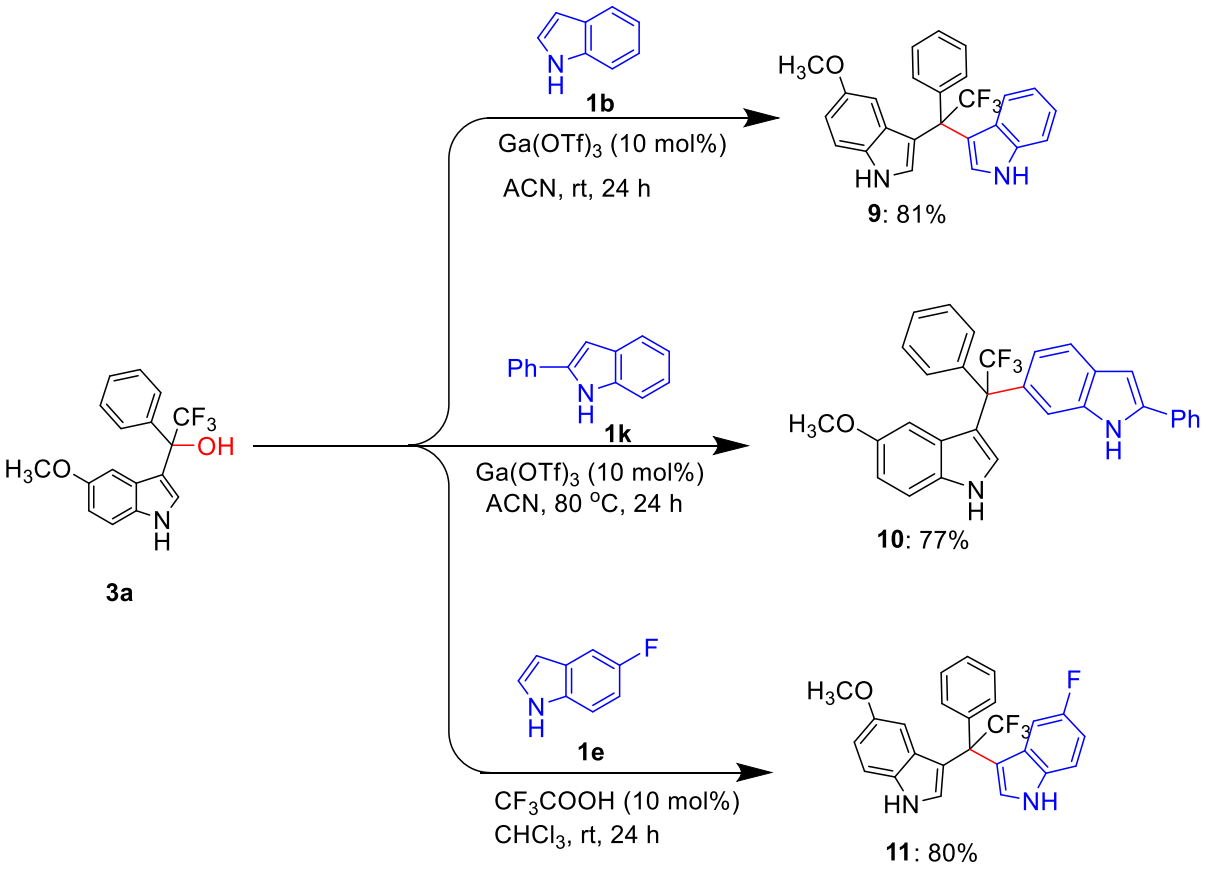


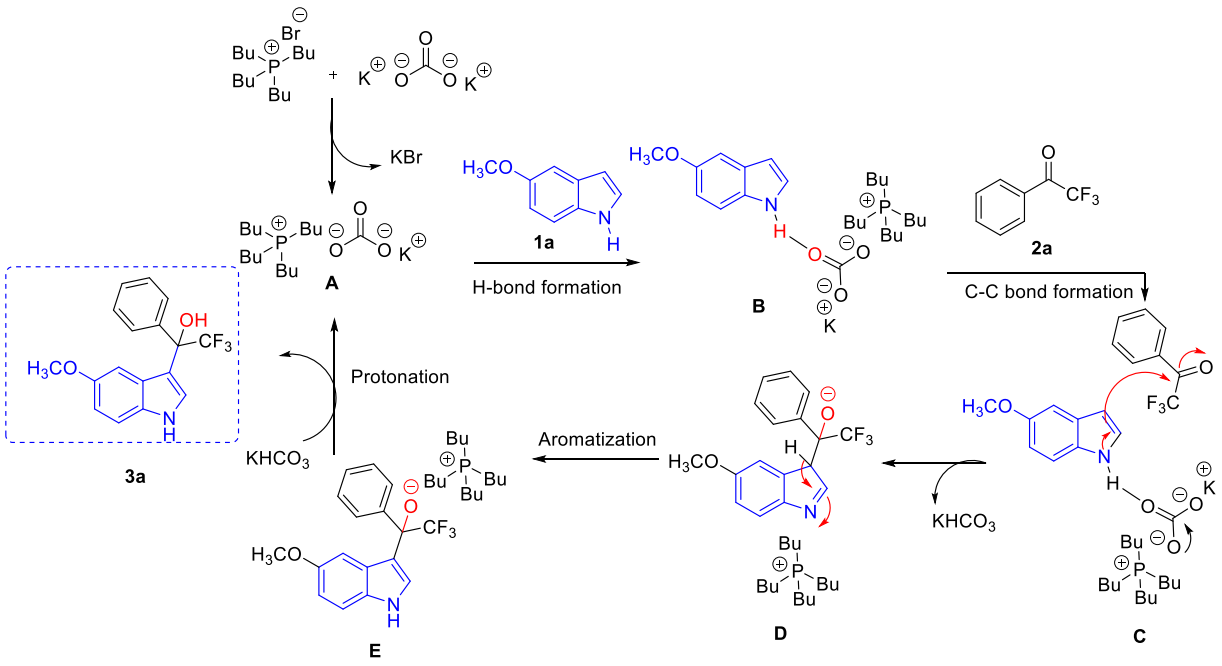
Figure 3. Recyclability of the catalytic system *n*Bu$_4$PBr/K$_2$CO$_3$ for the preparation of 2,2,2-trifluoro-1-(5-methoxy-1*H*-indol-3-yl)-1-phenylethan-1-ol (**3a**).

3-Indolylmethanols are versatile pre-electrophiles for C-C functionalization at the 3 position of indoles. Particularly, the Friedel-Crafts alkylation of 3-indolylmethanols with indoles has become a useful method for the preparation of 3,3'-, and 3,6'-DIMs, which are known to possess a wide variety of biological activities, including anti-inflammatory, and anti-cancer effects. Therefore, we decided to synthesize DIMs from **3a**, which reacted with indole (**1b**) or 2-phenylindole (**1k**) in the presence of Ga(OTf)$_3$ in ACN at room temperature or at 80 ^{o}C reported by Ling, Y. et al [15]. As indicated in Scheme 2, the desired unsymmetrical 3,3'-DIMs (**9**: 81%) and 3,6'-DIMs (**10**: 77%) with quaternary center were afforded in good yields. Besides, the protocol reported by Sasaki, S. et al [16]. also employed for the synthesis of 3,3'-DIMs in good yield, see for example the product **11** (80%, Scheme 2).



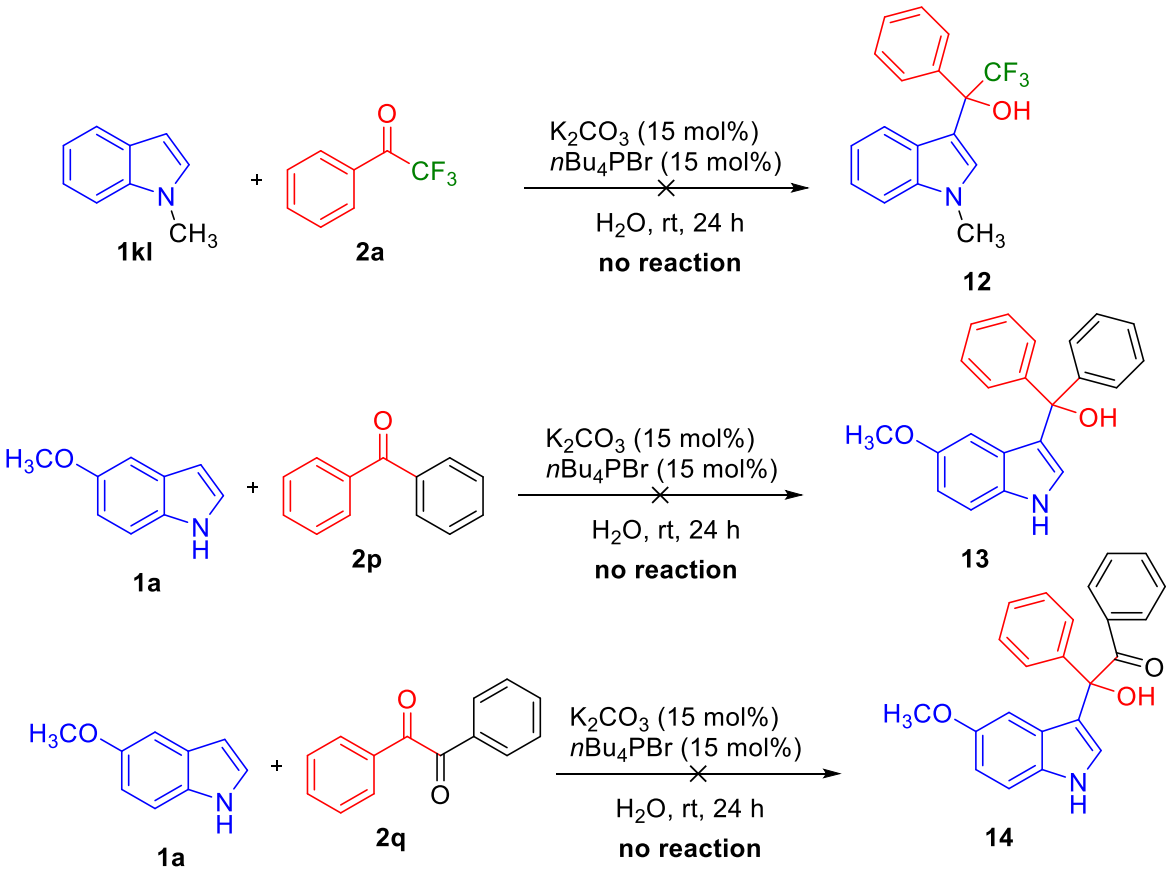
Scheme 2. Synthesis of trifluoromethylated unsymmetrical 3,3'- and 3,6'-DIMs (**9-11**).

Next, a plausible mechanism for the preparation of multihalogens-alkylated-1-(1*H*-indol-3-yl)-1-phenylethan-1-ols is proposed as indicated in Scheme 3. Based on literature [17], this reaction initiates by the formation of salt *n*Bu$_4$P+KCO$_3$- (A) from the interaction of *n*Bu4PBr and K$_2$CO$_3$. Intermediate A makes hydrogen bond interaction with NH of the 5-methoxyindole (**1a**) and form the adduct B. This interaction assists **1a** reacting with an electrophilic ketone (**2a**) to form the intermediate D *via* C-C bond formation (C). Re-aromatization of D generates E, which then protonates to form the desired product **3a** by excluding A for the next catalytic cycle.



Scheme 3. Proposed mechanism for the preparation of **3a** as an example.

Further, to prove this hypothesis the following control experiments were demonstrated. Reaction of 1-methylindole (**1l**) with **2a** failed to provide the product (Scheme 4). It suggests that the indole having free NH-functionality is important to interact with base, thereby initiating the reaction. To find the importance of electrophilicity of ketones, different enolizable and nonenolizable ketones were screened with the reaction of 5-methoxyindole (**1a**). The enolizable ketones **2j-l** failed to provide the products (see Table 2). Similarly, nonenolizable ketones **2p-q** (Scheme 4) failed to provide the products. This observation suggests that the multihalogens-substituted enhanced the electrophilicity of the ketone for the Friedel-Crafts hydroxyalkylation reaction of indole.



Scheme 4. Control experiments

Conclusions

In conclusion, we have developed an efficient and practical protocol for the preparation of trifluoromethyl-indolyl-phenylethanols, which are of significant interest serving as pre-electrophiles for C-C functionalization at the 3 position of indoles. Particularly, the Friedel-Crafts alkylation of 3-indolylmethanols with indoles has become a useful method for the preparation of 3,3'-, and 3,6'-DIMs, which are known to possess a wide variety of biological activities, including anti-inflammatory, and anti-cancer effects. The developed new synthetic protocol for the preparation of trifluoromethyl-indolyl-phenylethanols is operationally simple and provided products in high yields without requiring silica gel column chromatography. The reaction has a broad substrate scope and proceeds with high regioselectivity. The recovery and

reusability of the catalytic system and large-scale synthesis of products, which would further transform into biological active indole-derived compounds, are further advantages of this protocol.

Supporting information:

The following data are available online. Materials and methods and detailed synthetic procedures and spectroscopic data of all compounds. Figure S1: ORTEP-type plot of the molecular structure of **3a**, Figure S2-S25: NMR spectra, Table S1–S3: Crystal data and structure refinement for compound **3a**.

Acknowledgments: T.P. is grateful to Alexander von Humboldt (AvH) foundation and to Bayer Pharma for a postdoctoral fellowship. G.S. thanks Prof. Dr. A. C. Filippou and Prof. Dr. D. Menche for providing X-ray infrastructure.

Conflicts of Interest: The authors declare no conflict of interest.

ORCID® iDs

Thanigaimalai Pillaiyar: http://orcid.org/0000-0001-5575-8896

References

1. For reviews, see: (a) Mei, G.-J.; Shi, F.; *J. Org. Chem.* **2017**, *82*, 7695−7707; (b) Wang, L.; Chen, Y.; Xiao, J. *J. Org. Chem.* **2015**, *80*, 1841−1848; (c) Tan, W.; Du, B.-X.; Li, X.; Zhu, X.; Shi, F.; Tu, S.-J. *J. Org. Chem.* **2014**, *79*, 4635−4643; (d) Liu, Y.; Zhang, H.-H.; Zhang, Y.-C.; Jiang, Y.; Shi, F.; Tu, S.-J. *Chem. Commun.* **2014**, *50*, 12054−12057.

2. (a) He, Y.-Y.; Sun, X.-X.; Li, G.-H.; Mei, G.-J.; Shi, F. *J. Org. Chem.* **2017**, *82*, 2462−2471; (b) Inamdar, S. M.; Gonnade, R. G.; Patil, N. T. *Org. Biomol. Chem*. **2017**, *15*, 863−869; (c) Xiao, J.; Wen, H.; Wang, L.; Xu, L.; Hao, Z.; Shao, C.-L.; Wang, C.-Y. *Green Chem.* **2016**, *18*, 1032−1037; (d) Suarez, A.; Martínez, F.; Sanz, R. *Org. Biomol. Chem.* **2016**, *14*, 11212−11219; (e) Wen, H.; Wang, L.; Xu, L.; Hao, Z.; Shao, C.-L.; Wang, C.-Y.; Xiao, J. *Adv. Synth. Catal.* **2015**, *357*, 4023−4030; (f) Zeng, X.-F.; Ji, S.-J.; Wang, S.-Y. *Tetrahedron* **2005**, *61*, 10235−10241; (g) Pillaiyar, T.; Gorska, E.; Schnakenburg, G.; Müller, C.E. *J. Org. Chem.* **2018**, *83*, 9902−9913; (h) Deb, M. L.; Das, C.; Deka, B.; Saikia, P.J.; Baruah, P.K. *Synlett* **2016**, *27*, 2788−2794; (i) Jadhav, S.D.; Singh, A. *J. Org. Chem.* **2016**, *81*, 522−531; (j) Lancianesi, S.; Palmieri, A.; Petrini, M. *Adv. Synth. Catal.* **2012**, *354*, 3539− 3544; (k) Sun, F.-L.; Zheng, X.-J.; Gu, Q.; He, Q.-L.; You, S.-L. *Eur. J. Org. Chem.* **2010**, 47−50.

3. Reviews and some examples for preparation of indole derivatives from 3-indolylmethanols, see: (a) Zhu, S.; Xu, L.; Wang, L.; Xiao, J. *Chin. J. Org. Chem.* **2016**, *36*, 1229-1240; (b) Kasztelan, A.; Biedrzycki, M.; Kwiatkowskia, P. *Adv. Synth. Catal.* **2016**, *358*, 2962-2969; (c) Zhang, C.; Zhang, L.-X.; Qiu, Y.; Xu, B.; Zong, Y.; Guo, Q.-X. *RSC Adv.* **2014**, *4*, 6916-6919; (d) Guo, Z.-L.; Xue, J.-H.; Fu, L.-N.; Zhang, S.-E.; Guo, Q.-X. *Org. Lett*. **2014**, *16*, 6472-6475; (e) Xu, B.; Shi, L.-L.; Zhang, Y.-Z.; Wu, Z.-J.; Fu, L.-N.; Luo, C.-Q.; Zhang, L.-X.; Peng, Y.-G.; Guo, Q.-X. *Chem. Sci.* **2014**, *5*, 1988-1991; (f) Xu, B.; Guo, Z.-L.; Jin, W.-Y.; Wang, Z.-P.; Peng, Y.-G.; Guo, Q.-X. A*ngew. Chem. Int. Ed.* **2012**, *51*, 1059-1062; (g) Guo, Q.-X.; Peng, Y.-G.; Zhang, J.-W.; Song, L.; Feng, Z.; Gong, L.-Z. *Org. Lett.* **2009**, 11, 4620-4623.

4. Sarubin-Fragakis, Allison; Thomson, Cynthia; Association, American Dietetic (2007-01-01). The Health Professional's Guide to Popular Dietary Supplements. American Dietetic Associati. p. 312. *ISBN 9780880913638*.

5. Park, N. I.; Kim, J. K.; Park, W. T.; Cho, J. W.; Lim, Y. P.; Park, S. U. *Mol. Biol. Rep.* ***2010,*** 38*,* 4947-4953.
6. Chemical entities of biological Interest (ChEBI), The European bioinformatics institute (EBI). "indole-3-methanol (CHEBI:24814)" (*www.ebi.ac.uk*. retrieved 2016-03-25)
7. (a) Prakash Reddy, V. Organofluorine compounds in biology and medicine, Elsevier, **2015**; (b) Kirsch, P. Modern fluoroorganic chemistry: Synthesis, reactivity, applications, second Edition. Wiley-VCH GmbH & Co. KGaA. **2013**; (c) Uneyama, K. Organofluorine chemistry Wiley-Blackwell: Oxford, **2006**; (d) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071-1081.
8. (b) Jiang, H.-X.; Zhuang, D.-M.; Huang, Y.; Cao, X.-X.; Yao, J.-H.; Li, J.-Y.; Wang, J.-Y.; Zhang, C.; Jiang, B. *Org. Biomol. Chem.* **2014**, *12*, 3446-3458.
9. Bandini, M.; Sinisi, R. *Org. Lett.* **2009**, *11*, 2093-2096.
10. Liu, X.-D.; Wang, Y.; Ma, H.-Y.; Xing, C.-H.; Yuan, Y.; Luc, L. *Tetrahedron* **2017***, 73*, 2283-2289.
11. Hua, Y.-Z.; Chen, J.-W.; Yang, H.; Wang, M.-C. *J. Org. Chem.* **2018**, *83*, 1160-1166.
12. Safrygin, A.V.; Irgashev, R.A.; Barabanov, M.A.; Sosnovskikh, V. Y. *Tetrahedron* **2016**, *72*, 227-233.
13. Wang, Y.; Yuan, Y.; Xing, C.-H.; Lu, L. *Tetrahedron Lett.* **2014**, *55,* 1045-1048.
14. (a) Pillaiyar, T.; Köse, M.; Sylvester, K.; Weighardt, H.; Thimm, D.; Borges, G.; Förster, I.; von Kügelgen, I.; Müller*,* C. E. *J. Med. Chem.* 2017, **60**, 3636-3655. (b) Pillaiyar, T.; Dawood, M.; Irum, H.; Müller, C. E. *Arkivoc* **2018**, part III, 1-19; (c) Pillaiyar, T.; Uzair, M.; Ullah, S.; Schnakenburg, G.; Müller, C. E. *Adv. synth. catal.* **2019**, *17*, 4286-4293.
15. Ling, Y.; An, D.; Zhou, Y.; Rao, W. *Org. Lett.* **2019**, *21*, 3396-3401.

16. Sasaki, S.; Ikekame, Y.; Tanayama, M.; Yamauchi, T.; Higashiyama K. *Synlett* **2012**, *23*, 2699-2703.

17. Muthukumar, A.; Sekar, G. *J. Org. Chem.* **2018**, *83*, 16, 8827-8839.