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Efficient Guanidine-Catalyzed Alkylation of Indoles with Fluoromethyl Ketones in the presence of Water

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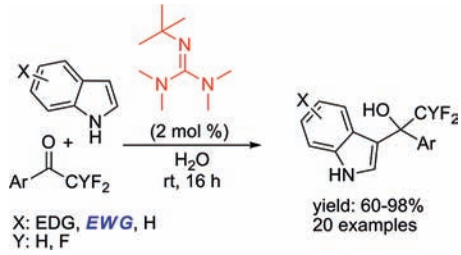
ABSTRACT



A simple and efficient guanidine-catalyzed methodology for the direct preparation of trifluoromethyl-indolyl-phenylethanols in the presence of water is reported. This synthetically viable class of compounds is obtained in excellent yields (up to 98%) through Friedel−Crafts-type alkylation of indoles with aromatic fluoromethyl ketones. Exceptional reaction scope of indoles and alkylating agents is described.

Aromatic organo-fluorine compounds are receiving a great deal of attention in pharmaceutical, agrochemical and material sciences, due to the unique features brought by the fluorine atom/s to the physical and chemical features of the molecule.[1] In this scenario, indolyl rings and trifluoromethyl groups are frequently combined in complex molecular architectures.

Catalytic FC-type alkylations of indoles with trifluoromethylcarbonyl compounds are practical and enable routes to the creation of benzylic stereocenters.[2] Despite the widespread interest in these targets, at the present, organometallic[3a] and metal-free[3b,c] catalyzed methodologies have been mostly applied to activated 3,3,3-trifluoromethylpyruvates and only a handful of catalytic indole alkylations with simple trifluoromethyl ketones and aldo-derivatives are known.[4]

As a continuation of our ongoing interest in catalytic indole functionalizations[5] and use of *simple* trifluoromethyl ketones for the construction of CF_3-containing quaternary stereocenters,[6] we envisioned a confluence of these topics as a straighforward means for the preparation of a family of

(1) (a) Ojima, I.; McCarthy, J. R.; Welch, J. T. *Biomedical Frontiers of Fluorine Chemistry*; American Chemical Society: Washington, DC, 1996. (b) Himaya, T. *Organofluorine Compounds*; Springer-Verlag: Berlin, Feidelberg, 2001. (c) Paquette, L. *Fluorine-Containing Reagents*; Wiley-VCH: Weinheim, 2007. (d) Ma, J.-A.; Cahard, J. *Chem. Rev.* **2004**, *104*, 6119–6146. (e) Ma, J.-A.; Cahard, J. *J. Fluorine Chem.* **2007**, *128*, 975–996.

(2) For representative reviews on catalytic FC-alkylations see: (a) Jørgensen, K. A. *Synthesis* **2003**, 1117–1125. (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550–556. (c) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199–1222. (d) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903–2915. (e) Sheng, Y.-F.; Zhang, A. J.; Zheng, X.-J.; You, S.-L. *Chin. J. Org. Chem.* **2008**, *28*, 605–616.

(3) (a) Zhuang, W.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2001**, *66*, 1009–1013. (b) Török, B.; Abid, M.; London, G.; Esquibel, J.; Török, M.; Mhadgut, S. C.; Yan, P.; Prakash, G. K. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3086–3089. (c) Abid, M.; Török, B. *Org. Lett.* **2008**, *10*, 933–935.

(4) (a) Abid, M.; Török, B. *Adv. Synth. Catal.* **2005**, *347*, 1797–1803. (b) Zhang, G.-W.; Wang, L.; Nie, J.; Ma, J.-A. *Adv. Synth. Catal.* **2008**, *350*, 1457–1463.

(5) (a) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1424–1425. (b) Bandini, M.; Eichholzer, A.; Monari, M.; Piccinelli, F.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2007**, *291*, 7–2920. (c) Bandini, M.; Eichholzer, A.; Tragni, M.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 3238–3241.

(6) Bandini, M.; Sinisi, R.; Umani-Ronchi, A. *Chem. Commun.* **2008**, 4360–4362.

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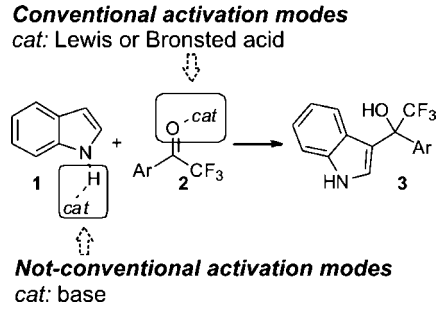
important synthetic building blocks such as 2,2,2-trifluoro-1-(1*H*-indol-3-yl)-1-phenylethanols **3** under mild catalytic conditions.[7]

Selective catalytic addition of an indolyl nucleus to simple carbonyl compounds (aldehydes and ketones), still represents a quite unexplored field if we consider the challenging isolation of unstable indol-3-ylcarbinols under acidic conditions.[8,9]

The present working idea deals with the use of catalytic amounts of organic base, as an alternative to conventional acid catalysis, to activate the indolyl core toward FC-functionalization, with the concomitant minimization of bis-indolylmethane formation (Scheme 1).[8]

Scheme 1. Conventional vs Not-Conventional Activation Modes in Catalytic FC-Alkylations of Indoles

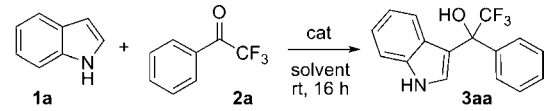


In this context, we have recently documented[5b,c] the suitability of basic indole-activation (pK_a values of *N*-H indole range between 12.36 and 19.50),[10] in catalytic FC chemistry.

As a proof of concept, we surveyed a range of organic bases as well as acid additives in the condensation of **1a** with **2a** as the model reaction partners. A summary of results is reported in Table 1.

As expected, classical Lewis (entries 1−3) and Brønsted[11] (i.e., pTSA, entry 4) acid catalysts for FC alkylations furnished the desired indole-3-carbynol **3aa** in low yields (≤27%), leading to variable amounts of side products/reactions such as bis-indolylmethanes and oxidative dimerization of **1a**. Unacceptable chemical outcomes were also observed with moderately basic pyridine and aliphatic tertiary amines (i.e., TEA, DIPEA, quinine), but delightfully, catalytic amounts of TMG (tetramethylguanidine, pK_a = 13.6)[12]

Table 1. Optimization of the Reaction Parameters[a]



entry	cat (%)	solvent	**1a/2a**	yield **3aa** (%)[b]
1	$InBr_3$ (10)	dioxane	5/1	10
2	$FeCl_3$ (10)	dioxane	5/1	8
3	$BF_3{\cdot}Et_2O$ (10)	dioxane	5/1	27
4	pTSA (10)	dioxane	5/1	10
5	pyridine (10)	dioxane	5/1	–[c]
6	TEA (10)	dioxane	5/1	9
7	DIPEA (10)	dioxane	5/1	11
8	Quinine (10)	dioxane	5/1	–[c]
9	TMG (10)	dioxane	5/1	98
10	*t*BuTMG (10)	dioxane	5/1	98
11	*t*BuTMG (5)	dioxane	1.1/1	98
12	*t*BuTMG (5)	H_2O	1.1/1	98
13	*t*BuTMG (2)	H_2O	1.1/1	94

[a] Reactions were carried out open to the air and with no precautions taken to exclude moisture, unless otherwise specified. In the absence of catalyst the reaction could not proceed at all. [b] Isolated yields after flash chromatography. [c] No reaction.

and Barton's base-*t*BuTMG (2-*t*Bu-1,1,3,3-tetramethylguanidine, pK_a = 14)[12] (**1a**:**2a** ratio: 5:1, 16 h, entries 9, 10) led to **3aa** in quantitative yield. Then, in order to discriminate between these bases, a further survey of reaction parameters such as catalyst loading, reaction time and reagent ratio was performed. From this investigation, *t*BuTMG (5 mol %) emerged as the catalyst of choice enabling the isolation of **3aa** in quantitative yield even with indole:ketone ratio of 1.1:1.[13]

Pointing toward sustainability, we envisioned the possibility to run the present FC reaction in the presence of water.[14] Interestingly, although no detailed kinetic investigations were undertaken, comparable reaction rates with organic media and in the presence of water were observed (entries 11 and 12). Finally, it was possible to lower the loading of the catalyst up to 2 mol %, mantaining comparable chemical outputs (entry 13). Although the reaction seemed to occur in the concentrated organic phase constituted by the reagents, the presence of water assisted the reaction course causing the precipitation of the product **3**.[15,16]

(7) For a recent elegant example of Zr-catalyzed stereoselective addition of pyrrole to trifluoromethyl ketones see: Blay, G.; Fernández, I.; Monleón, A.; Pedro, J. R.; Vila, C. *Org. Lett.* **2009**, *11*, 441–444.

(8) (a) Remers, W. A. In *Indoles*, *Heterocyclic Compounds*; Houlihan, W. J., Ed.; John Wiley & Sons: London, 1972. (b) *Indoles*; Sudberg, R. J., Ed.; Academic Press: London, 1996.

(9) For a leading study see: Li, H.; Wang, Y.-Q.; Deng, L. *Org. Lett.* **2006**, *8*, 4063–4065.

(10) Yagil, G. *Tetrahedron* **1967**, *23*, 2855–2861.

(11) During the submission of the manuscript an enantioselective arylation of trifluomethyl ketones (CH_2Cl_2) was described in the presence of BINOL-derived chiral phosphoric acids: Nie, J.; Zhang, G.-W.; Wang, L.; Fu, A.; Zheng, Y.; Ma, J.-A. *Chem. Commun.* **2009**, DOI: 10.1039/b900474b.

(12) The reported pK_a values refer to the conjugated acids.

(13) For reviews regarding the use of guanidine in organic synthesis see: (a) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737–752. (b) Leow, D.; Tan, C.-H. *Chem. Asian J.* **2009**, *4*, 488–507.

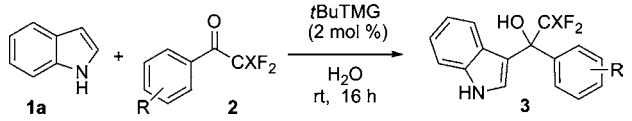
(14) For representative examples of FC-alkylations in water see: (a) Manabe, K.; Aoyama, N.; Mikami, K. *Adv. Synth. Catal.* **2001**, *343*, 174–176. (b) Zhuang, W.; Jørgensen, K. A. *Chem. Commun.* **2002**, 1336–1337. (c) Shirakawa, S.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 4939–4942. For a comprehensive review on C−C bond forming processes in water see: Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095–3166, and references therein.

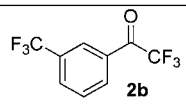
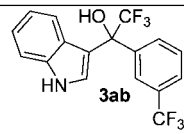
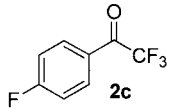
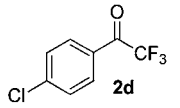
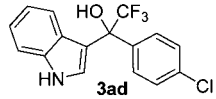
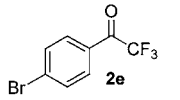
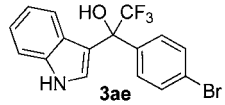
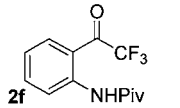
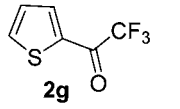
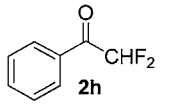
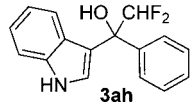
(15) (a) Klijn, J. E.; Engberts, B. F. N. *Nature (London)* **2005**, *435*, 746–747. (b) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100–8102. (c) Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8103–8104.

(16) Although in many cases camparable results in terms of reaction rate and isoltated yield were obtained in water or under neat conditions, the presence of water became fundamental when fluoroketones (i.e., **2d**, **2e**) were employed.

With optimal reaction conditions in hand (*t*BuTMG, 2 mol %, H_2O, 16 h, rt), we assessed the scope of electrophilic agents by reacting a range of trifluoromethyl ketones (**2b**−**g**) with **1a** and the results are listed in Table 2.

Table 2. Scope of Fluoromethylaryl Ketones **2** in the *t*BuTMG-Catalyzed Alkylation of **1a**



entry	ketone	product	yield **3** (%)[a]
1	 **2b**	 **3ab**	98
2	 **2c**	 **3ac**	98
3	 **2d**	 **3ad**	98
4	 **2e**	 **3ae**	98
5	 **2f**	 **3af**	60
6	 **2g**	 **3ag**	98[b]
7	 **2h**	 **3ah**	66

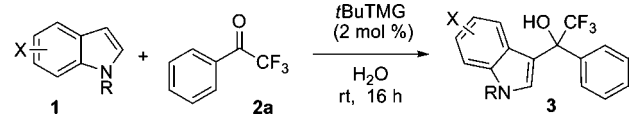
[a] Isolated yields after flash chromatography. [b] Reaction time 48 h, **1a**:**2g** = 5:1.

High tolerance toward aryl-substitution of the fluoroketone was highlighted by the excellent yields obtained with ketones **2b**−**e** (entries 1−4). Interestingly, while the introduction of a sterically demanding substituent (i.e., PivNH-, **2f**) close to the carbonyl group led a decreased isolated yield in the final product (yield = 60%, entry 5), trifluoromethyl ketone **2g** bearing electron-rich heteroaryl unit (i.e., thiophene) proved to be a competent candidate for the alkylation of **1a** (yield = 98%, entry 6).[17]

Finally, the role of the fluorine atoms in the reaction outcome was clarified by subjecting α,α-difluoro-1-phenyl ethanone (**2h**) to the *t*BuTMG-catalyzed condensation with **1a**. Satisfyingly, the desired difluoro-compound **3ah** was isolated in 66% yield (entry 7).

Great scope of indoles was finally documented by the runs collected in Table 3. Here a number of commercially available substituted indoles were reacted with **2a** under the best reaction conditions.

Table 3. Proving the Scope of Indoles in the *t*BuTMG-Catalyzed Alkylation Process with **2a**



entry	indole	product	yield **3** (%)[a]
1	**1b**, X: 5-F, R: H	**3ba**	98
2	**1c**, X: 5-Br, R: H	**3ca**	98
3	**1d**, X: 5-CN, R: H	**3da**	98
4	**1e**, X: 5-NO_2, R: H	**3ea**	98
5	**1f**, X: 6-F, R: H	**3fa**	98
6	**1g**, X: 6-Cl, R: H	**3ga**	94
7	**1h**, X: 5-OMe, R: H	**3ha**	98
8	**1i**, X: 5-OBn, R: H	**3ia**	66
9	**1j**, X: 2-Me, R: H	**3ja**	86
10	**1k**, X: 2-Me/7-Br, R: H	**3ka**	75
11	**1l**, X: 7-Me, R: H	**3la**	98
12	**1m**, X: H, R: Me	**3ma**	—[b]
13	**1n**, 7-azaindole	**3na**	96[c]

[a] Isolated yields after flash chromatography. [b] No reaction. [c] With 5 mol % of catalyst. Dioxane:H_2O 9:1 was used as the solvent.

The results listed in Table 3 entries 1−6 represent one of the strong points of the methodology. In fact, indolyl-rings bearing electron-withdrawing substituents (i.e., CN, NO_2) are generally recognized as unwilling substrates for FC-alkylation reactions.[18] On the contrary, the present *t*BuTMG-catalyzed methodology allowed electron-deficient indoles (**1b**−**g**) to be readily transformed into the corresponding fluorinated indol-3-yl-1-phenylethanols (**3ba**−**3ga**) in excellent yield.[19] Electron-dontating groups at *C*-2, *C*-5 and *C*-7 positions are also well tolerated (yield 66−98%), with the possibility to further extend the protocol to the FC-reluctant 7-azaindole **1n** (yield: 96%, entry 13).[20]

Finally, *N*-methylindole proved to be inert under optimal reaction conditions (entry 12), stressing the existence of a key *N*H-*base* interaction in the present FC-alkylation methodology.

(17) Limitation of the protocol comprises the use of enolizable aliphatic trifluoromethyl ketones that resulted unreactive under best reaction parameters.

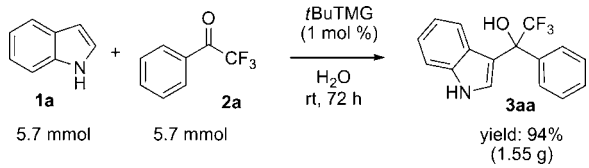
(18) For representative examples see: (a) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 5386–5389. (b) Moran, J.; Suen, T.; Beauchemin, A. M. *J. Org. Chem.* **2006**, *71*, 676–679. (c) Desimoni, G.; Faita, G.; Toscanini, M.; Boiocchi, M. *Chem.−Eur. J.* **2008**, *14*, 3630–3636.

(19) Also pyrroles were found suitable substrates for the present *t*BuTMG-catalyzed methodology. As an example the condensation of 2,4-dimethylpyrrole with **2a** (*t*BuTMG 5 mol%, 16 h, rt) led to the corresponding 1-(3,5-dimethyl-1*H*-pyrrol-2-yl)-2,2,2-trifluoro-1-phenylethanol in 75% yield.

(20) Popowycz, F.; Routier, S.; Joseph, B.; Mérour, J.-Y. *Tetrahedron* **2007**, *63*, 1031–1067.

The process was also carried out on a multigram scale. Here, the loading of the *t*BuTMG was lowered up to 1.0 mol %, obtaining **3aa** in 94% yield after 72 h reaction time.[21] The rigorous use of a 1:1 (**1a**:**2a**) mixture allowed the final product to be isolated by filtration without the need for organic solvents both in the reaction course and workup procedure (Scheme 2).

Scheme 2. *t*BuTMG-Catalyzed Multigram Scale FC-Alkylation of **1a** with **2a**



In conclusion, we have documented an unprecedented practical and efficient *t*BuTMG-catalyzed addition of indoles to fluoromethylaryl ketones in the presence of water. Wide scope and mildness of the reaction parameters emerged from the survey of substrates. Attempts to develop an enantioselective version of the present protocol and to extend the method to aldehydes and enolizable ketones are currently underway in our laboratories.

Acknowledgment. We acknowledge the MIUR (Rome), FIRB Project (Progettazione, preparazione e valutazione biologica e farmacologica di nuove molecole organiche quali potenziali farmaci innovativi), Consorzio C.I.N.M.P.I.S. (Bari), and University of Bologna.

Supporting Information Available: Experimental procedures, $^{1}H/^{13}C/^{19}F$-NMR spectra and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) General procedure for multigram scale FC-alkylation. A sample vial containing distilled water (4.0 mL) was charged with **1a** (5.7 mmol, 672 mg), ketone **2a** (1.0 g, 5.7 mmol) and 9.8 mg of *t*BuTMG (1.0 mol %). The reaction was vigorously stirred at the room temperature for 72 h. Pure product **3aa** was recovered by filtration, washed with water (5 mL), and dried under vacuum (1.55 g, yield: 94%).