Green Chemistry

Accepted Manuscript

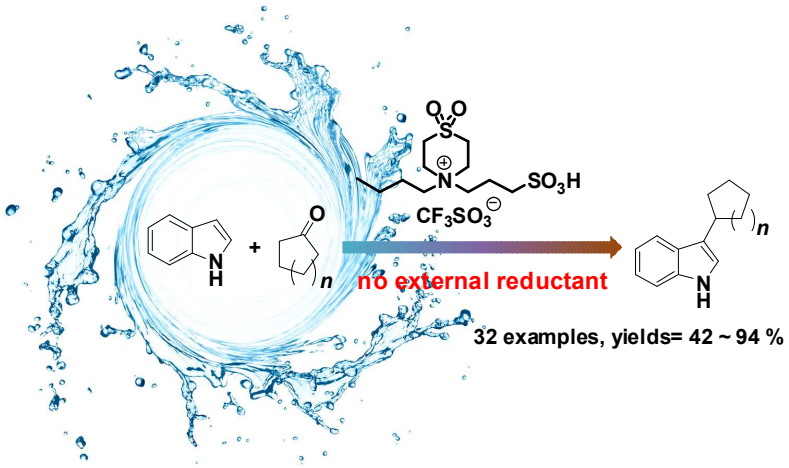
ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/greenchem

Graphic Abstract

Brønsted acid ionic liquid-catalyzed reductive Friedel-Crafts alkylation of indoles and cyclic ketones without using external reductant

Amir Taheri, Bingbing Lai, Cheng Cheng, and Yanlong Gu*



C3-Cycloalkylated indole was synthesized from indole and cyclic ketone in the absence of reductant with the aid of acid catalyst.

Journal Name

RSCPublishing

COMMUNICATION

Brønsted acid ionic liquid-catalyzed reductive Friedel-Crafts alkylation of indoles and cyclic ketones without using external reductant

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

Amir Taheri,[a] Bingbing Lai,[a] Cheng Cheng,[a] and Yanlong Gu[a,b*]

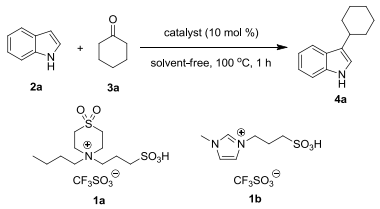
In the absence of external reductant, C3-cycloalkylated indole could be synthesized through reductive alkylation of indole with cyclic ketone by using a sulfonyl-functionalized Brønsted acid ionic liquid as catalyst. Water generated in the initial stage of the reaction played a key role in rendering the reductive coupling possible. The reaction proceeds most likely in a radical way.

Because of the great structural diversity of biologically active indoles, the indole ring system has become an important structural component in many pharmaceutical agents.[1,2] Among various indole derivatives, C3-cycloalkylindoles have garnered significant attention in the literature because of their presence in various natural products and pharmaceutically relevant compounds.[3] Previously, synthesis of C3-cycloalkylindoles relies heavily on a two-step method involving (i) acid- or base-catalyzed condensation of indoles with cyclic ketones, and (ii) a reduction of the generated product.[4] To simplify the operational procedure, one-pot reductive alkylations of indoles with cyclic ketones have also been studied by using either H_2 or Et_3SiH as reducing reagent.[5] Recently, direct alkylation methods for the synthesis of C3-cycloalkylindoles have been reported by using cycloalkyl alcohol as alkylating reagent. For example, a metal catalyst-mediated alkylation of indole has been established, which involves a well-known "hydrogen-borrowing" mechanism.[6] Quite recently, Wu reported an elegant Brønsted acid-mediated alkylation method by using catalytic amount of ketone as surrogate. It is the key in Wu's system that the alcoholic substrate can be oxidized to the corresponding ketone in the presence of acid, which was then trapped by indole to form an indolyl cation intermediate.[7] A metal catalyst-mediated atom-economic reaction, hydroarylation of cyclic alkene with indole, has also been utilized in the synthesis of C3-cycloalkylindoles.[8] Although these reported methods have improved the synthetic efficiency over the classical routes, they are not environmentally safe because of the use of expensive metal-based catalysts, hazardous reagents, volatile organic solvents and also there is often no recovery of the catalysts.

We have recently developed a sulfonyl-containing Brønsted acid ionic liquid that has displayed outstanding performance in various organic reactions.[9] In particular, alkenylations of indoles with simple ketones proceeded very well with the aid of this acidic ionic liquid catalyst, which offered an eco-efficient route to access 3-vinylindoles.[10] Interestingly, when cyclohexanone was used as substrate in this alkenylation reaction, an unexpected product, 3-cyclohexylindole, was detected. This gives us impetus to investigate the possibility of establishing an acid-catalyzed reductive Friedel-Crafts alkylation of indole with ketones. Herein, we disclose successful outcome of this endeavor in which C3-cycloalkylindoles were synthesized through a Brønsted acid-catalyzed reductive alkylation of indole with cyclic ketone *without adding any external reductant*. This reaction not only offered an efficient route to access C3-cycloalkylated indoles but also involved a hitherto unreported reaction mechanism that may be invaluable for organic synthesis.

Initially, a reaction of indole **2a** and cyclohexanone **3a** was investigated. The reaction was performed under solvent-free conditions at 100 ^oC, and the ratio of **3a**/**2a** is 1.2/1.0. In the presence of 10 mol % of a sulfonyl-containing Brønsted acid ionic liquid **1a**, a reductive alkylation product **4a** was obtained in 92 % of yield (**Table 1**, entry 1). The structure of **4a** was confirmed by ^1H NMR, ^{13}C NMR, GC-MS and IR.[11] We have also compared the spectra with that of an authentic sample.[12] With all these measurements, we are very confident to confirm the structure of **4a**. When ionic liquid **1a** was replaced by a Forbes's ionic liquid **1b**, the yield of **4a** decreased to 72 % (entry 2). To understand the nature of this reductive Friedel-Crafts alkylation, some common strong Brønsted acids, such as toluenesulfonic acid and triflic acid, were also used. The reaction proceeded as well, but only moderate yields were obtained under the identical conditions (entries 3 and 4). A Lewis acid, $Fe(OTf)_3$, showed also similar catalytic ability in this reaction as triflic acid (entry 5). Trifluoroacetic acid and $Zn(OTf)_2$, which are relatively mild compared with triflic acid or $Fe(OTf)_3$, were found to be ineffective for the model reaction (entries 6 and 7). Only starting materials were recovered in the absence of catalyst (entry 8). Further investigation revealed that the reaction was also affected by the ratio of **3a**/**2a** and catalyst amount, and the optimal conditions were **3a**/**2a** = 1.2/1.0 and 10 mol % of **1a** catalyst. Recyclability of **1a** was also studied in the model reaction. After removing the organic compounds by extraction with ethyl acetate, **1a** could be readily recovered. ^1H and ^{13} NMR study showed that its structure remained unchanged after the reaction.[11] Reuse experiments manifested that **1a** can be reused at least 6 times without significant loss of its activity (**Table 1**, entry 1).

Table 1. Reductive alkylation of **2a** with **3a**.[a]



entry	catalyst	yield (%)
1	**1a**	92 (90)[d]
2	**1b**	72
3	PTSA	60
4	TfOH	51
5	$Fe(OTf)_3$	55
6	TFA	< 5
7	$Zn(OTf)_2$	< 5
8	—	0
9	**1a**	71[b]
10	**1a**	62[c]

[a]: **2a**, 2.5 mmol; **3a**, 3.0 mmol; 100 °C, 1 h. [b]: ratio of **3a**/**2a** = 1.0/1.0; [c]: catalyst amount is 5 mol %; [d]: **1a** was reused in the sixth time.

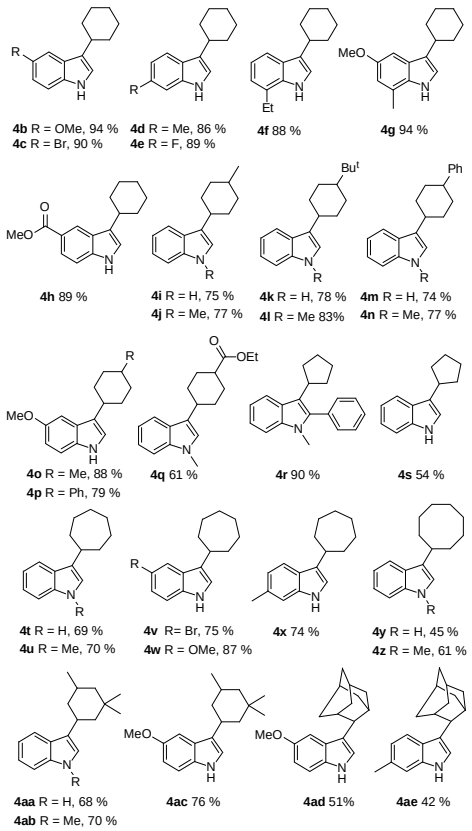
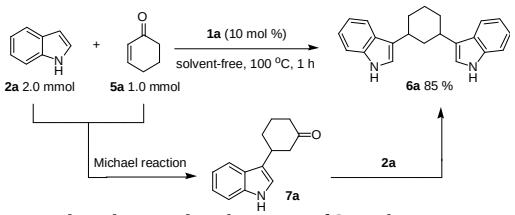


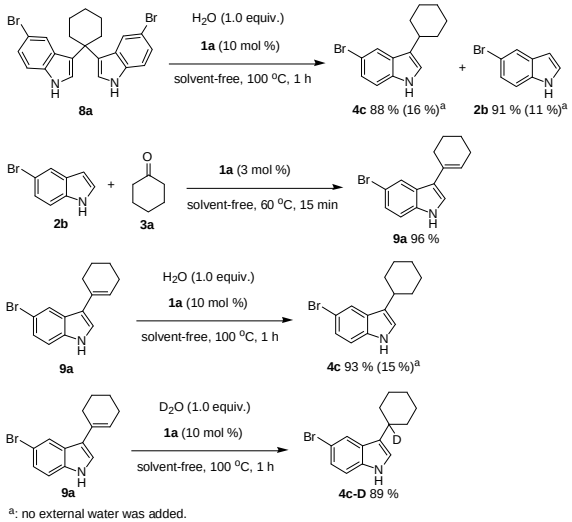
Figure 1. Substrate scope of **1a**-catalyzed reductive Friedel-Crafts alkylation reactions of indoles with cyclic ketones.

With the optimized conditions in hand, we probed the scope of the reaction with respect to both the indole and the ketone components. As evidenced by the results in **Figure 1**, indoles with different substituents smoothly reacted with cyclohexanone **3a**, producing C3-cyclohexylindoles in generally good yield. Both electron-rich (methyl, methoxy) and electron-poor (phenyl and methoxycarboxyl) indoles readily participated in the reaction (**4b** to **4h**). The scope of the reaction with respect to cyclic ketone was next investigated and found to be excellent. As **Figure 1** illustrates, a broad range of cyclohexanones could be employed without significantly affecting the yield of the product C3-cyclohexylindoles (**4i** to **4q**). Ester group in the ketone can be delivered uneventfully to the product without any damage of ester carbonyl group (**4q**). It was also possible to use other cyclic ketones, such as cyclopentanone, cycloheptanone and cyclooctanone in this reductive Friedel-Crafts alkylation reaction (**4r** to **4ac**). 2-Adamantanone can be successfully used as well with the aid of ionic liquid **1a** (**4ad** and **4ae**). However, attempt to use linear ketones failed to obtain the expected reductive alkylation product. Interestingly, when 2-cyclohexen-1-one **5a** was used to react with **2a**, a symmetrical molecule, 1,3-di(indol-3-yl)cyclohexane **6a** was obtained in good yield (**Scheme 1**). The reaction might proceed through a reaction sequence involving (i) a Michael addition of **2a** to **5a**, which generated a 1-(indol-3-yl)cyclohexane **7a**; and (ii) a reductive Friedel-Crafts alkylation of **7a** with **2a**.



Scheme 1. Ionic liquid **1a**-catalyzed reaction of **2a** and **5a**.

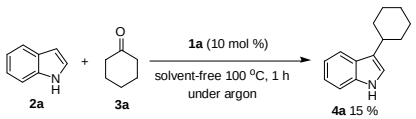
To find the oxidation product, the extract obtained in the model reaction was also analysed by both GC/MS and LC/MS. However, the reaction seems very selective, and no peak was identified as the counter product from an oxidation. To shed light on the mechanism of the reductive Friedel-Crafts alkylation, various control experiments were done. It is well known that a diindolylmethane derivative **8a** could be formed when **2b** and **3a** was treated with an acid catalyst. [13] We therefore considered **8a** as a possible intermediate. Treatment of **8a** with ionic liquid **1a** at 100 °C in the presence of one equivalent of water affords **4c** in 88 % yield (equation 1). Presence of water seems critical for the formation of **4c** as only 16 % of yield was obtained without addition of water. Ionic liquid **1a** has been demonstrated to be an effective catalyst for promoting the alkenylation of indoles and simples ketones.[10] Indeed, 1-(5-bromoindol-3-yl)-1-cyclohexene **9a** could be obtained in 96 % of yield in the presence of 3 mol % of **1a** catalyst at 60 °C (equation 2). Intriguingly, in the presence of one equivalent of water, **9a** can be converted smoothly into **4c** at 100 °C in the presence of 10 mol % of **1a** (equation 3). When water was replaced by D_2O in the reaction of **9a**, a deuterated product, **4c**-D, was obtained in 89 % yield (equation 4). All these results manifested that water played a key role in the model Friedel-Crafts alkylation.



a: no external water was added.

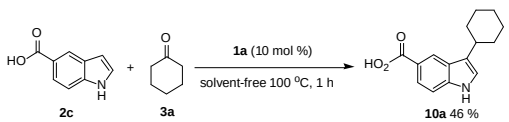
Figure 2. Control experiments for understanding the mechanism.

An ionic liquid **1a**-catalyzed reaction of **2a** and **3a** under argon atmosphere gives only 15 % of yield (**Scheme 2**). This result implies that oxygen play also a key role in the reaction.



Scheme 2. Reductive alkylation of **2c** with **3a** under argon.

We have also found that an aqueous solution of a reaction mixture of **2a** and **3a** is able to change the color of potassium iodide-starch test paper to blue. More interestingly, when indole-5-carboxylic acid **2c** was used in the reductive alkylation reaction, a peroxyindole-5-carboxylic acid **10a** was obtained (**Scheme 3**). All these results led us to believe that hydrogen peroxide was formed during the reductive coupling reaction.



Scheme 3. Ionic liquid **1a**-catalyzed reductive alkylation of **2c** with **3a**.

A reaction solution of **2a** and **3a** was subjected to an analysis of electronic paramagnetic resonance (EPR), which can detect radical species. It was found that there is indeed a radical species in the reaction system as a response signal was clearly observed (**Figure 3**). Interestingly, a similar peak was also observed when indole was treated by **1a** in the absence of **3a**. After 1 hour of reaction at 100 °C, a solid compound was isolated, which is highly polar. An intensive signal was observed in the same region when the solution of the obtained solid was subjected to EPR analysis. NMR analysis results shows that the solid compound is most likely an oligomer indole radical cation (see ESI).[14]

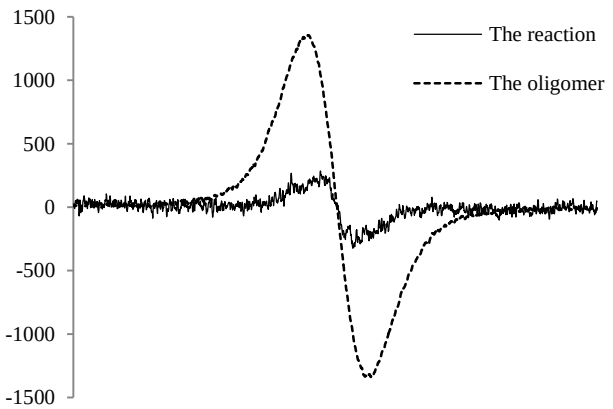


Figure 3. EPR analysis of the reaction solution and indole oligomer solution. The EPR spectra were recorded on a JEOL FA200 spectrometer at room temperature. The crossing point is central field, 326.667 mT. EPR measurements were conducted using a microwave radiation of 9.146 GHz (X band) a modulation frequency of 100 kHz a modulation width of 0.1 mT a sweep width of 20 mT a center field of 326.67 mT a scan time of 30 s a time constant of 0.01 s a microwave power of 5 mW.

On the basis of all these results, a plausible mechanism was then proposed (**Figure 4**). The initial event of the reaction was the formation of an indolyl cation (**I**) from **2a** and **3a** in the presence of acidic catalyst. It can be possibly converted into **8b** or **9b** by eliminating one molecule of water.[10] Meanwhile, oxidative oligomerization of indole occurred as well. Presence of acid and oxygen is the key for rendering the reaction possible. The generated oligomer of indole can be converted to a cationic radical species under acidic conditions.[15] This species may play a role of radical initiator to convert the (**I**) to a cationic radical intermediate (**II**). Then, the generated water somehow reacted with (**II**) to form the desired product **4a**. This step may release hydroxyl radical, which was then converted to hydrogen peroxide. The unique acidic environment offered by the ionic liquid **1a** catalyst should be the key for initiating the reductive alkylation as a super acid-induced reductive alkylation has been used for the synthesis of diphenylmethane derivatives from benzaldehyde diacetals.[16] In addition, the cationic radicals from linear ketones may not as stable as that generated from cyclic ketones, therefore, linear ketones cannot be used in this system.

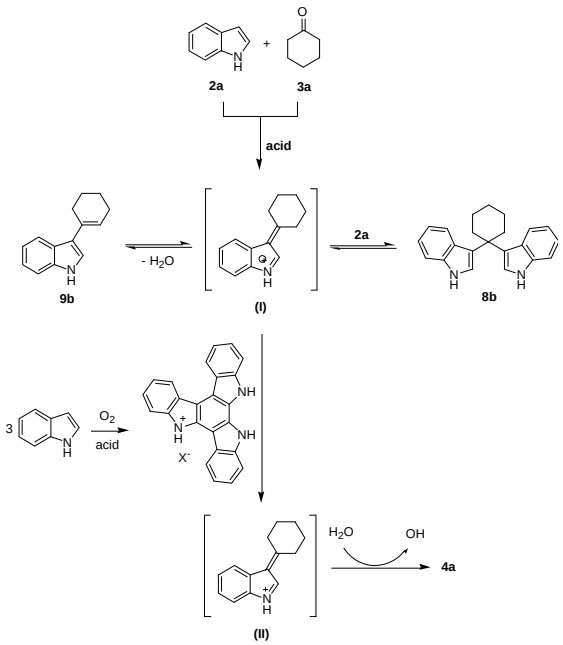
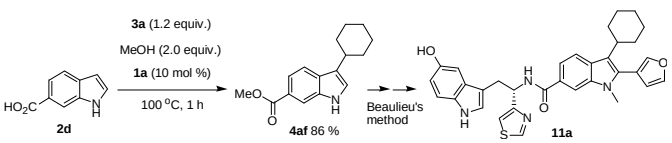


Figure 4. The proposed mechanism.

Methyl 3-cyclohexyl-1*H*-indole-6-carboxylate **4af** has been used as an intermediate to synthesize an effective non-nucleoside allosteric inhibitor of the NS5B polymerase of the hepatitis C virus, **11a** (**Scheme 4**).[17,16] However, the reported method for the synthesis of **4af** is rather tedious as it involves the following three steps: (i) a base-catalyzed condensation of indole-6carboxylic acid **2d** with **3a**; (ii) Pd-catalyzed hydrogenation of the obtained product, and (iii) esterification of the hydrogenation product.[18] By using **1a** as catalyst, **4af** could be synthesized in excellent yield through a reductive Friedel-Crafts alkylation of **2d** and **3a** in the presence of methanol. This one-step reaction not only offered a straightforward method to access **4af**, but also demonstrated the great usefulness of the reductive Friedel-Crafts alkylation established based on ionic liquid **1a** catalyst.



Scheme 4. Synthesis of **4af** from **2d** using ionic liquid **1a**.

Conclusions

An acid-induced reductive Friedel-Crafts alkylation of indole with cyclic ketones was disclosed, which offered a new and an efficient way to synthesize C3-cycloalkylindole derivatives. A sulfonyl-containing Brønsted acid ionic liquid was demonstrated to be the best catalyst among all the acids examined. The established method possesses many characters of green organic synthesis, such as solvent-free conditions, high synthetic efficiency, recyclable catalyst and easy product isolation. The reaction might proceed in a radical way. An oligomer of indole, which was formed through oxidative oligomerization in the presence of acid and oxygen, was identified to be most likely a radical initiator. The reductive alkylation product was formed from a cationic radical that was generated from a carbocation intermediate. Water was also involved as a key component of the reaction in the mechanism.

The authors thank for National Natural Science Foundation of China for the financial support (21173089 and 21373093). The authors are also grateful to the Analytical and Testing Centre of HUST. Chutian Scholar Program of the Hubei Provincial Government and the Cooperative Innovation Center of Hubei Province are also acknowledged. This work is also supported by the Fundamental Research Funds for the Central Universities of China (2014ZZGH019).

Notes and references

[a]*Key Laboratory for Large-Format Battery Materials and System, Ministry of Education, School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology (HUST), 1037 Luoyu road, Hongshan District, Wuhan 430074, China. Fax: (0)86-(0)27-87 54 45 32;*

E-mail: klgyl@hust.edu.cn

[b] *State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Lanzhou, 730000 (P.R. China)*

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

1 For selected recent reviews, see: (a) J. M. Finefield, J. C. Frisvad, D. H. Sherman, R. M. Williams, *J. Nat. Prod*. **2012**, *75*, 812-833; (b) M, Shiri, *Chem. Rev*. **2012**, *112*, 3508-3549; (c) M. Shiri, M. A. Zolfigol, H. G. Kruger, Z. Tanbakouchian, *Chem. Rev*. **2010**, *110*, 2250-2293; (d) G. R. Humphrey, J. T. Kuethe, *Chem. Rev*. **2006**, *106*, 2875. (e) P. S. Bhadury, J. Pang, *Curr. Org. Chem*. **2014**, *18*, 2108-2124.

2 For reviews on synthesis of indoles, see: (a) G. W. Gribble, *In Comprehensive Heterocyclic Chemistry II*; A. R. Katritzky, C. W. Rees, E. F. V. Scriven, Eds.; Pergamon: Oxford, UK, **1996**; Vol. 2, p 207; (b) M. Bandini, A, Eichholzer, *Angew. Chem. Int. Ed*. **2009**, *48*, 9608-9645; (c) *Indole and its Derivatives*, J. A. Joule in *Science of Synthesis* (Houben-Weyl Methods of Molecular Transformations), Vol. 10 (Ed.: E. J. Thomas), Thieme, Stuttgart, **2000**, chap. 10.13.

3 (a) M. D. Cummings, T. Lin, L. Hu, A. Tahri, D. McGowan, K. Amssoms, S. Last, B. Devogelaere, M. –C. Rouan, L. Vijgen, J. M. Berke, P. Dehertogh, E. Fransen, E. Cleiren, L. van der Helm, G. Fanning, K. V. Emelen, O. Nyanguile, K. Simmen, P. Raboisson, and S. Vendeville, *Angew Chem. Int. Ed*. **2012**, *51*, 4637-4640; (b) M. D. Cummings, T. Lin, L. Hu, A. Tahri, D. McGowan, K. Amssoms, S. Last, B. Devogelaere, M. –C. Rouan, L. Vijgen, J. M. Berke, P. Dehertogh, E. Fransen, E. Cleiren, L. van der Helm, G. Fanning, O. Nyanguile, K. Simmen, P. V. Remoortere, P. Raboisson, and S. Vendeville, *J. Med. Chem*. **2014**, *57*, 1880−1892; (c) K. J. Eastman, Z. Yang, J. A. Bender, K. Mosure, J. A. Lemm, N. A. Meanwell, S. B. Roberts, J. Knipe, J. F. Kadow, *Bioorg. Med. Chem. Lett*. **2014**, *24*, 1993-1997; (d) S. R. LaPlante, M. Bös, C. Brochu, C. Chabot, R. Coulombe, J. R. Gillard, A. Jakalian, M. Poirier, J. Rancourt, T. Stammers, B. Thavonekham, P. L. Beaulieu, G. Kukolj, and Y. S. Tsantrizos, *J. Med. Chem*. **2014**, *57*, 1845-1854; (e) S. Zeuzem, V. Soriano, T. Asselah, J. –P. Bronowicki, A. W. Lohse, B. Müllhaupt, M. Schuchmann, M. Bourlière, M. Buti, S. K. Roberts, E. J. Gane, J. O. Stern, R. Vinisko, G. Kukolj, J. –P. Gallivan, W. –O. Böcher, and F. J. Mensa, *New Engl. J. Med*. **2013**, *369*, 630-639.

4 (a) J. Crawforth, S. Goodacre, R. Maxey, S. Bourrain, S. Patel, R. Marwood, D. O'Connor, R. Herbert, P. Hutson, and M. Rowley, *Bioorg. Med. Chem. Lett*. **2000**, *10*, 2701-2703; (b) P. L. Beaulieu, M. Bös, M. G. Cordingley, C. Chabot, G. Fazal, M. Garneau, J. R. Gillard, E. Jolicoeur, S. LaPlante, G. McKercher, M. Poirier, M. –A. Poupart, Y. S. Tsantrizos, J. Duan, and G. Kukolj, *J. Med. Chem*. **2012**, *55*, 7650-7666.

5 (a) J. R. Rizzo, C. A. Alt, T. Y. Zhang, *Tetrahedron Lett*. **2008**, *49*, 6749-6751; (b) L. –L. Cao, D. –S. Wang, G. –F. Jiang, Y. –G. Zhou, *Tetrahedron Lett*. **2011**, *52*, 2837-2839.

6 (a) A. E. Putra, K. Takigawa, H. Tanaka, Y. Ito, Y. Oe, and T. Ohta, *Eur. J. Org. Chem.* 2013, 6344-6354; (b) R. Cano, M. Yus, D. J. Ramón, *Tetrahedron Lett*. **2013**, *54*, 3394-3397.

7 X. Han and J. Wu, *Angew. Chem. Int. Ed*. **2013**, *52*, 4637-4640.

8 M. –Z. Wang, M. –K. Wong, and C. –M. Che, *Chem. Eur. J*. **2008**, *14*, 8353-8364.

9 T. Amir, X. Pan, C. Liu, and Y. Gu, *ChemSusChem*. **2014**, *7*, 2094-2098.

10 A. Taheri, C. Liu, B. Lai, C. Cheng, X. Pan, and Y. Gu, *Green Chem*. **2014**, *16*, 3715-3719.

11 See Electronic Supporting Information (ESI).

12 W. –L. Chen, Y. –R. Gao, S. Mao, Y. –L. Zhang, Y. –F. Wang, Y. –Q. Wang, *Org. Lett*. **2012**, *14*, 5920-5923.

13 R. Tayebee, M. M. Amini, F. Nehzat, O. Sadeghi, M. Armaghan, *J. Mol. Catal. A. Chem*. **2013**, *366*, 140-148.

14 H. Ishii, K. Murakami, E. Sakurada *(nee* Kawanabe), K. Hosoya, Y. Murakami, *J. Chem. Soc. Perkin Trans. I*, **1988**, 2377-2385.

15 L. Greci, G. Tommasi, R. Petrucci, G. Marrosu, A. Trazza, P. Sgarabotto, L. Righi, A. Alberti, *J. Chem. Soc., Perkin Trans. 2*, **2000**, 2337-2342.

16 A superacid-catalyzed reductive Friedel-Crafts reaction of arenes using arenecarbaldehyde acetals has been reported: S. –I. Fukuzawa, T. Tsuchimoto, and T. Hiyama, *J. Org. Chem*. **1997**, *62*, 151-156.

17 P. L. Beaulieu, Y. Bousquet, J. Gauthier, J. Gillard, M. Marquis, G. McKercher, C. Pellerin, S. Valois, and G. Kukolj, *J. Med. Chem*. **2004**, *47*, 6884-6892.

18 P. L. Beaulieu, J. Gillard, D. Bykowski,_ C. Brochu, N. Dansereau, J. –S. Duceppe, B. Haché, A. Jakalian, L. Lagacé, S. LaPlante, G. McKercher, E. Moreau, S. Perreault, T. Stammers, L. Thauvette, J. Warrington, and G. Kukolj, *Bioorg. Med. Chem. Lett*. **2006**, *16*, 4987-4993.

