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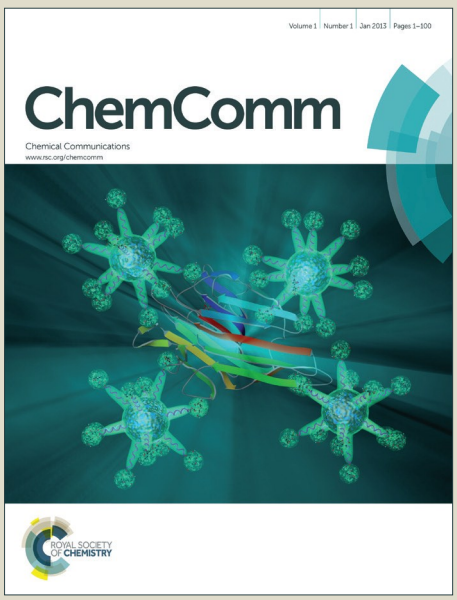

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Iron-catalyzed domino indole fluorination/allenic aza–Claisen rearrangement

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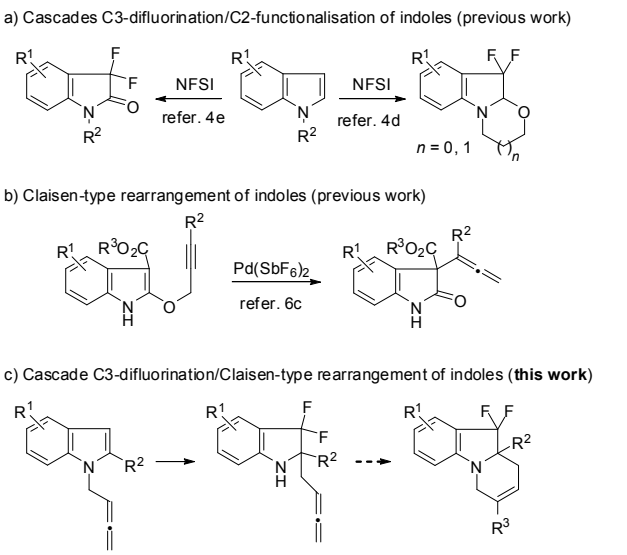
The synthesis of 2-allenyl-2-substituted-3,3-difluoroindolines has been accomplished taking advantage of the reaction between *N*-allenyl-indoles and Selectfluor under iron catalysis.

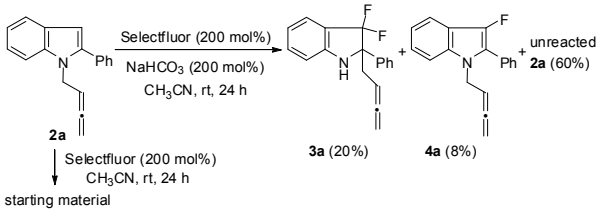
Fluoroorganic molecules feature peculiar biological activities because of their improved lipophilicity and metabolic stability.[1] The difluoromethyl moiety is particularly relevant due to its isopolar and isosteric nature with the $C(CH_3)_2$, C=O or hydroxyl groups.[2] On the other hand, the dearomatization of indoles has received considerable attention in organic synthesis because of the bioactivity of the resulting indolines.[3] Considerable efforts have been devoted to the fluorination of functionalised indoles [Scheme 1, Eq. (1a)],[4] because this methodology is a direct entry to diverse fluorinated indoline structures. However, to the best of our knowledge, there is lack of studies of the fluorofunctionalisation of the allenic indole moiety. This is rather surprising taking into account the rich chemistry of the allene moiety.[5]

As far as we know, the allene N1–C2 Claisen rearrangement of indoles has not been previously reported, being the C2–C3 Claisen rearrangement of indoles to form allenyl oxindoles the only related precedent [Scheme 1, Eq. (1b)].[6] We envisioned that allenic fluorinated indolines could be formed if a rearrangement step is associated to the fluorination sequence. This would be a highly valuable transformation because an additional allene moiety would be installed in the product serving as a platform for further functionalization. Considering the important properties of both polyfluorinated molecules as well as fused indolines, the β-amino 1,2-diene moiety of 2-allenyl-2-substituted-3,3-difluoroindolines may be a useful handle for cyclization reactions, and consequently for the achievement of difluorinated *N*-fused indolines. Herein we report an iron-catalyzed tandem process, namely, fluorination/allenic aza–Claisen rearrangement[6] which forms 2-allenyl-2-substituted-3,3-difluoroindolines [Scheme 1, Eq. (1c)].



Scheme 1 Indole as platform for difluorination and allenic Claisen-type rearrangement: Previous and current proposals.

Our initial efforts focused on the application of electrophilic fluorination to the selective construction of difluoroindolines having a quaternary center. Allenic indole **2a** was chosen as a model substrate for the fluorofunctionalisation reaction. Attempts to profitably generate a difluoroindoline structure from **2a** by using Selectfluor without additives failed.[7] A more promising result was encountered through the addition of sodium bicarbonate, although the more of the starting material kept unreacted. Besides, 3,3-difluoroindoline **3a** was isolated along with a minor component, the unstable 3-fluoroindole **4a** (Scheme 2).



Scheme 2 Reaction of 1-allenyl-2-phenyl-indole **2a** with Selectfluor.

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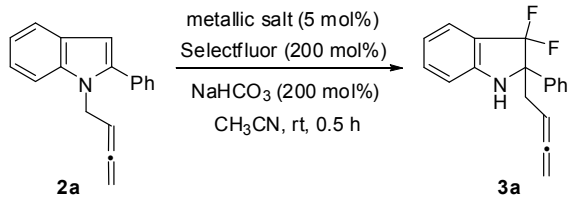
To mitigate the poor reactivity of allenylindole **2a** as well as the formation of intermediate **4a**, we intended the activation of the allene moiety through Lewis acid catalysis (Table 1). Initially, in order to get a better result in the formation of product **3a**, we attempted a gold-catalyzed reaction.[8] Fortunately, the addition of $[(Ph_3P)AuNTf_2]$ (5 mol%) allow us to efficiently transform in just one hour substrate **2a** into 2-allenyl-2-phenyl-3,3-difluoroindoline **3a** in a totally selective fashion (Table 1, entry 1). It was interesting at this point to test the catalytic abilities of different metallic salts. The difluorination/rearrangement sequence could also be catalyzed by $PtCl_2$, $InCl_3$, and $HfCl_4$ but with slightly diminished effectiveness. Interestingly, the use of $Fe(OTf)_3$ gave similar results to the Gagosz' catalyst (Table 1, entry 5). Taking into account the inexpensiveness and eco-friendliness of iron(III) salts, we decided to develop further the $Fe(OTf)_3$-catalyzed fluoro-rearrangement. When Selectfluor (200 mol%) was used as the fluorination reagent, the spots on the tin-layer chromatographic (TLC) plate of the reaction mixture look very clean. However, alternative fluorine sources such as *N*-fluorobenzenesulfonimide afforded poorer results. Among all the solvents examined, acetonitrile proved to be the best choice, affording product **3a** in a good 81% yield (Scheme 3). The metal-catalysed reaction between indole **2a** and Selectfluor in absence of $NaHCO_3$ did not go to completion, thus highlighting the importance of the base for the success of the difluoroindoline formation.

Table 1. Selective fluorination/rearrangement sequence of allenyl indole **2a** under modified metal-catalyzed conditions.



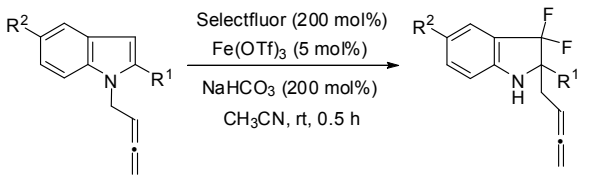
2a **3a**

Entry	metallic salt	Yield[a]
1	$[(Ph_3P)AuNTf_2]$	83%
2	$PtCl_2$	71%
3	$InCl_3$	63%
4	$HfCl_4$	64%
5	$Fe(OTf)_3$	81%

[a]Yield of pure, isolated product with correct analytical and spectral data.

To explore the effects of various substrates on fluorofunctionalisation reactions, a number of new indole-tethered allenes were synthesized. As shown in Scheme S1 (see ESI†), starting materials, allenes **2a–m** were made from the corresponding terminal alkynes **1a–m** by treatment with paraformaldehyde in the presence of diisopropylamine and copper(I) bromide (Crabbé reaction).[9]

With an optimized fluorofunctionalisation system in hand, we investigated the behaviour of 1-(buta-2,3-dienyl)-2-aryl-1*H*-indoles **2b–i**. As shown in Scheme 3, all 1-allenyl-2-aryl-substituted substrates exhibited excellent reactivity in the domino indole fluorination/allenic aza–Claisen rearrangement. The steric properties of the substituents in the indole moiety did not affect significantly the reactivity, with *tert*-butylphenyl and naphthalen-2-yl functionalized indoles **2e**,**f** performing well in the difluoroindolines **3e**,**f** formation. Besides, no matter whether electron-withdrawing (such as $4\text{-}ClC_6H_4$ and $4\text{-}FC_6H_4$) or electron-donating groups (such as $4\text{-}MeC_6H_4$) are introduced to the 2-aryl substituent as far as conversions are concerned. The presence of substituents at the benzene fused ring provided the same reactivity pattern independently of the electronic nature, such as in substrates **2g,h**, bearing EDG, or in substrates **2i–k**, bearing EWG. Taking into account all the examples of Scheme 3, the reaction proved to be functional group tolerant. Complete conversion was observed by TLC and ^1H NMR analysis of the crude reaction mixtures of indole-tethered allenes **2**, and no side-products were detected. Unfortunately, some decomposition was observed on sensitive fluoroindolines **3** during purification by flash chromatography, which may be responsible for the moderate isolated yields. Nicely, using deactivated silica gel during chromatographic purification resulted in a detectable (5–10%) improvement in the isolated yields of products **3** and **5**. Even more interestingly, nitro- and cyano-derivatives **3j** and **3k** did not require further purification and were obtained in excellent yields.



2a R^1 = Ph, R^2 = H	**3a** (83%)
2b R^1 = 4-ClC_6H_4, R^2 = H	**3b** (66%)
2c R^1 = 4-FC_6H_4, R^2 = H	**3c** (40%)
2d R^1 = 4-MeC_6H_4, R^2 = H	**3d** (48%)
2e R^1 = 4-*t*BuC_6H_4, R^2 = H	**3e** (43%)
2f R^1 = naphthalen-2-yl, R^2 = H	**3f** (55%)
2g R^1 = 4-MeC_6H_4, R^2 = Me	**3g** (52%)
2h R^1 = 4-MeC_6H_4, R^2 = OMe	**3h** (42%)
2i R^1 = 4-MeC_6H_4, R^2 = F	**3i** (44%)
2j R^1 = Ph, R^2 = NO_2	**3j** (92%)[a]
2k R^1 = Ph, R^2 = CN	**3k** (97%)[a]

Scheme 3 Synthesis of 2-aryl-2-(buta-2,3-dienyl)-3,3-difluoroindolines **3a–i**. [a]Chromatographic purification was not necessary.

Despite its usefulness, the catalytic C–F bond formation at sp^3 carbon centres using electrophilic reagents remains a synthetic challenge, because incorporation of fluorine into sp^3–hybridized carbons is achieved through nucleophilic fluorination reactions.[10] Originally, we were attempting the iron-catalysed difluorofunctionalisation/rearrangement sequence of *N*-allenylindole **2l** under Fe(III) catalysis (5 mol%) in the presence of Selectfluor (200 mol%). The expected product **3l** was the minor component, but, surprisingly, a 20% yield of the trifluoroindoline **5l** was obtained. Consequently, our studies focused on developing a more efficient transformation. The reaction product **5l** could only be obtained in reasonable yield using a higher fluorination reagent loading. Worthy of note, after considerable experimentation we were able to find suitable conditions for the controllable formation of both type of adducts **3** and **5** (Scheme 4). 1-Allenyl-2-methyl-indoles **2** on exposure to the system $Fe(OTf)_3$ (5 mol%), $NaHCO_3$

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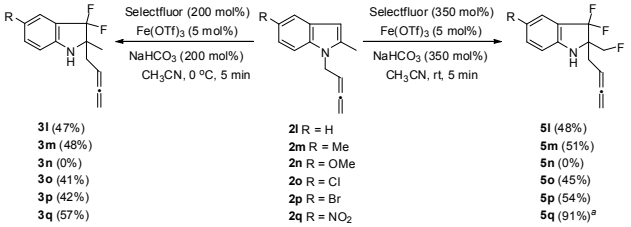
(200 mol%), and Selectfluor (200 mol%) in acetonitrile at 0 °C, exclusively afforded 2-methyl-3,3-difluoroindolines **3** in just 5 minutes. By contrast, the reaction of substrates **2** with $Fe(OTf)_3$ (5 mol%), $NaHCO_3$ (350 mol%), and Selectfluor (350 mol%) in acetonitrile at room temperature, did allow the sole formation of 2-fluoromethyl-3,3-difluoroindolines **5**. Unfortunately, compound **2n**, with a methoxy substituent at the C5 indole moiety, only led to several unidentified products upon treatment with Selectfluor. Nitro adduct **5q** did not require further purification and was obtained in nearly quantitative yield.

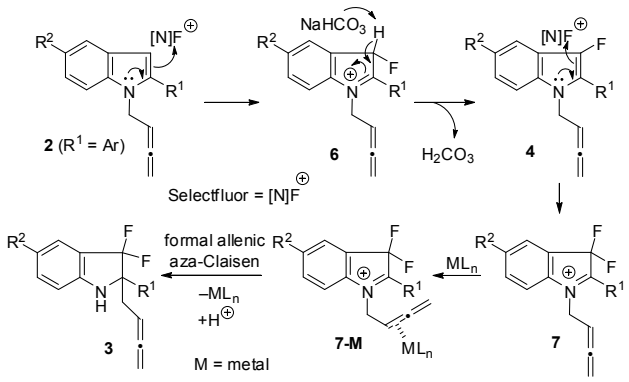


Scheme 4 Synthesis of 2-(buta-2,3-dienyl)-3,3-difluoro-2-methyl indolines **3** and 2-(buta-2,3-dienyl)-2-fluoromethyl-3,3-difluoroindolines **5**. [a]Chromatographic purification was not necessary.

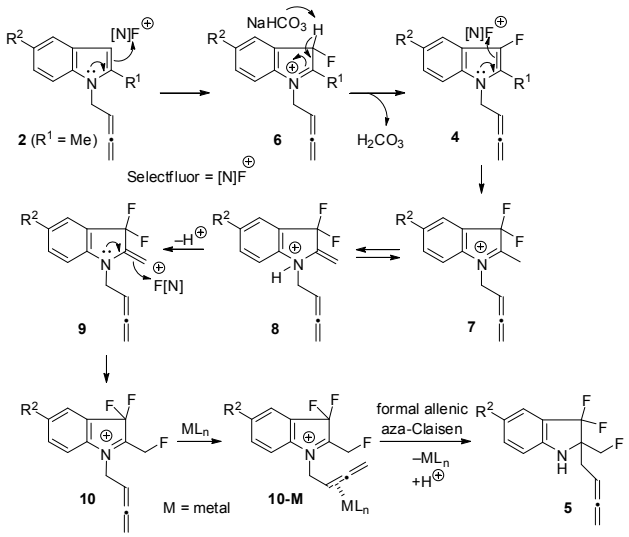
We monitored the reaction of *N*-allenylindole **2b** by both ^1H NMR and ^{19}F NMR spectroscopy in order to track the reaction intermediates (Figures S1 and S2, see ESI†). Because of the paramagnetic character of $Fe(OTf)_3$ we did select $[(Ph_3P)AuNTf_2]$ as catalyst. Unfortunately, results were inconclusive. Although merely speculative at this time, the iron-catalysed generation of 2-(allenyl)-2-aryl-3,3-difluoroindolines **3** should proceed as outlined in Scheme 5. Accordingly, we initially propose a Selectfluor-assisted indole monofluorination to form 2-substituted-3-fluoroindoles **4** as represented by intermediate **6**. Taking into account that the reaction does not work without $NaHCO_3$, it may be safe to propose that $NaHCO_3$ should act as a base to facilitate the deprotonation of iminium species **8** to give the aromatic 3-fluoroindoles **4**.[11,12] After delivering the first fluorine atom, again Selectfluor attacks the indole C2–C3 double bond to form difluorospecies **7**. This attack occurs because of the stability of the resulting intermediate iminium cation **7**. Next, the metallic catalyst and **7** forms metal-coordinate allene **7-M**, further inducing a formal allenic aza–Claisen rearrangement, which liberates 2-substituted-2-(buta-2,3-dienyl)-3,3-difluoroindolines **3** with concomitant regeneration of the catalytic species.

To investigate the reversibility of the fluorination/rearrangement process, 2-(allenyl)-2-phenyl-3,3-difluoroindoline **3a** was treated under metal-catalyzed conditions. Interestingly, it was found that 1-(buta-2,3-dienyl)-3-fluoro-2-phenyl-1*H*-indole **4a** was produced, which may point to a formal retro-allenic aza-Claisen rearrangement process, with the concomitant formation of 3-fluoro-2-phenyl-1*H*-indole, in which a N–C bond cleavage has occurred (Scheme S2, see ESI†). This outcome demonstrated that the fluorination/rearrangement sequence had a certain degree of reversibility under the promotion of $[(Ph_3P)AuNTf_2]$ or $Fe(OTf)_3$.

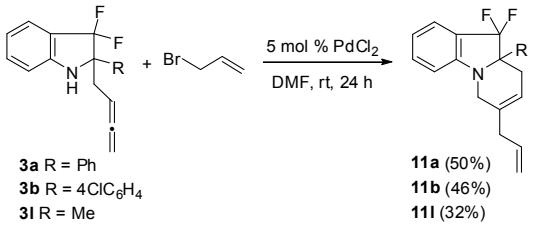
A related pathway for the iron-catalysed generation of 2-(allenyl)-2-fluoromethyl-3,3-difluoroindolines **5** is outlined in Scheme 6. A similar scenario to the first and second fluorination can be postulated for the third fluorination, through the attack of Selectfluor to the enamine double bond of **9** to form iminium species **10**. Thus, whereas the 1-(allenyl)-2-aryl-1*H*-indoles exclusively lead to 2-aryl-3,3-difluoroindoline adducts **3**, the 2-methyl counterparts produce 2-fluoromethyl-3,3-difluoroindoline products **5**.



Scheme 5 Tentative mechanistic explanation for the Selectfluor-promoted metal-catalyzed synthesis of 2-(allenyl)-2-aryl-3,3-difluoroindolines **3**.



Scheme 6 Tentative mechanistic explanation for the Selectfluor-promoted metal-catalyzed synthesis of 2-(allenyl)-2-fluoromethyl-3,3-difluoroindolines **5**.



Scheme 7 Synthesis of 10,10-difluoro-tetrahydropyrido[1,2-*a*]indoles **11** and **12**.

N-Fused indolines are widely spread natural products which exhibit relevant biological properties.[13,14] Owing to the efficacy and functional group tolerance of transition metal catalyzed coupling reactions in forming C–heteroatom bonds starting from allenes, we envisioned that our 2-allenyl-3,3-difluoroindolines may be synthetically interesting building

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blocks for the preparation of *N*-fused indoline derivatives. The carbocyclization–functionalisation of the aminoallene subunit was realized when allyl bromide was added in the palladium-catalyzed transformation of 2-allenyl-1*H*-indoles **3** to generate *N*-fused indolines **11** (Scheme 7).

In conclusion, an efficient iron-catalyzed Selectfluor-assisted synthetic route to 2-allenyl-2-substituted-3,3-difluoroindolines from easily accessible *N*-allenyl-indole substrates under mild conditions has been reported. The Fe(III)/Selectfluor system enables the highly selective difluorofunctionalisation/aza–Claisen rearrangement sequence of various 1-allenyl-2-aryl-indoles at ambient temperature. Besides, trifluoroderivatives can be achieved starting from 1-allenyl-2-methyl substrates. Future work could be directed towards the development of an asymmetric version.

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Notes and references

1 *(a) Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications*, V. Gouverneur and K. Müller, Imperial College Press, London, 2012; *(b) Fluorine in Medicinal Chemistry and Chemical Biology*, I. Ojima, Wiley-Blackwell, Chichester, U.K., 2009; *(c) Bioorganic and Medicinal Chemistry of Fluorine*, J.-P. Bégué and D. Bonnet-Delpon, John Wiley & Sons, Hoboken, 2008; *(d)* D O'Hagan, *Chem. Soc. Rev.,* 2008, **37**, 308; *(e)* S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.,* 2008, **37**, 320.

2 For a review, see: N. A. Meanwell, *J. Med. Chem.,* 2011, **54**, 2529.

3 For reviews on dearomatization of indoles and heteroaromatic compounds, see: *(a)* N. Denizot, T. Tomakinian, R. Beaud, C. Kouklovsky and G. Vincent, *Tetrahedron Lett.,* **2015**, *56*, 4413; *(b)* S. P. Roche, J.-J. Y. Tendoung, and B. Tréguier, *Tetrahedron,* **2015**, *71*, 3549; *(c)* Q. Ding, X. Zhou, and R. Fan, *Org. Biomol. Chem.,* **2014**, *12*, 4807. For bioactive indolines, see: *(d)* T. Hata, Y. Sano, R. Sugawara, A. Matsumae, K. Kanamori, T. Shima and T. Hoshi, *J. Antibiot. Ser. A*, 1956, **9**, 141; (*e*) M. Bös, F. Jenck, J. R. Martin, J. L. Moreau, V. Mutel, A. J. Sleight and U. Widmer, *Eur. J. Med. Chem.*, 1997, **32**, 253; (*f*) M. Goldbrunner, G. Loidl, T. Polossek, A. Mannschreck and E. V. Angerer, *J. Med. Chem.*, 1997, **40**, 3524; *(g)* H. Zhao, X. He, A. Thurkauf, D. Hoffman, A. Kieltyka, R. Brodbeck, R. Primus and J. W. F. Wasley, *Bioorg. Med. Chem. Lett.,* 2002, **12**, 3111; *(h)* B. D. Ames, X. Liu and C. T. Walsh, *Biochemistry*, 2010, **49**, 8564; *(i)* D. Zhang, H. Song and Y. Qin, *Acc. Chem. Res.*, 2011, **44**, 447; *(j)* S. Cai, L. Du, A. L. Gerea, J. B. King, J. You and R. H. Cichewicz, *Org. Lett.*, 2013, **15**, 4186.

4 (*a*) J. Z. M. Fong, S. S. S. Choo, J.-A. Richard, M. V. Garland, L. Guo, C. W. Johannes and T. M. Nguyen, *Eur. J. Org. Chem.*, 2015, 995; (*b*) T. Wang, D. L. Hoon and Y. Lu, *Chem. Commun.,* 2015, **51**, 10186; (*c*) B. Tréguier and S. P. Roche, *Org. Lett.,* 2014, **16**, 278; (*d*) T. M. Nguyen, H. A. Duong, J.-A. Richard, C. W. Johannes, F. Pincheng, D. K. J. Ye and E. L. Shuying, *Chem. Commun.,* 2013, **49**, 10602; (*e*) Y. H. Lim, Q. Ong, H. A. Duong, T. M. Nguyen and C. W. Johannes, *Org. Lett.*, 2012, **14**, 5676; (*f*) O. Lozano, G. Blessley, T. Martínez del Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman, V. Gouverneur, *Angew. Chem. Int. Ed.*, 2011, **50**, 8105; (*g*) R. Lin, S. Ding, Z. Shi and N. Jiao, *Org. Lett.*, 2011, **13**, 4498; (*h*) N. Shibata, T. Tarui, Y. Doi and K. L. Kirk, *Angew. Chem. Int. Ed.*, 2001, **40**, 4461; (*i*) Y. Takeuchi, T. Tarui, N. Shibata, *Org. Lett.*, 2000, **2**, 639.

5 For a themed issue in allene chemistry, see: *(a) Chem. Soc. Rev.*, 2014, **43**, 2879-3206, issue 9, eds. B. Alcaide and P. Almendros. For selected reviews, see: *(b)* T. Lechel, F. Pfrengle, H.-U. Reissig and R. Zimmer, *ChemCatChem*, 2013, **5**, 2100; *(c)* S. Yu and S. Ma, *Angew. Chem. Int. Ed.,* 2012, **51**, 3074; *(d)* N. Krause and C. Winter, *Chem. Rev.,* 2011, **111**, 1994; *(e)* C. Aubert, L. Fensterbank, P. Garcia, M. Malacria and A. Simonneau, *Chem. Rev.,* 2011, **111**, 1954; *(f)* A. S. K. Hashmi, *Angew. Chem. Int. Ed.,* 2000, **39**, 3590.

6 For a review on the aza–Claisen rearrangement, see: *(a)* K. C. Majumdar, T. Bhattacharyya, B. Chattopadhyay and B. Sinha, *Synthesis,* 2009, 2117. For the C2–C3 Claisen rearrangement of indoles to form allenyl oxindoles, see: *(b)* T. Cao, E. C. Linton, J. Deitch, S. Berritt and M. C. Kozlowski, *J. Org. Chem.,* 2012, **77**, 11034; *(c)* T. Cao, J. Deitch, E. C. Linton and M. C. Kozlowski, *Angew. Chem. Int. Ed.,* 2012, **51**, 2448.

7 For a fluoro-heterocyclisation reaction promoted by Selectfluor in the absence of any metal catalyst or base, see: D. Parmar and M. Rueping, *Chem. Commun.,* 2014, **50**, 13928.

8 Gold complexes have been used extensively for the synthetic community due to their powerful soft Lewis acidic nature. For selected reviews on gold catalysis, see: *(a)* A. S. K. Hashmi, *Accounts Chem. Res.,* 2014, **47**, 864; (*b*) C. Obradors and A. M. Echavarren, *Accounts Chem. Res.,* 2014, **47**, 902; (*c*) B. Alcaide and P. Almendros, *Accounts Chem. Res.,* 2014, **47**, 939; (*d*) L. Fensterbank and M. Malacria, *Accounts Chem. Res.,* 2014, **47**, 953; (*e*) M. Rudolph and A. S. K. Hashmi, *Chem. Soc. Rev.,* 2012, **41**, 2448; (*f*) A. Corma, A. Leyva-Pérez and M. J. Sabater, *Chem. Rev.,* 2011, **111**, 1657; (*g*) N. Krause and C. Winter, *Chem. Rev.,* 2011, **111**, 1994; (*h*) A. S. K. Hashmi, *Angew. Chem. Int. Ed.,* 2010, **49**, 5232. For the gold(I)-catalyzed propargyl Claisen rearrangement, see: (*i*) B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.,* 2004, **126**, 15978. (j) For the gold(I)-catalyzed tandem alkoxylation/Claisen rearrangement, see: H. Wu, W. Zi, G. Li, H. Lu and F. D. Toste, *Angew. Chem. Int. Ed.,* 2015, **54**, 8529.

9 *(a)* J. Kuang and S. Ma, *J. Org. Chem.,* 2009, **74**, 1763; *(b)* P. Crabbé, H. Fillion, D. André and J. L. Luche, *J. Chem. Soc., Chem. Commun.,* 1979, 860.

10 For a recent review, see: J. Wu, *Tetrahedron Lett.,* 2014, **55**, 4289.

11 Although the isolation of 1-(buta-2,3-dienyl)-3-fluoro-2-phenyl-1*H*-indole **4a** from the uncatalyzed reaction of **2a** outlined in Scheme 2 was fortuitous, some information has been gathered in favor of the pathway shown in Scheme 6.

12 In order to see if compound **4a** is able to rearrange to **3a** under metal catalysis, reaction of **4a** with a catalytic amount of either $Fe(OTf)_3$ or $[(Ph_3P)AuNTf_2]$ was conducted in the presence of Selectfluor and $NaHCO_3$. The reaction did proceed well to give 3,3-difluoroindoline **3a**. Therefore, we have enough evidence to propose that 3-fluoroindole **4a** is indeed an intermediate.

13 *(a)* T. Hata, Y. Sano, R. Sugawara, A. Matsumae, K. Kanamori, T. Shima and T. Hoshi, *J. Antibiot. Ser. A*, 1956, **9**, 141; (*b*) M. Bös, F. Jenck, J. R. Martin, J. L. Moreau, V. Mutel, A. J. Sleight and U. Widmer, *Eur. J. Med. Chem.*, 1997, **32**, 253; (*c*) M. Goldbrunner, G. Loidl, T. Polossek, A. Mannschreck and E. V. Angerer, *J. Med. Chem.*, 1997, **40**, 3524; *(d)* B. D. Ames, X. Liu and C. T. Walsh, *Biochemistry*, 2010, **49**, 8564; *(e)* D. Zhang, H. Song and Y. Qin, *Acc. Chem. Res.*, 2011, **44**, 447; *(f)* S. Cai, L. Du, A. L. Gerea, J. B. King, J. You and R. H. Cichewicz, *Org. Lett.*, 2013, **15**, 4186.

14 The angular tricyclic hydropyrido[1,2-*a*]-indole core is a precursor of alkaloids and related bioactive products: *(a)* M. V. Riofski, J. P. John, M. M. Zheng, J. Kirshner and D. A. Colby, *J. Org. Chem.,* **2011**, *76*, 3676; (*b*) D. B. England and A. Padwa, *J. Org. Chem.,* **2008**, *73* , 2792; (*c*) D. L. Taylor, P. S. Ahmed, P. Chambers, A. S. Tyms, J. Bedard, J. Duchaine, G. Falardeau, J. F. Lavallée, W. Brown, R. F. Rando and T. Bowlin, *Antiviral Chem. Chemother.,* **1999**, *10*, 79; *(d)* T. Iino, M. Katsura and K. Kuriyama, *J. Pharmacol. Exp. Ther.,* **1996**, *278*, 614; *(e)* M. Kato, S. Nishino, K. Ito and H. Takasugi, *Chem. Pharm. Bull.,* **1995**, *43*, 1346.