Heterocycle Synthesis

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Transition-Metal-Free Synthesis of *N*-Hydroxy Oxindoles by an Aza-Nazarov-Type Reaction Involving Azaoxyallyl Cations

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Abstract: *A novel transition-metal-free method to construct N-hydroxy oxindoles by an aza-Nazarov-type reaction involving azaoxyallyl cation intermediates is described. A variety of functional groups were tolerated under the weak basic reaction conditions and at room temperature. A one-pot process was also developed to make the reaction even more practical. This method provides alternative access to oxindoles and their biologically active derivatives.*

Oxindoles are widely present in natural products,[1] and also in pharmacologically active compounds such as NMDA antagonists,[2] calcium channel blockers,[3] and agents with anti-angiogenic,[4] anticancer,[5] and analgesic effects[6] (Figure 1). Past decades have seen the development of

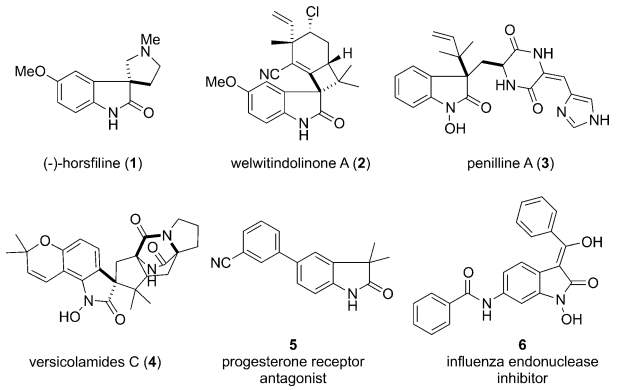
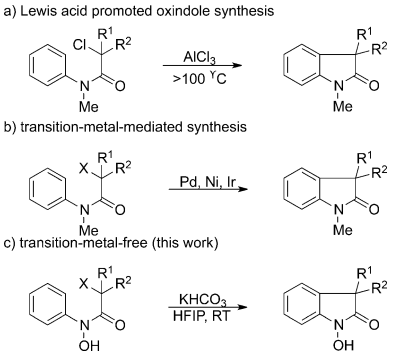


Figure 1. Representative natural products and pharmacologically active compounds containing oxindole core.

numerous methods to synthesize oxindoles containing a variety of functionalities,[7] and these methods include the derivatization of either isatin or indoles,[8] radical cyclizations of aniline derivatives,[9] Friedel–Crafts-type cyclizations,[10] and transition-metal-mediated reactions,[11,9n] among others. One of the most efficient modes to construct oxindoles is their conversion from α-halo anilides (Scheme 1). As early as the 1930s, Stollé et al. used $AlCl_3$ to promote cyclization from



Scheme 1. Access to oxindoles from α-halo anilides.

α-halo anilides,[10a,b] but the reaction conditions were very harsh and problematic with some substrates (Scheme 1 a). Some of the other preparations of oxindoles from α-halo anilides include Buchwald's synthesis of oxindoles by a palladium-catalyzed C–H functionalization[11a] and Lei's nickel-catalyzed cyclization.[11p] Recently, Yu and co-workers reported another method to convert 2-bromoanilides, containing two electron-withdrawing substituents, into 3,3-disubstituted oxindoles by visible-light-promoted photoredox catalysis.[9t] However, most of these reactions require costly metal catalysts which can contaminate products.

Transition-metal-free reactions have emerged in recent years as important methods for the formation of C–C, C–N, C–O, and even C–S bonds.[12] Although typical examples of metal-free cyclizations to prepare oxindoles are processes involving radicals,[9a–e] a potassium *tert*-butoxide promoted synthesis of oxindoles reported by the group of Bolm was believed to proceed through an S_NAr reaction.[13] Additionally, both the groups of Zhu[14] and Zhao[15] developed metal-free approaches to oxindoles using a hypervalent iodine(III) reagent, but the reaction has limited scope and requires an external oxidant. Herein, we describe a transition-metal-free and oxidant-free access to oxindoles under mild reaction conditions.

Azaoxyallylic cations are reactive intermediates which have not yet been studied extensively. In the 1960s, the azaoxyallyl cation was first suggested as an intermediate when Sheehan studied α-lactam chemistry.[16] In 1993, the group of Kikugawa showed evidence for azaoxyallyl cation intermediates,[17] but there had not been much progress until Jeffrey and co-workers reported the first practical [4+3] cycloaddition involving azaoxyallyl cations.[18,19] Very recently, the groups of Jeffrey[20] and Wu,[21] and ourselves[22] reported a dearomative [3+2] cycloaddition of azaoxyallyl cationic intermediates. Our group has also explored the application of azaoxyallyl cations as synthons in synthetic approaches towards (±)-minfiensine.[22] Considering that this intermediate could be trapped by

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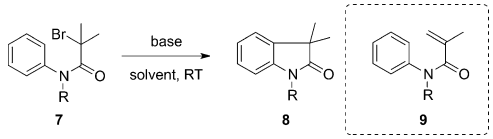
a benzene ring to construct an oxindole skeleton, we initiated our screenings to generate azaoxyallyl cations from anilides under mild reaction conditions: a $KHCO_3$/1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) system. It was found that the substituent on the anilide nitrogen atom is a key factor, as no reaction occurred when the substituent was H, methyl, methoxy, or benzyl (Table 1, entries 1–4). To our delight,

Table 1: Optimization of the reaction conditions.[a]



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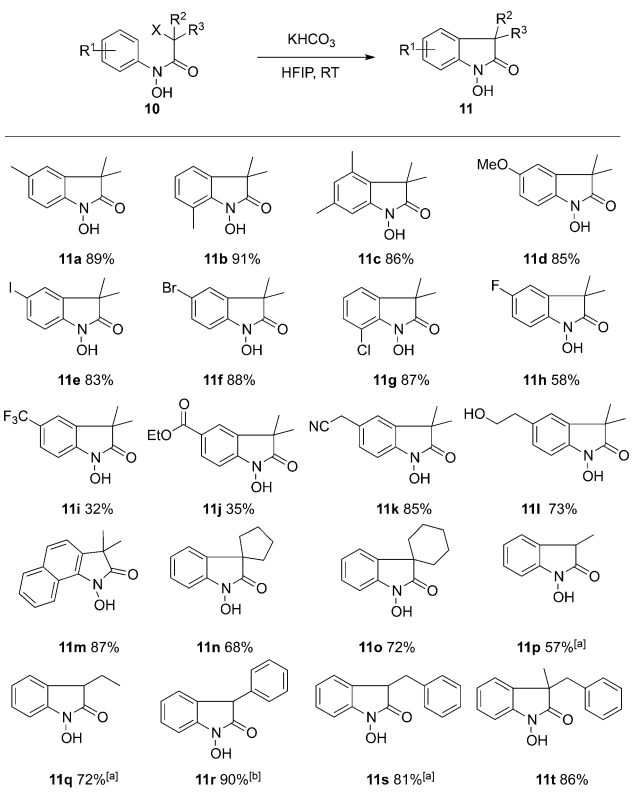
Entry	R	Base	Solvent	Yield [%][b]
1	H	$KHCO_3$	HFIP	n.r.
2	Me	$KHCO_3$	HFIP	n.r.
3	Bn	$KHCO_3$	HFIP	n.r.
4	OMe	$KHCO_3$	HFIP	n.r.
5	OH	$KHCO_3$	HFIP	90
6	OH	Et_3N	HFIP	83
7	OH	K_2CO_3	HFIP	52
8	OH	$KHCO_3$	THF	no
9	OH	$KHCO_3$	CH_2Cl_2	no
10	OH	$KHCO_3$	MeCN	no
11	OH	$KHCO_3$	toluene	no

[a] Reaction conditions: **7** (0.3 mmol, 1.0 equiv) and base (1.1 equiv) in solvent (2 mL) at room temperature (RT) for 5 h. [b] The yield is that of isolated product. n.r. = no reaction, no = no desired product **8**, THF = tetrahydrofuran.

when α-bromo-*N*-hydroxy anilide (**7**, R = OH) was subjected to the system,[20–22] the desired oxindole **8** (R = OH) was obtained in 90% yield (entry 5). Thus, **7** (R = OH) was chosen as the model substrate for the initial survey. Replacing $KHCO_3$ with either K_2CO_3 or Et_3N as the base resulted in lower yield (entries 6 and 7). The solvent was so crucial that the reaction conducted in common solvents gave the elimination product **9** as the main product without forming **8** (entries 8–11).

Having identified the optimized reaction conditions, we next explored the substrate scope. A variety of N-hydroxy anilides were subjected to the $KHCO_3$/HFIP reaction system (Scheme 2). Functional groups such as methyl, methoxy, halogens, ester, nitrile, or hydroxy were found to be well tolerated in the system (**11a**–**m**). The position of substituents at the *para, meta*, or *ortho* positions did not affect the reaction. The substituted anilides with electron-withdrawing groups tended to have poor yields (**11i**,**j**). Spiro-oxindoles (**11n**,**o**) with five-membered or six-membered rings were readily prepared in this method. Both 3-monosubstituted and 3,3-disubstituted substrates gave oxindoles in good yields (**11p**–**t**), but the former (**11p**–**s**) reacted more slowly (12 h) than did the latter (**11t**). Besides α-bromo-*N*-hydroxy anilides, α-chloro-*N*-hydroxy anilide (**11r**) also reacted smoothly.

Since N-hydroxy anilides can be prepared readily by reacting phenylhydroxylamine (**12**) with either acyl chloride or bromide,[23] we turned our attention to testing the possibility of a one-pot process for the synthesis of **11** and **8** (Scheme 3). In the one-pot process, 2-bromo-2-methylpropanoyl bromide (**13**; $R^2 = R^3 = Me$, $X^1 = X^2 = Br$) was added dropwise to a mixture of **12** and $KHCO_3$ in ether, with

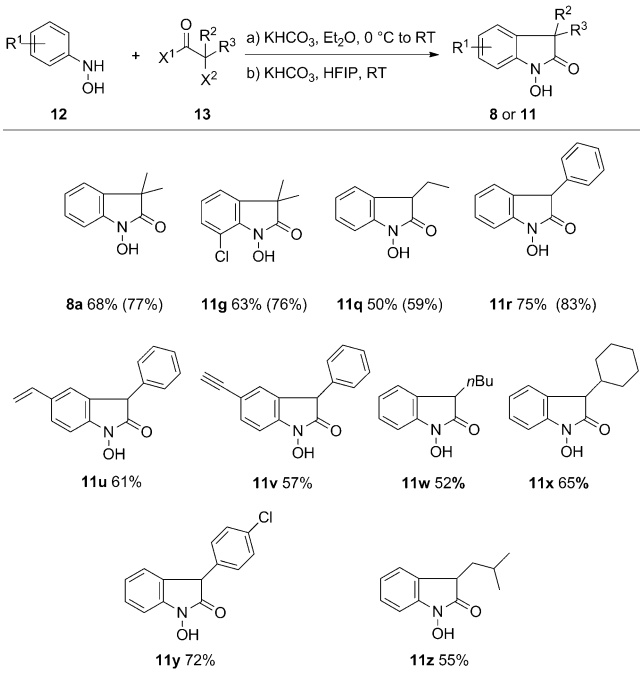


Scheme 2. Substrate scope for the reaction. Yield is that of the isolated product. X = Br. Reaction conditions: **10** (0.3 mmol, 1.0 equiv), and $KHCO_3$ (1.1 equiv) in HFIP (2 mL) at room temperature (RT) for 5 h. [a] Reaction time: 12 h. [b] X = Cl. 12 h.

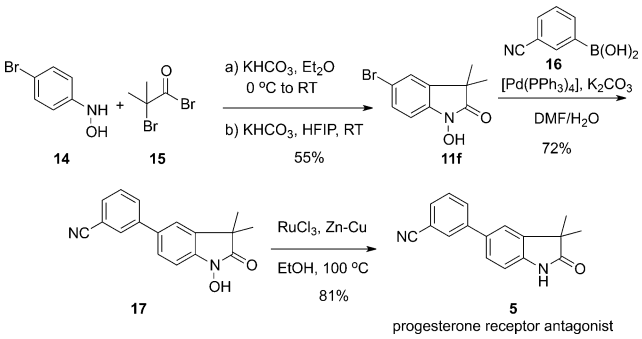
subsequent evaporation of the ether solvent and addition of HFIP. The reaction mixture was then stirred for another 5 hours at room temperature, thus resulting in the desired product **8a** in 68% yield. Because various phenylhydroxylamines and acyl halides are either commercially available or can be prepared readily, this one-pot procedure is more practical than the two-step method, albeit in lower, but acceptable yield (**11g**, **11q**, **11r**, **11u**–*z*).

Given the versatility of the one-pot process, it was applied to the synthesis of the progesterone receptor antagonist **5**[24](Scheme 4). The synthesis began with treatment of *N*-(4-bromophenyl)hydroxylamine (**14**) with the acyl bromide **15** in a one-pot process to give the oxindole **11f** in 55% yield. The oxindole **11f** was then reacted with the boronic acid **16** under Suzuki coupling conditions to afford the precursor **17** in 72% yield.[25] Cleavage of the N–O bond of **17** afforded **5** in 81% yield.[26]

It was found that when the substituent on the anilide nitrogen atom was either H, methyl, benzyl, or methoxy, the reaction did not afford the desired product **8**. In addition, an attempt with *N*-benzyl-2-bromo-*N*-hydroxy-2-methylpropanamide (**18**) under the standard reaction conditions to prepare the six-membered ring compound **19** gave the olefin **20** in almost quantitative yield without even trace amount of **19** formed (Scheme 5). Thus, the reactivity of **7** can possibly be ascribed to the nitrogen atom attached directly to the benzene ring. Based on these results and previous mechanistic studies of azaoxyally cations,[17–21] we hereby

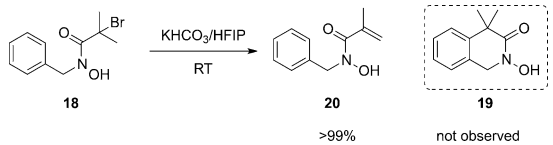


Scheme 3. One-pot process. Yield is that of the isolated product. The yield within parentheses is the overall yield of the two-step process when the reaction was carried out in a stepwise fashion. Reaction conditions: X^1 or X^2 = Br or Cl. a) **12** (0.5 mmol, 1.0 equiv), **13** (1.1 equiv) and $KHCO_3$ (1.2 equiv) in Et_2O (3 mL) at 0 °C for 1 h and at room temperature (RT) for 1 h, followed by removal of solvent. b) $KHCO_3$ (1.1 equiv) in HFIP (3 mL) at RT for 5 h.

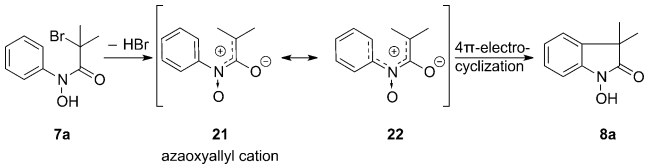


Scheme 4. Application in synthesis of the progesterone receptor antagonist **5**. DMF = *N*,*N*-dimethylformamide.

propose one possible pathway in Scheme 6. Dehydrohalogenation of **7a** leads to the azaoxyallyl cation **21**, which is further stabilized by delocalization of positive charge to generate the more stable form **22**. Then, a 4π electrocyclization occurs to afford the final product **8a**.[28] In the azaoxyallyl cation, the lone pair of electrons on the hydroxy played a pivotal role in stabilizing the cation.[17–21] Additional



Scheme 5. Control experiment.



Scheme 6. Proposed pathway of the reaction.

evidence to support this proposed mechanism is that the anilides substituted with electron-withdrawing groups [EtOC(O) and CF_3] formed the desired products in poor yields (Scheme 2**; 11i,j**). In addition, use of HFIP as the solvent is the key, since it presumably stabilizes the transition state through hydrogen-bond interactions with the oxygen atom of the azaoxyallyl cation.[18–21,27]

To conclude, we developed a transition-metal-free method to construct oxindoles by an aza-Nazarov-type reaction involving azaoxyallyl cation intermediates. The reaction can be carried out under very mild reaction conditions and has broad functional-group tolerance. In addition, a one-pot procedure was developed to make the method yet more practical. This reaction provides an alternative access to oxindoles and their biologically active derivatives. More detailed mechanistic studies are ongoing and will be reported in due course.

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Keywords: azaoxyallylic cations · cyclizations · heterocycles · oxindoles · synthetic methods

[1] a) C. V. Galliford, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2007**, *46*, 8748; *Angew. Chem.* **2007**, *119*, 8902; b) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209.

[2] T. H. Kang, Y. Murakami, K. Matsumoto, H. Takayama, M. Kitajima, N. Aimi, H. Watanabe, *Eur. J. Pharmacol.* **2002**, *455*, 27.

[3] A. M. Swensen, J. Herrington, R. M. Bugianesi, G. Dai, R. J. Haedo, K. S. Ratliff, M. M. Smith, V. A. Warren, S. P. Arneric, C. Eduljee, D. Parker, T. P. Snutch, S. B. Hoyt, C. London, J. L. Duffy, G. J. Kaczorowski, O. B. McManus, *Mol. Pharmacol.* **2012**, *81*, 488.

[4] J. L. Whatmore, E. Swann, P. Barraja, J. J. Newsome, M. Bunderson, H. D. Beall, J. E. Tooke, C. J. Moody, *Angiogenesis* **2002**, *5*, 45.

[5] S. Peddibhotla, *Curr. Bioact. Compd.* **2009**, *5*, 20.

[6] C. Abbadie, O. B. McManus, S. Y. Sun, R. M. Bugianesi, G. Dai, R. J. Haedo, J. B. Herrington, G. J. Kaczorowski, M. M. Smith, A. M. Swensen, V. A. Warren, B. Williams, S. P. Arneric, C. Eduljee, T. P. Snutch, E. W. Tringham, N. Jochnowitz, A. Liang, D. Euan MacIntyre, E. McGowan, S. Mistry, V. V. White, S. B. Hoyt, C. London, K. A. Lyons, P. B. Bunting, S. Volksdorf, J. L. Duffy, *J. Pharmacol. Exp. Ther.* **2010**, *334*, 545.

[7] For reviews on oxindole synthesis, see: a) J. E. M. N. Klein, R. J. K. Taylor, *Eur. J. Org. Chem.* **2011**, 6821; b) R. Dalpozzo, G. Bartoli, G. Bencivenni, *Chem. Soc. Rev.* **2012**, *41*, 7247; c) N. R. Ball-Jones, J. J. Badillo, A. K. Franz, *Org. Biomol. Chem.* **2012**, *10*, 5165; d) M. M. M. Santos, *Tetrahedron* **2014**, *70*, 9735; e) M. Xia, R. Ma, *J. Heterocycl. Chem.* **2014**, *51*, 539; f) J. Chen, X. Yu, W. Xiao, *Synthesis* **2015**, 604.

[8] a) R. J. Sundberg, *Indoles*, Academic Press, London, **1996**, pp. 17, 152–154; b) R. Shintani, M. Inoue, T. Hayashi, *Angew. Chem. Int. Ed.* **2006**, *45*, 3353; *Angew. Chem.* **2006**, *118*, 3431; c) I. D. Hills, G. C. Fu, *Angew. Chem. Int. Ed.* **2003**, *42*, 3921; *Angew. Chem.* **2003**, *115*, 4051; d) Y. H. Lim, Q. Ong, H. A. Duong, T. M. Nguyen, C. W. Johannes, *Org. Lett.* **2012**, *14*, 5676; e) D. Tomita, K. Yamatsugu, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 6946.

[9] For selected examples of nonmetal-mediated radical cyclization, see: a) M. Zhou, R. Song, X. Ouyang, Y. Liu, W. Wei, G. Deng, J. Li, *Chem. Sci.* **2013**, *4*, 2690; b) K. Matcha, R. Narayan, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2013**, *52*, 7985; *Angew. Chem.* **2013**, *125*, 8143; c) H. Wang, L. Guo, X. Duan, *Org. Lett.* **2013**, *15*, 5254; d) T. Shen, Y. Yuan, N. Jiao, *Chem. Commun.* **2014**, *50*, 554; e) X. Duan, X. Yang, P. Jia, M. Zhang, B. Han, *Org. Lett.* **2015**, *17*, 6022; for selected examples of metal mediated radical cyclization, see: f) W. Wei, M. Zhou, J. Fan, W. Liu, R. Song, Y. Liu, M. Hu, P. Xie, J. Li, *Angew. Chem. Int. Ed.* **2013**, *52*, 3638; *Angew. Chem.* **2013**, *125*, 3726; g) Y. Li, M. Sun, H. Wang, Q. Tian, S. Yang, *Angew. Chem. Int. Ed.* **2013**, *52*, 3972; *Angew. Chem.* **2013**, *125*, 4064; h) H. Wang, L. Guo, X. Duan, *Chem. Commun.* **2013**, *49*, 10370; i) X. Wei, Y. Zhou, T. Yang, S. Yang, *Org. Lett.* **2013**, *15*, 4158; j) M. Zhou, C. Wang, R. Song, Y. Liu, W. Wei, J. Li, *Chem. Commun.* **2013**, *49*, 10817; k) Q. Dai, J. Yu, Y. Jiang, S. Guo, H. Yang, J. Cheng, *Chem. Commun.* **2014**, *50*, 3865; l) F. Yin, X. Wang, *Org. Lett.* **2014**, *16*, 1128; m) J. Li, Z. Wang, N. Wu, G. Gao, J. You, *Chem. Commun.* **2014**, *50*, 15049; n) J. Wang, Y. Su, F. Yin, Y. Bao, X. Zhang, Y. Xu, X. Wang, *Chem. Commun.* **2014**, *50*, 4108; o) M. Lu, T. Loh, *Org. Lett.* **2014**, *16*, 4698; p) T. Shen, Y. Yuan, S. Song, N. Jiao, *Chem. Commun.* **2014**, *50*, 4115; q) Z. Li, Y. Zhang, Z. Liu, *Org. Lett.* **2014**, *16*, 382; r) Z. Xu, C. Yan, Z. Liu, *Org. Lett.* **2014**, *16*, 5670; s) L. Zhang, D. Liu, Z. Liu, *Org. Lett.* **2015**, *17*, 2534; For selected examples of photo-induced radical cyclization, see: t) X. Ju, Y. Liang, P. Jia, W. Li, W. Yu, *Org. Biomol. Chem.* **2012**, *10*, 498; u) J. Xie, P. Xu, H. Li, Q. Xue, H. Jin, Y. Cheng, C. Zhu, *Chem. Commun.* **2013**, *49*, 5672; v) X. Tang, C. Thomoson, W. R. Dolbier, Jr., *Org. Lett.* **2014**, *16*, 4594; w) L. Zheng, H. Huang, C. Yang, W. Xia, *Org. Lett.* **2015**, *17*, 1034; x) W. Ji, H. Tan, M. Wang, P. Li, L. Wang, *Chem. Commun.* **2016**, *52*, 1462.

[10] For selected examples of Friedel–Crafts-type cyclization, see: a) R. Stollé, *J. Prakt. Chem.* **1922**, *105*, 137; b) R. Stollé, R. Bergdoll, M. Luther, A. Auerhahn, W. Wacker, *J. Prakt. Chem.* **1930**, *128*, 1; c) A. H. Beckett, R. W. Daisley, *Tetrahedron* **1968**, *24*, 6093; d) H. Aoyama, Y. Omote, T. Hasegawa, H. Shiraishi, *J. Chem. Soc. Perkin Trans. 1* **1976**, 1556; e) D. Ben-Ishai, N. Peled, I. Sataty, *Tetrahedron Lett.* **1980**, *21*, 569; f) I. Gorokhovik, L. Neuville, J. Zhu, *Org. Lett.* **2011**, *13*, 5536; g) D. C. Fabry, M. Stodulski, S. Hoerner, T. Gulder, *Chem. Eur. J.* **2012**, *18*, 10834; h) M. Zhang, W. Sheng, Q. Jiang, M. Tian, Y. Yin, C. Guo, *J. Org. Chem.* **2014**, *79*, 10829.

[11] For selected transition-metal-mediated syntheses, see: a) E. J. Hennessy, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 12084; b) A. Pinto, Y. Jia, L. Neuville, J. Zhu, *Chem. Eur. J.* **2007**, *13*, 961; c) Y. Jia, J. M. Hillgren, E. L. Watson, S. P. Marsden, E. P. Kundig, *Chem. Commun.* **2008**, 4040; d) M. Wasa, J. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 14058; e) Y. Jia, E. P. Kundig, *Angew. Chem. Int. Ed.* **2009**, *48*, 1636; *Angew. Chem.* **2009**, *121*, 1664; f) A. Perry, R. J. K. Taylor, *Chem. Commun.* **2009**, 3249; g) L. Ackermann, R. N. Vicente, N. Hofmann, *Org. Lett.* **2009**, *11*, 4274; h) S. Ueda, T. Okada, H. Nagasawa, *Chem. Commun.* **2010**, *46*, 2462; i) G. An, W. Zhou, G. Zhang, H. Sun, J. Han, Y. Pan, *Org. Lett.* **2010**, *12*, 4482; k) S. Jaegli, J. Dufour, H. Wei, T. Piou, X. Duan, J. P. Vors, L. Neuville, J. Zhu, *Org. Lett.* **2010**, *12*, 4498; l) L. Liu, N. Ishida, S. Ashida, M. Murakami, *Org. Lett.* **2011**, *13*, 1666; m) T. Wu, X. Mu, G. Liu, *Angew. Chem. Int. Ed.* **2011**, *50*, 12578; *Angew. Chem.* **2011**, *123*, 12786; n) C. Tsukano, M. Okuno, Y. Takemoto, *Angew. Chem. Int. Ed.* **2012**, *51*, 2763; *Angew. Chem.* **2012**, *124*, 2817; o) X. Mu, T. Wu, H. Wang, Y. Guo, G. Liu, *J. Am. Chem. Soc.* **2012**, *134*, 878; p) C. Liu, D. Liu, W. Zhang, L. Zhou, A. Lei, *Org. Lett.* **2013**, *15*, 6166; q) B. Zhou, W. Hou, Y. Yang, H. Feng, Y. Li, *Org. Lett.* **2014**, *16*, 1322; r) S. Shi, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2015**, *54*, 1646; *Angew. Chem.* **2015**, *127*, 1666; s) C. Li, S. Yang, *Org. Lett.* **2015**, *17*, 2142.

[12] For review on transition-metal-free reactions, see: a) V. P. Mehta, B. Punji, *RSC Adv.* **2013**, *3*, 11957; b) C. Sun, Z. Shi, *Chem. Rev.* **2014**, *114*, 9219; c) R. Narayan, K. Matcha, A. P. Antonchick, *Chem. Eur. J.* **2015**, *21*, 14678.

[13] A. Beyer, J. Buendia, C. Bolm, *Org. Lett.* **2012**, *14*, 3948.

[14] H. Wei, T. Piou, J. Dufour, L. Neuville, J. Zhu, *Org. Lett.* **2011**, *13*, 2244.

[15] J. Wang, Y. Yuan, R. Xiong, D. Zhang-Negrerie, Y. Du, K. Zhao, *Org. Lett.* **2012**, *14*, 2210.

[16] I. Lengyel, J. C. Sheehan, *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 25; *Angew. Chem.* **1968**, *80*, 27.

[17] Y. Kikugawa, M. Shimada, M. Kato, T. Sakamoto, *Chem. Pharm. Bull.* **1993**, *41*, 2192.

[18] a) C. S. Jeffrey, K. L. Barnes, J. A. Eickhoff, C. R. Carson, *J. Am. Chem. Soc.* **2011**, *133*, 7688; b) A. Acharya, J. A. Eickhoff, C. S. Jeffrey, *Synthesis* **2013**, 1825; c) A. Acharya, J. A. Eickhoff, K. Chen, V. J. Catalano, C. S. Jeffrey, *Org. Chem. Front.* **2016**, *3*, 330.

[19] For a review on azaoxyallic cations, see: K. L. Barnes, A. K. Koster, C. S. Jeffrey, *Tetrahedron Lett.* **2014**, *55*, 4690.

[20] A. Acharya, D. Anumandla, C. S. Jeffrey, *J. Am. Chem. Soc.* **2015**, *137*, 14858.

[21] M. C. DiPoto, R. P. Hughes, J. Wu, *J. Am. Chem. Soc.* **2015**, *137*, 14861.

[22] W. Ji, L. Yao, X. Liao, *Org. Lett.* **2016**, *18*, 628.

[23] K. N. Hojczyk, P. Feng, C. Zhang, M. Ngai, *Angew. Chem. Int. Ed.* **2014**, *53*, 14559; *Angew. Chem.* **2014**, *126*, 14787.

[24] A. Fensome, R. Bender, J. Cohen, M. A. Collins, V. A. Mackner, L. L. Miller, J. W. Ullrich, R. Winneker, J. Wrobel, P. Zhang, Z. Zhang, Y. Zhu, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3487.

[25] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.

[26] H. Fukuzawa, Y. Ura, Y. Kataoka, *J. Organomet. Chem.* **2011**, *696*, 3643.

[27] For reviews on fluorinated solvents, see: a) I. A. Shuklov, N. V. Dubrovina, A. Borner, *Synthesis* **2007**, 2925; b) S. Khaksar, *J. Fluorine Chem.* **2015**, *172*, 51.

[28] For selected examples of aza-Nazarov reactions, see: a) K. Matoba, T. Terada, M. Sugiura, T. Yamazaki, *Heterocycles* **1987**, *26*, 55; b) J. Dieker, R. Frohlich, E. U. Wurthwein, *Eur. J. Org. Chem.* **2006**, 5339; c) D. A. Klumpp, Y. Zhang, M. J. Connor, P. M. Esteves, L. S. Almeida, *Org. Lett.* **2007**, *9*, 3085; d) N. Ghavtadze, R. Frohlich, E. U. Wurthwein, *Eur. J. Org. Chem.* **2008**, 3656; e) R. Narayan, C. G. Daniliuc, E. U. Wurthwein, *Eur. J. Org. Chem.* **2012**, 6021; f) I. Karthikeyan, D. Arunprasath, G. Sekar, *Chem. Commun.* **2015**, *51*, 1701.

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Communications

Heterocycle Synthesis

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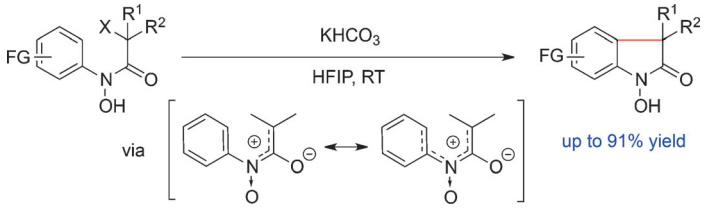
Transition-Metal-Free Synthesis of *N*-Hydroxy Oxindoles by an Aza-Nazarov-Type Reaction Involving Azaoxyallyl Cations



A bit weak: In the title reaction, a variety of functional groups are tolerated under weakly basic reaction conditions and at room temperature. This method provides alternative access to oxindoles and their biologically active derivatives. FG = functional group, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.