ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2016, 52, 5328

Received 23rd February 2016,
Accepted 10th March 2016

DOI: 10.1039/c6cc01654e

www.rsc.org/chemcomm

Intermolecular dearomative C2-arylation of *N*-Ac indoles activated by $FeCl_3$†

Raj Kumar Nandi, Friederike Ratsch, Rodolphe Beaud, Régis Guillot, Cyrille Kouklovsky and Guillaume Vincent*

We report the $FeCl_3$-mediated direct addition of electron-rich arenes to the C2-position of electrophilic *N*-Ac indoles under mild conditions (room temperature, air). No functional group is required on the arene nucleophile: one of its C–H bonds is added to the C2=C3 double bond of the indole nucleus in a Friedel–Crafts-type reaction. This dearomatisation process delivered a broad range of C2-arylated indolines.

The functionalization of indole derivatives *via* dearomatisation reactions is a field of intense synthetic efforts due to the biological relevance of the heterocyclic scaffolds obtained.[1] In this context, we have recently described several methods for the dearomative C3-arylation of indoles[2] *via* $FeCl_3$-activation of 3-substituted *N*-Ac indoles[3] or oxidation of indoles with NIS[4] or from *N*-hydroxyindoles[5] using the electrophilicity of indoles.[6] Our next goal was to achieve the related C2-arylation of indoles due to the presence of the C2-arylindoline motif in several natural products such as phalarine, hinckdentine A or tabernaebovine (Fig. 1).[7]

The arylative dearomatisation of indoles also allows transformation of a flat heterocycle into a 3-D structure which is more poised to explore chemical space in the context of drug discovery.[8]

Indoles **1** are widely known to be highly nucleophilic at the C3-position leading, in the presence of electrophiles or acids, to indolium ions **2** which can be trapped by nucleophiles at the C2-position and delivered functionalized indolines **3**, usually in the intramolecular mode (Scheme 1).[9] Due to the propensity of indolium ions **2** to form dimeric compounds *via* attack of indole **1** at C2,[10] intermolecular addition of aryl nucleophiles to indoliums such as **2** is very rare.[11] Only a few nucleophiles such as allylboranes or hydrides could be added to **2** in the intermolecular mode.[12]

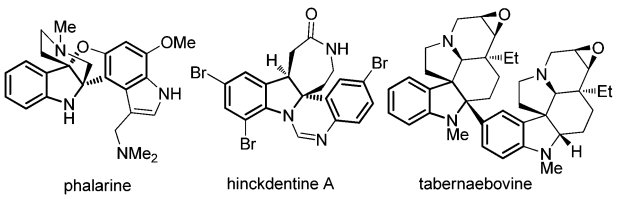
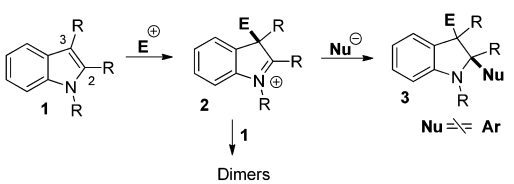


Fig. 1 C2-arylindoline-containing natural products.

Usually, the C2-arylative dearomatisation of indoles relies on intramolecular reactions with the aryl substituent attached to the nitrogen of the indole nucleus. In this case, the aryl group is introduced by transformation of an aryl–halogen bond *via* palladium-catalysed[13] or radical reactions.[14]

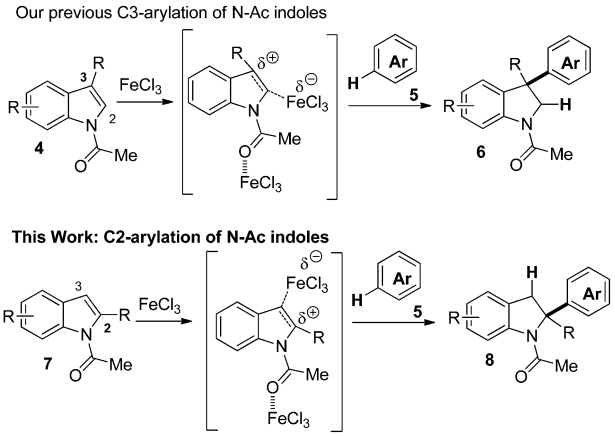
In the intermolecular mode, the C2-arylation of indoles could take place by the 1,4 addition of Grignard reagents to indoles containing a strong electron withdrawing group at C3.[15] An elegant palladium-catalyzed 3-oxy-2-arylation of 3-unsubstituted indoles with phenylboronic acids and TEMPO was described.[16] These methods rely on the use of a functional group on the aromatic nucleophile. Alternatively, during the total synthesis of dideepoxytabernaebovine, a rare and straightforward addition of electron rich arenes to an indolium intermediate such as **2** was deployed.[11a] A formal [4+2] cycloaddition with a *N*-phenyl iminium intermediate was also described.[17] We achieved the 3-oxy-2-arylation of indoles during the DDQ-mediated oxidative



Scheme 1 Innate reactivity of the indole nucleus.

Univ Paris Sud, CNRS, Université Paris-Saclay, Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO), Equipe Méthodologie, Synthèse et Molécules Thérapeutiques (MS&MT), Orsay, 91405, France. E-mail: guillaume.vincent@u-psud.fr

† Electronic supplementary information (ESI) available: Experimental procedures, characterisation and NMR spectra of new compounds and X-ray data. CCDC 1450298–1450300. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6cc01654e



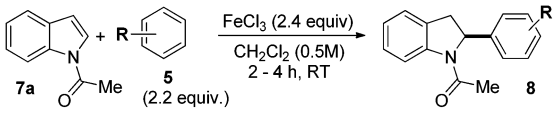
Scheme 2 Arylative dearomatisation of *N*-Ac indoles mediated by $FeCl_3$.

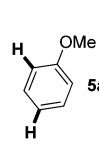
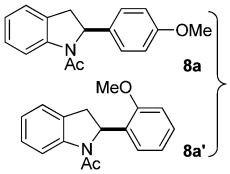
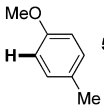
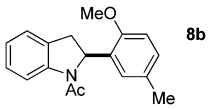
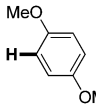
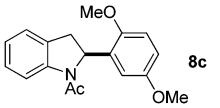
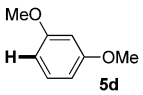
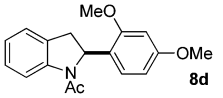
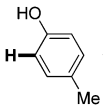
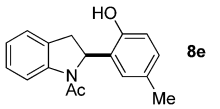
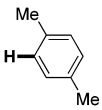
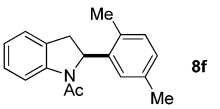
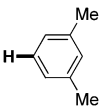
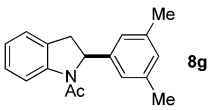
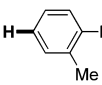
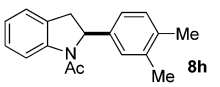
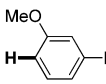
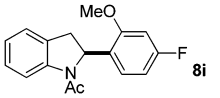
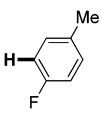
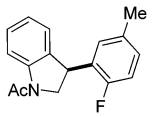
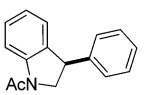
coupling between phenols and 3-substituted *N*-Ac-indoles activated by $FeCl_3$.[18]

Despite these achievements, we felt that a general method for the C2-arylation of indoles by the functionalization of the C–H bond of the aromatic nucleophile was lacking. To achieve the C2-regioselective addition of a C–H bond across the C2=C3 double bond of indoles, our experience in the activation of *N*-Ac-indoles by $FeCl_3$ was crucial to induce a Friedel–Crafts process.[3] We discovered that the $FeCl_3$-mediated hydroarylation of 3-unsubstituted *N*-Ac-indoles proceeds at the C2-position. We can postulate that the complexation of $FeCl_3$ by the oxygen of the acetyl leads to the sequestration of the nitrogen lone pair by conjugation, the C2=C3 bond could then be activated by an acid species and formally lead to a positive charge at C2 or C3.[3b] If a substituent is present at C3, the positive charge could be more stabilized at C3 by the formation of a tertiary benzylic carbocation.[3a,b] If the C3 position lacks substitution, the resulting secondary benzylic carbocation at C3 would be less stabilized than a positive charge at C2, due to the effect of the lone pair of the nitrogen. The latter would lead to the C2-regioselective hydroarylation of indoles which is the subject of this report (Scheme 2).

We started with *N*-Ac indole **7a** as the electrophilic indole and we investigated a broad range of aromatic nucleophiles **5** at room temperature in dichloromethane in the presence of 2.4 equivalents of $FeCl_3$ (Table 1). Anisole **5a** reacts selectively at the C2-position of **7a** in an 86% yield with a 1 : 1 mixture of addition products at the *para* and *ortho* positions of **5a** (entry 1). Arenes containing strong electron donating groups such as 4-methyl anisole **5b**, 1,4-dimethoxybenzene **5c**, 1,3-dimethoxybenzene **5d**, and 4-methylphenol **5e** delivered regioselectively and efficiently the C2-arylated *N*-Ac indoles **8b–e** in 86–46% yields (entries 2–5).[19] Xylenes **5f–h** were also good partners for the regioselective C2-hydroarylation leading to **8f–h** in 60–47% yields (entries 6–8). Fluorine-containing arene **5i** also delivered **8i** in 57% yield (entry 9). Finally, less electron rich arenes **5j,k** surprisingly delivered moderate yields of 3-arylated indolines **6j,k** (entries 10 and 11). It seems that the regioselectivity of the hydroarylation is also dependent on the arene nucleophile. The rationale for this observation is, presently, unclear to us.

Table 1 Scope of aromatic nucleophiles **5**



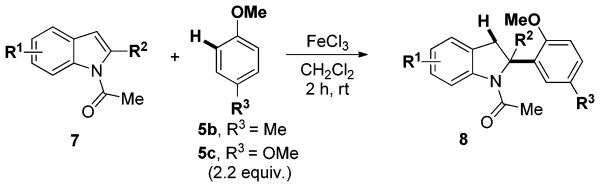
Entry	Arene **5**	Product	Yield[a] (%)
1	 **5a**	 **8a** / **8a'**	86 (1 : 1)
2	 **5b**	 **8b**	86
3	 **5c**	 **8c**	59
4	 **5d**	 **8d**	48
5	 **5e**	 **8e**	46
6	 **5f**	 **8f**	54
7	 **5g**	 **8g**	60
8	 **5h**	 **8h**	47
9	 **5i**	 **8i**	57
10	 **5j**	 **6j**	22
11	 **5k**	 **6k**	27

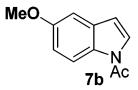
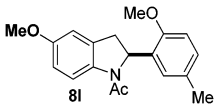
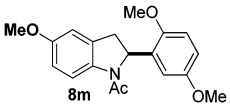
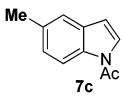
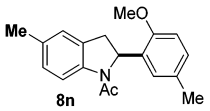
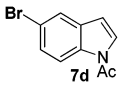
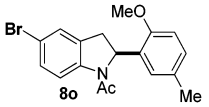
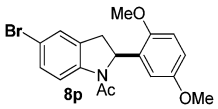
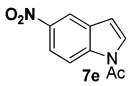
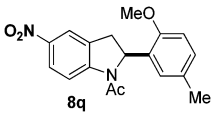
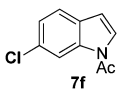
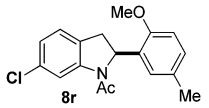
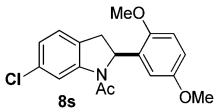
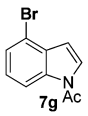
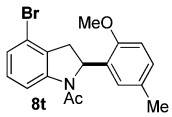
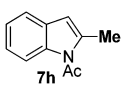
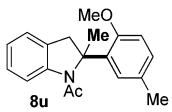
[a] Isolated yield.

We then turned our attention to the scope of *N*-Ac indoles **7** with 4-methylanisole **5b** and 1,4-dimethoxybenzene **5c** as nucleophiles (Table 2).

At the 5-position, indoles containing electron donating groups such as methoxy and methyl groups reacted efficiently with **5b** delivering **8l,n** in 67% and 74% yields (entries 1 and 3). The reaction between 5-methoxy-*N*-Ac indole **7b** and **5c** afforded moderate yield of **8m** (entry 2). The 5-bromo-*N*-Ac indole

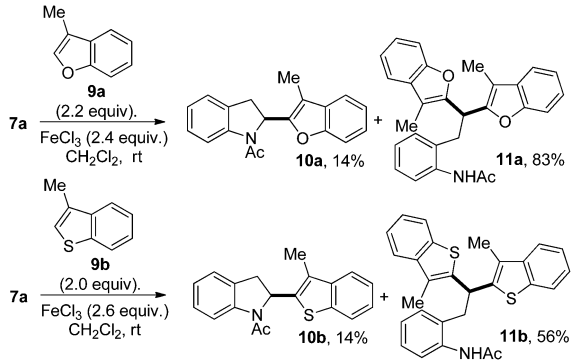
Table 2 Scope of electrophilic indoles **7**



Entry	Indole 7	R^3	Product 8	Yield[a] (%)
1		–Me		67
2	**7b**	–OMe		35
3		–Me		74
4		–Me		83
5	**7d**	–OMe		54
6		–Me		40
7		–Me		55
8	**7f**	–OMe		62
9		–Me		85
10		–Me		30[b]

[a] Isolated yield. [b] 28% of 3-acetyl-2-methyl-indoles was isolated.

reacted well with **5b,c** leading to **8o,p** in 83% and 54% yields (entries 4 and 5). Remarkably, a strong electron withdrawing group such as nitro at the 5-position afforded 40% yield of **8q** (entry 6). At the 6-postion the chloro derivative **7f** delivered **8r,s** in 55% and 62% yields with **5b,c** (entries 7 and 8). Substitution at the 4-position was also tolerated and 4-bromo-arylated indoline **8t** was obtained in 85% yield (entry 9). Finally, indoline **8u**, containing an arylated quaternary carbon, was obtained in 30% yield from 2-methyl-*N*-Ac indole **7h** (entry 10). In this case,



Scheme 3 Addition of heterocycles to *N*-Ac indoles.

the hydroarylation reaction is in competition with the migration of the acetyl from the *N*-position to the C3-position.

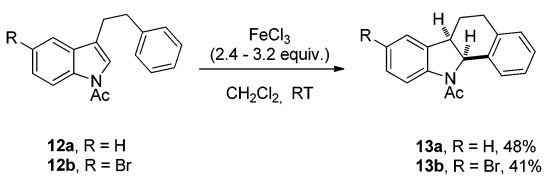
In order to obtain more diversified drug-like compounds, we studied the C2-addition of heterocycles such as benzofuran **9a** or benzothiophene **9b** to *N*-Ac indole **7a** (Scheme 3).

Surprisingly, along with the expected C2-hydroarylated compounds **10a,b** we also observed as the major products, compounds **11a,b**.[19]

Compounds **11a,b** most probably formed by the unexpected opening of the indole ring of **10a,b** with the cleavage of the C2–NAc bond assisted by the lone-pair of the oxygen or sulfur atom. The resulting benzylic cationic intermediate could then be attacked by the addition of a second heteroarene. Such transformations have been observed during the trimerisation of indoles under acidic conditions.[20]

On a final note, we achieved the intramolecular 6-*endo*-trig arylation of **12a,b** which contain an aryl group on the C3-side chain of the indole leading to tetracyclic compounds **13a,b** arylated at the C2-position (Scheme 4).[19] This is in contrast to the usual hydroarylation of 3-substituted *N*-Ac indoles which proceeds at the C3-position.[3]

The structures of compounds **8b**, **11a** and **13b** were confirmed by X-ray crystallography (Fig. 2).[19]



Scheme 4 Intramolecular C2-arylation.

Fig. 2 X-Ray structures of compounds **8b**, **11a**, and **13b**.

We have achieved the dearomative C2-arylation of *N*-Ac indoles by functionalization of the C–H bond of electron rich arenes at room temperature, in air with a cheap and non-toxic promoter. A broad scope of *N*-Ac indoles and arene nucleophiles is tolerated. Presumably, the key of this reaction is the generation of an electrophilic indole by activation of the *N*-Ac indole with $FeCl_3$ which triggers a Friedel–Crafts reaction.

The research leading to these results has received funding from the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme FP7/2007-2013/ under REA grant agreement no. 623422 (IIF-2013 postdoctoral fellowship to R. K. N.). We also gratefully acknowledge the ANR (JCJC program 2012, ANR-12-JS07-0002; "CouPhIn"), the Université Paris Sud and the CNRS for financial support. The X-ray diffractometer was purchased with funds from Région Ile de France (SESAME program 2012, No. 12018501), IUF, LabEx CHARM3AT, Univ. Paris Sud and CNRS.

Notes and references

1 S. P. Roche, J.-J. Youte Tendoung and B. Tréguier, *Tetrahedron*, 2015, **71**, 3549–3591.
2 For a review: N. Denizot, T. Tomakinian, R. Beaud, C. Kouklovsky and G. Vincent, *Tetrahedron Lett.*, 2015, **56**, 4413–4429.
3 (*a*) R. Beaud, R. Guillot, C. Kouklovsky and G. Vincent, *Angew. Chem., Int. Ed.*, 2012, **51**, 12546–12550; (*b*) R. Beaud, R. Guillot, C. Kouklovsky and G. Vincent, *Chem. – Eur. J.*, 2014, **20**, 7492–7500; (*c*) R. Beaud, T. Tomakinian, N. Denizot, A. Pouilhès, C. Kouklovsky and G. Vincent, *Synlett*, 2014, 432–440; (*d*) R. K. Nandi, R. Guillot, C. Kouklovsky and G. Vincent, submitted; for inspiring studies:; (*e*) K. Nishida, E. Yanase and S.-I. Nakatsuka, *ITE Lett. Batteries, New Technol. Med.*, 2006, **7**, 59–62.
4 (*a*) N. Denizot, A. Pouilhès, M. Cucca, R. Beaud, R. Guillot, C. Kouklovsky and G. Vincent, *Org. Lett.*, 2014, **16**, 5752–5755; (*b*) N. Denizot, R. Guillot, C. Kouklovsky and G. Vincent, *Chem. – Eur. J.*, 2015, **21**, 18953–18956.
5 T. Tomakinian, C. Kouklovsky and G. Vincent, *Synlett*, 2015, 1269–1275.
6 M. Bandini, *Org. Biomol. Chem.*, 2013, **11**, 5206–5212.
7 (*a*) P. A. Cockrum, S. M. Colegate, J. A. Edgar, K. Flower, D. Gardner and R. I. Willing, *Phytochemistry*, 1999, **51**, 153–157; (*b*) A. J. Blackman, T. W. Hambley, K. Picker, W. C. Taylor and N. Thirasasana, *Tetrahedron Lett.*, 1987, **28**, 5561–5562; (*c*) T. P. Lien, C. Kamperdick, T. Van Sung, G. Adam and H. Ripperger, *Phytochemistry*, 1998, **49**, 1797–1799.
8 F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756.
9 (*a*) C. C. J. Loh and D. Enders, *Angew. Chem., Int. Ed.*, 2012, **51**, 46–48; for selected examples: (*b*) S. A. Lakatosh, Y. N. Luzikov and M. N. Preobrazhenskaya, *Org. Biomol. Chem.*, 2003, **1**, 826–833; (*c*) S. A. Lakatosh, Y. N. Luzikov and M. N. Preobrazhenskaya, *Tetrahedron*, 2005, **61**, 8241–8248; (*d*) B. Han, Y.-C. Xiao, Y. Yao and Y.-C. Chen, *Angew. Chem., Int. Ed.*, 2010, **49**, 10189–10191; (*e*) J.-J. Wang, A.-X. Zhou, G.-W. Wang and S.-D. Yang, *Adv. Synth. Catal.*, 2014, **356**, 3356–3362.
10 (*a*) H. F. Hodson and G. F. Smith, *J. Chem. Soc.*, 1957, 3544–3545; (*b*) G. F. Smith and A. E. Walters, *J. Chem. Soc.*, 1961, 940–943.
11 (*a*) J. W. Medley and M. Movassaghi, *Angew. Chem., Int. Ed.*, 2012, **51**, 4572–4576; (*b*) C. Charlet-Fagnère, J. Laronze, J.-Y. Laronze, L. Toupet, R. Vistelle, D. Lamiable, C. Mouchard, P. Renard and G. Adam, *Bull. Soc. Chim. Fr.*, 1996, **1**, 39–50.
12 (*a*) Y. N. Bubnov, I. V. Zhun', E. V. Klimkina, A. V. Ignatenko and Z. A. Starikova, *Eur. J. Org. Chem.*, 2000, 3323–3327; (*b*) F. Nowrouzi and R. A. Batey, *Angew. Chem., Int. Ed.*, 2013, **52**, 892–895; (*c*) Y.-C. Xiao, C. Wang, Y. Yao, J. Sun and Y.-C. Chen, *Angew. Chem., Int. Ed.*, 2011, **50**, 10661–10664.
13 (*a*) L. Zhao, Z. Li, L. Chang, J. Xu, H. Yao and X. Wu, *Org. Lett.*, 2012, **14**, 2066–2069; (*b*) C. Shen, R.-R. Liu, R.-J. Fan, Y.-L. Li, T.-F. Xu, J.-R. Gao and Y.-X. Jia, *J. Am. Chem. Soc.*, 2015, **137**, 4936–4939; (*c*) D. A. Petrone, A. Yen, N. Zeidan and M. Lautens, *Org. Lett.*, 2015, **17**, 4838–4841; (*d*) D. A. Petrone, M. Kondo, N. Zeidan and M. Lautens, *Chem. – Eur. J.*, 2016, DOI: 10.1002/chem.201600118.
14 (*a*) S. Yasuda, T. Hirasawa, S. Yoshida and M. Hanaoka, *Chem. Pharm. Bull.*, 1989, **37**, 1682–1683; (*b*) W. Zhang and G. Pugh, *Tetrahedron*, 2003, **59**, 3009–3018; (*c*) A. S. Kyei, K. Tchabanenko, J. E. Baldwin and R. M. Adlington, *Tetrahedron Lett.*, 2004, **45**, 8931–8934; (*d*) S. R. Flanagan, D. C. Harrowven and M. Bradley, *Tetrahedron Lett.*, 2003, **44**, 1795–1798.
15 L. Wang, Y. Shao and Y. Liu, *Org. Lett.*, 2012, **14**, 3978–3981.
16 (*a*) S. Kirchberg, R. Fröhlich and A. Studer, *Angew. Chem., Int. Ed.*, 2009, **48**, 4235–4238; (*b*) V. Ramella, Z. He, C. G. Daniliuc and A. Studer, *Org. Lett.*, 2015, **17**, 664–667.
17 Z. Song, Y.-M. Zhao and H. Zhai, *Org. Lett.*, 2011, **13**, 6331–6333.
18 T. Tomakinian, R. Guillot, C. Kouklovsky and G. Vincent, *Angew. Chem., Int. Ed.*, 2014, **53**, 11881–11885.
19 CCDC 1450298 (**8b**), 1450300 (**11b**) and 1450299 (**13b**).
20 W. Noland and W. Kuryla, *J. Org. Chem.*, 1960, **25**, 486–487.