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Deconstructive di-functionalization of unstrained, benzo cyclic amines by C-N bond cleavage using a recyclable tungsten catalyst

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With H_2WO_4 as catalyst and H_2O_2 as oxidant, we herein report a deconstructive difunctionalization of C-N bond in unstrained, benzo cyclic amines to generate ester group and nitro group simulateously. The preliminary mechanistic studies suggested that the corresponding hydroxamic acid is the key intermediate for this transformation. Importantly, with the utilization of this transformation, we achieved an interesting approach for the ring contraction of quinoline to indole, an example of scaffold hopping in hetero-aromatic system.

Skeletal diversification of bioactive molecules is a robust tool for synthetic chemists in pharmaceutical industry.[1] Recently, a powerful synthetic strategy, deconstructive functionalization of saturated cyclic amine[2], has been developed to achieve some interesting skeletal diversification reactions[3] (Fig. 1). Importantly, the formation of hemi-aminal are the key step for these transformations. First, the oxidative cleavage of C(sp3)–C(sp3) single bond of hemi-aminal and sequential decarboxylative functionalization could install fluorine atom (Fig. 1a). Second, C-O bond, C-N bond, C-Cl bond and C-Br bond could be formed through the cleavage of C(sp3)–N single bond of hemi-aminal by White, Sarpong and other groups (Fig. 1b). Notably, on the basis of deconstructive diversification reaction, the ring contraction of piperidines to pyrrolidines could be accomplished efficiently by the Sarpong and co-workers[3f] (Fig. 1c), which is an example of scaffold hopping in medicinal chemistry[4]. Inspired by this work, we wondered if this synthetic strategy could be extended to aromatic system for achieving the ring contraction of quinoline[5] to indole[6] (Fig. 1d). The scaffold hopping between Pitavastatin and Fluvastatin is one of the most famous examples for drug discovery.

The reduction of quinolines could efficiently provide 1,2,3,4-tetrahydroquinolines,[7] which is an important moiety in modern organic synthesis and widely exists in natural products and bioactive molecules[8] (Fig. 2A). On the basis of our recent studies for selective oxidation of amines[9], we envisioned the deconstructive diversification of 1, 2, 3, 4-tetrahydro-quninolines with C-N bond cleavage could provide an opportunity to achieve the ring contraction of quinolines to indoles (Fig. 2B). The deconstructive functionalization of 1, 2, 3, 4-tetrahydroquinolines through the formation of hemi-aminal should be much more challenging than that of piperidines because of the following reasons: 1) tetrahydroisoquinoline-derived hemi-aminal gave lower concentration of the reactive aldehyde[10]; 2) the undesired aromatization pathway to generate thermally stable quinolines.[11] In order to conquer the these challenges, a new activation mode is needed.

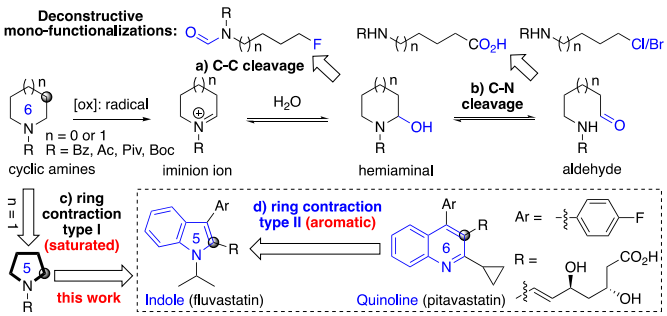

Figure 1. Reported deconstructive mono-functionalization of piperidine and further ring contraction.

With the formation of electrophilic tungsten peroxides from H_2O_2 and Na_2WO_4, Marahashi and co-workers reported the oxidation of 1, 2, 3, 4-tetrahydroquinolines to generate cyclic hydroxamic acids.[12] Inspired by their work, we believed that the usage of tungsten catalyst possessing proper structure ([W]) could not only avoid the aromatization pathway, but also further activate the C-N bond of hydroxamic acids[13] to generate ester and nitro group simultaneously (Fig. 2B). Moreover, this newly formed **6** could be further transformed into indoles using known methods including Baeyer-Emmerling indole synthesis.[14]

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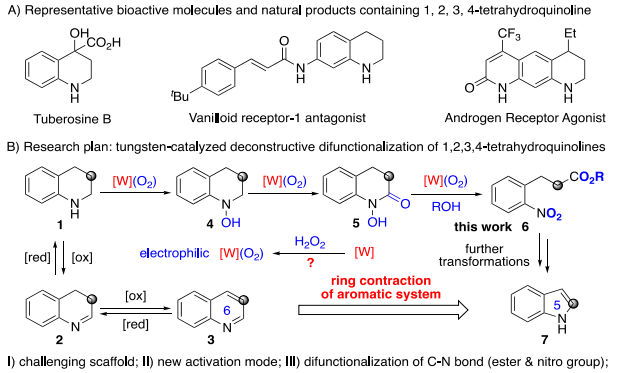
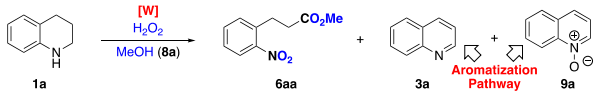


Figure 2. Hypothetic deconstructive di-functionalization of 1, 2, 3, 4-tetrahydroquinolines and further ring contraction.

We began our investigation by establishing the conditions for the desired transformation using 1, 2, 3, 4-tetrahydroquinolines and methanol as the starting materials. In preliminary experiment, the desired product **6aa** was obtained in 9% yield altogether with the undesired aromatization products (quinoline **3a** in 31% yield and quinoline *N*-oxide **9a** in 24% yield), when Na_2WO_4 was used as catalyst and H_2O_2 (50%, w/w) was used as oxidant (entry 1).

Table 1. Selected optimization experiments [a,b]

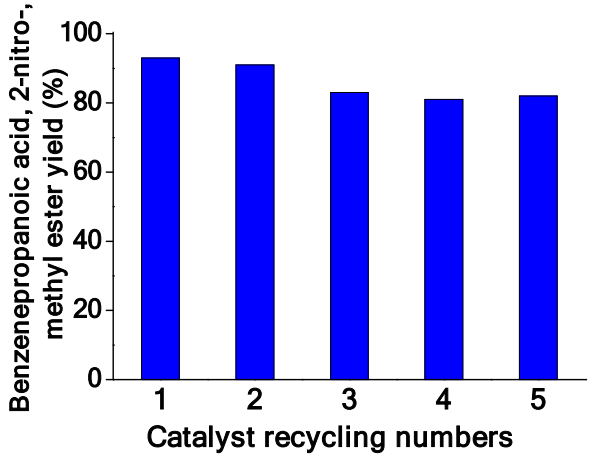


Entry	[W]	Yield (6aa)	Yield (3a)	Yield (9a)
1	Na_2WO_4	9%	31%	24%
2	$H_4[SiO_4(W_3O_9)]$• x H2O	4%	50%	29%
3	$Na_3PO4•12WO_3$• x H_2O	39%	12%	24%
4	$Na_2H_5[P\ (W_2O_7)_6]$	40%	14%	12%
5	H_3PO_4•12 WO_3• x H2O	33%	14%	31%
6	WO_3	11%	23%	14%
7	H_2WO_4	75%	9%	10%
8	H_3PO_4	trace	48%	17%
9[c]	H_2WO_4	46%	28%	15%
10[d]	H_2WO_4	83%	3%	2%
11[d,e]	H_2WO_4	94%[f]	3%	2%
12[g]	H_2WO_4	31%	23%	23%
13[h]	H_2WO_4	65%	14%	15%
14[i]	H_2WO_4	-	-	-

[a]Reaction conditions: 0.2 mmol (W, Mo, P) catalyst, (entries 1-3, 0.2mmol W), 0.5 mmol 1,2,3,4-tetrahydroquinoline, 5 mmol H_2O_2 (50%, w/w), 2 mL CH_3OH, 65 °C, 500 rps, 11 h. [b]The yields were determined by GC-FID with external standard method. [c]0.1 mmol catalyst. [d]0.4 mmol catalyst. [e]24 hours. [f]Isolated yield = 83%. [g]50 °C. [h]3 mmol H_2O_2. [i]Without H_2O_2.

The evaluation of tungsten catalysts showed that H_2WO_4 catalyzed the target transformation efficiently and **6aa** was obtained in 75% yield (entries 2-7). The good performance of H_2WO_4 might be attributed to the in-situ generation of $H_2[WO(O_2)_2(OH)_2]$ in the presence of H_2O_2.[15] Only trace amount of **6aa** were given, while H_3PO_4 was used as catalyst instead of H_2WO_4 (entry 8). With 20 mol % loading of H_2WO_4 (entry 9), the yield of **6aa** decreased to 46%. We identified the optimized conditions shown in entries 10 and 11, which used 80 mol % loading of H_2WO_4 at 65°C for 24 hours. The high loading of H_2WO_4 (80 mol%) should be needed to generate high enough concentration of $H_2[WO(O_2)_2(OH)_2]$ for the selective formation of **6aa**. Both reaction temperature and the amount of H_2O_2 were crucial to the efficiency of this reaction (entries 13 and 14).

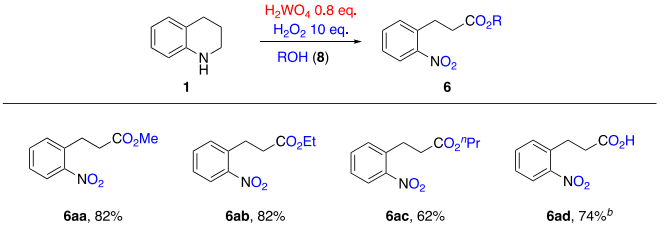
The recovery experiments were proceeded with several steps using a NEt_3-HNO_3 method16 (for more details, please see SI). The catalyst was reused for five times with **6aa** as substrate and the yields of the product were obtained in 94%, 91%, 83%, 81%, 82% respectively (Scheme 1).



Scheme 1. Recyclability of H_2WO_4

With optimal conditions in hand, we examined the substrate scope of alcohols in Table 2. Methanol, ethanol and propan-1-ol were competitive partners for this deconstructive difunctionalization reaction and provided **6aa** in 82% yield, **6ab** in 82% yield and 6ac in 62% yield, respectively. Interestingly, when tert-butanol was used, acid **6ad** was obtained in 74% yield instead of the corresponding ester. The product **6ad** might be generated from the further hydrolysis of the corresponding *tert*-butyl ester in acidic conditions[17].

Table 2. Substrate scope of alcohols [a]



[a]Reaction conditions: 0.4 mmol (W) catalyst, 0.5 mmol 1,2,3,4-tetrahydroquinoline, 5 mmol H_2O_2 (50%, w/w), 2 ml CH_3OH, 65 °C, 500 rps, 24h, isolated yields. [b]1.5 mmol H_2WO_4 and 15 ml ^{t}BuOH were used.

The data in Table 3 outlined the effects of varying the structure of 1, 2, 3, 4-tetrahydroquinolines. First of all, the potentially reactive C_{Ar}-Br bonds in different positions of benzene ring were tolerated in this tungsten-catalyzed deconstructive difunctionalization reaction, thus providing a

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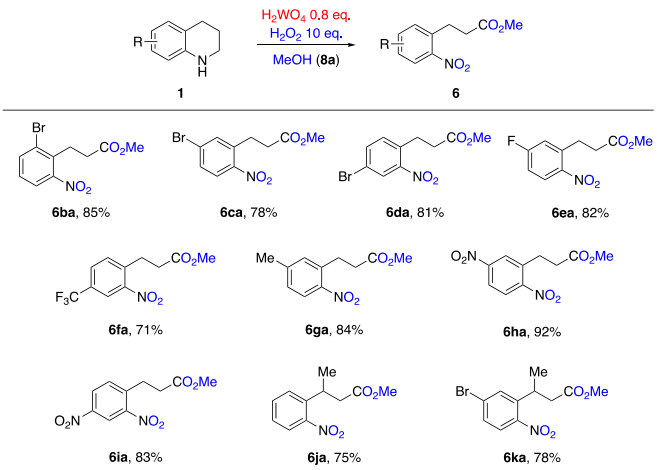
handle for the derivatization of **6ba**, **6ca** and **6da**. Moreover, the substitution of fluorine atom and trifluoromethyl group, which plays a very important role in drug industry[18], carried out the desired reaction effectively (**6ea** and **6fa**). A variety of electronically modified 1,2,3,4-tetrahydroquinolines still reacted efficiently (**6ga**, **6ha**, and **6ia**). Importantly, 4-methyl-1,2,3,4-tetrahydroquinolines carried out this transformation smoothly (**6ja-6ka**).

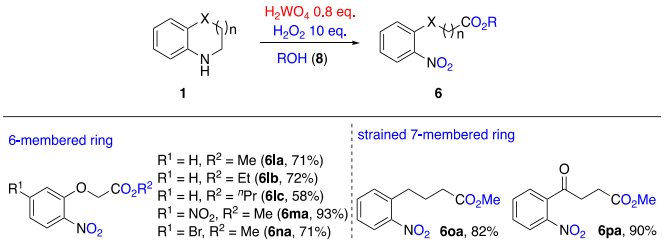
Table 3. Substrate scope of 1, 2, 3, 4-tetrahydroquinolines[a]



[a]Reaction conditions: 0.4 mmol H_2WO_4, 0.5 mmol 1, 2, 3, 4-tetrahydroquinoline, 5 mmol H_2O_2 (50%, w/w), 2 ml ROH, 65 °C, 500 rps, 24h, isolated yields.

On the other hand, we explored the substrate scope of other unstrained, benzo cyclic amines without the competitive aromatization pathway in Table 4. First, the 3,4-dihydro-2H-1,4-benzoxazines, which could not be oxidized to form stable aromatic rings, were also competent reaction partners, thus affording **6la**, **6lb**, **6lc, 6ma**, and **6na** in moderate to excellent yields. Second, the deconstructive difunctionalization of slightly strained seven-membered substrates provided **3oa** and **3pa** in good to excellent yields.

Table 4. Substrate scope of unstrained benzo cyclic amines without the competitive aromatization pathway [a]



[a]Reaction conditions: 0.4 mmol (W) catalyst, 0.5 mmol 1, 2, 3, 4-tetrahydroquinoline, 5 mmol (2 equiv.) H_2O_2 (50%, w/w), 2 ml ROH, 65 °C, 500 rps, 24h, isolated yields.

In order to identify the key intermediate of this transformation, quinoline (**3a**), quinoline N-oxide (**9a**), and 1-hydroxy-3,4-dihydroquinolin-2-(1H)-one (**5a**) were used as starting material in standard conditions. As shown in Figure 3, quinoline (**3a**) and quinoline N-oxide (**9a**) could not provide the desired **6aa** at all, while 1-hydroxy-3,4-dihydroquinolin-2-(1H)-one (**5a**) yielded **6aa** with 99% conversion and > 95% selectivity. Importantly, without the utilization of H_2WO_4, only 24% conversion was obtained, which indicated the H_2WO_4 could accelerate the ring opening process of **5a** dramatically.

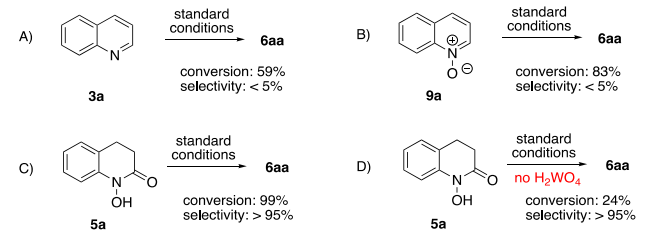


Figure 3. Exploring the reaction intermediates.

Furthermore, we monitored the standard reaction by GC-FID using external standard method. As shown in Figure 4, cyclic hydroxamic acid **5a** was observed and formed quickly in the first 3 hours. After 24 hours, compound **5a** was totally transformed into the desired product **6aa**. This reaction kinetic profile further illustrated that the cyclic hydroxamic acid **5a** was the key intermediate of the standard reaction.

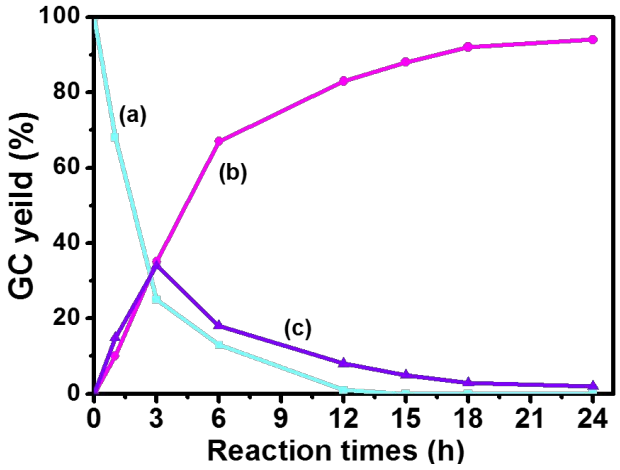
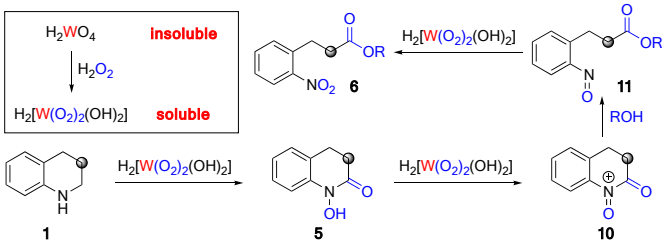


Figure 4. Monitoring the standard reaction: (a) **1a**, (b) **6aa** and (c) **5a**.

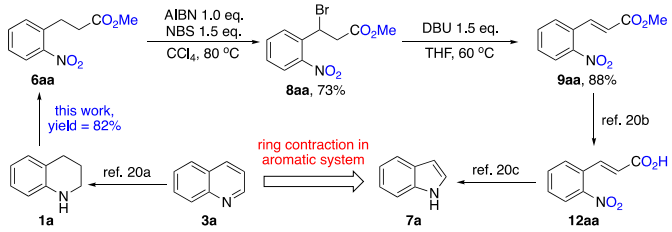
Based on the above experimental results and reported researches[10, 12, 13, 15], a plausible mechanism for this reaction was shown in Scheme 2. The active species $H_2[W(O_2)_2(OH)_2]$ formed in situ from the reaction of H_2WO_4 and H_2O_2. The oxidation of 1, 2, 3, 4-tetrahydro-quinolines **1** by $H_2[W(O_2)_2(OH)_2]$ yielded the key cyclic hydroxamic acids **5**. Further oxidation of **5** gave the oxoammonium **10**, which could



Scheme 2. Proposed Mechanism.

be attacked by alcohol to generate the ester **11**. After further oxidation, the desired product **6** could be produced finally.

Ring contraction, an example of molecule editing, plays an important role in medicinal chemistry[1, 4, 19]. As shown in Scheme 3, the ring contraction of quinolines to indoles was accomplished with the utilization of the reported reactions[20] and the following two new transformations: 1) the bromination of **6aa** providing the **8aa** in 73% yield; 2) Elimination of **8aa** yielding the key olefin **9aa** in the presence of base. On the other hand, **6aa** has been reported as a versatile intermediate in organic chemistry[21]. Moreover, the newly formed nitro group could be further transformed into other functional groups[22].



Scheme 3. Scaffold Hopping: Ring contraction of quinolines to indoles.

In summary, we developed an unprecedented deconstructive difunctionalization of the C–N bond in benzo cyclic amines to generate ester group and nitro group, respectively. Moreover, intermediates identification reactions and reaction kinetic study indicated that generating hydroxamic acid is assumed to be involved as a key step. Importantly, an interesting approach for the ring contraction of quinoline to indole was accomplished. Further development of this catalytic system is ongoing on our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 K. R. Campos, P. J. Coleman, J. C. Alvarez, S. D. Dreher, R. M. Garbaccio, N. K. Terrett, R. D. Tillyer, M. D. Truppo and E. R. Parmee, *Science*, 2019, **363**, 244-252.

2 A. Henninot, J. C. Collins and J. M. Nuss, *J. Med. Chem.*, 2017, **61**, 1382-1414.

3 (a) A. Shawcross and S. Stanforth, *J. Heterocycl. Chem.*, 1990, **27**, 367-369; (b) G. Han, M. C. McIntosh and S. M. Weinreb, *Tetrahedron Lett.*, 1994, **35**, 5813-5816; (c) R. Ito, N. Umezawa and T. Higuchi, *J. Am. Chem. Soc.*, 2005, **127**, 834-835; (d) M. Kaname, S. Yoshifuji and H. Sashida, *Tetrahedron Lett.*, 2008, **49**, 2786-2788; (e) T. J. Osberger, D. C. Rogness, J. T. Kohrt, A. F. Stepan and M. C. White, *Nature*, 2016, **537**, 214-219; (f) J. B. Roque, Y. Kuroda, L. T. Göttemann and R. Sarpong, *Nature*, 2018, **564**, 244-248; (g) J. B. Roque, Y. Kuroda, L. T. Göttemann and R. Sarpong, *Science*, 2018, **361**, 171-174.

4 (a) G. Schneider, W. Neidhart, T. Giller, G. Schmid, *Angew. Chem., Int. Ed.* 1999, **38**, 2894–2896; (b) Y. Hu, D. Stumpfe, J. Bajorath, *J. Med. Chem.* 2016, **59**, 4062−4076; (c) Y. Hu, D. Stumpfe, J. Bajorath, *J. Med. Chem.* 2017, **60**, 1238-1246.

5 (a) F. O'donnell, T. Smyth, V. Ramachandran and W. Smyth, *Int. J. Antimicrob. Ag.*, 2010, **35**, 30-38; (b) O. Afzal, S. Kumar, M. R. Haider, M. R. Ali, R. Kumar, M. Jaggi and S. Bawa, *Eur. J. Med. Chem.*, 2015, **97**, 871-910; (c) P. Y. Chung, Z. X. Bian, H. Y. Pun, D. Chan, A. S. C. Chan, C. H. Chui, J. C. O. Tang and K. H. Lam, *Future Med. Chem.*, 2015, **7**, 947-967.

6 (a) S. Ali, N. Ali, B. Ahmad Dar, V. Pradhan and M. Farooqui, *M. Chem. Rev.*, 2013, **13**, 1792-1800; (b) N. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. Kim, A. Verma and E. Choi, *Molecules*, 2013, **18**, 6620-6662; (c) S. Lancianesi, A. Palmieri and M. Petrini, *Chem. Rev.*, 2014, **114**, 7108-7149.

7 (a) W.-B. Wang, S. M. Lu, P. Y. Yang, X. W. Han and Y. G. Zhou, *J. Am. Chem. Soc.*, 2003, **125**, 10536-10537; (b) Y. G. Zhou, *Acc. Chem. Res.*, 2007, **40**, 1357-1366; (c) D. W. Wang, X. B. Wang, D. S. Wang, S. M. Lu, Y. G. Zhou and Y. X. Li, *J. Org. Chem.*, 2009, **74**, 2780-2787; (d) F. R. Gou, W. Li, X. Zhang and Y. M. Liang, *Adv. Synth. Catal.*, 2010, **352**, 2441-2444; (e) G. E. Dobereiner, A. Nova, N. D. Schley, N. Hazari, S. J. Miller, O. Eisenstein and R. H. Crabtree, *J. Am. Chem. Soc.*, 2011, **133**, 7547-7562.

8 V. Sridharan, P. A. Suryavanshi and J. C. Menéndez, *Chem. Rev.*, 2011, **111**, 7157-7259.

9 (a) X. Cui, F. Shi and Y. Deng, *Chem. Commun.*, 2012, **48**, 7586-7588; (b) X. Dai, J. Rabeah, H. Yuan, A. Brückner, X. Cui and F. Shi, *ChemSusChem*, 2016, **9**, 3133-3138; (c) Z. Ke, Y. Zhang, X. Cui and F. Shi, *Green Chem.*, 2016, **18**, 808-816; (d) Y. Zhang, S. Pang, Z. Wei, H. Jiao, X. Dai, H. Wang and F. Shi, *Nat. Commun.*, 2018, **9**, 1465-1474.

10 S.-L. Shi, X.-F. Wei, Y. Shimizu, M. Kanai, *J. Am. Chem. Soc.* 2012, **134**, 17019-17022.

11 (a) K. Kamata, J. Kasai, K. Yamaguchi and N. Mizuno, *Org. Lett.*, 2004, **6**, 3577-3580; (b) H. Choi and M. P. Doyle, *Chem. Commun.*, 2007, 745-747; (c) F. Li, J. Chen, Q. Zhang and Y. Wang, *Green Chem.*, 2008, **10**, 553-562; (d) K. Yamaguchi, J. W. Kim, J. He and N. Mizuno, *J. Catal.*, 2009, **268**, 343-349; (e) D. Ge, L. Hu, J. Wang, X. Li, F. Qi, J. Lu, X. Cao and H. Gu, *ChemCatChem*, 2013, **5**, 2183-2186; (f) S. Furukawa, A. Suga and T. Komatsu, *Chem. Commun.*, 2014, **50**, 3277-3280; (g) A. E. Wendlandt and S. S. Stahl, *J. Am. Chem. Soc.*, 2014, **136**, 11910-11913; (h) X. Cui, Y. Li, S. Bachmann, M. Scalone, A.-E. Surkus, K. Junge, C. Topf and M. Beller, *J. Am. Chem. Soc.*, 2015, **137**, 10652-10658; (i) D. V. Jawale, E. Gravel, N. Shah, V. Dauvois, H. Li, I. N. Namboothiri and E. Doris, *Chem. Eur. J.*, 2015, **21**, 7039-7042.

12 S. Murahashi, T. Oda, T. Sugahara and Y. Masui, *J. Org. Chem.*, 1990, **55**, 1744-1749.

13 (a) S. Prabhakar, A. M. Lobo, M. M. Marques, M. R. Tavares, *J. Chem. Res. (S),* 1985, 394-395; (b) R. Braslau *J. Org. Chem.* 1995, **60**, 6191-6193; (c) H. Lu, L. Kopcho, K. Ghosh, M. Witmer, M. Parker, S. Gupta, M. Paul, P. Krishnamurthy, B. Laksmaiah, D. Xie, J. Tredup, L. Zhang, L. M. Abell, *Anal. Biochem.* 2016, **501**, 56-65; (d) C. Yuan, B. Du, M.-M. Xun, B. Liu, *Tetrahedron*, 2017, **73,** 3622-3628.

14 A. Baeyer and A. Emmerling, *Ber Dtsch Chem Ges*, 1869, **2**, 679-682.

15 Y. Usui and K. Sato, *Green Chem.*, 2003, **5**, 373-375.

16 C. Ye, P. Jin, J. Liu, Y. Wen, H. Wei, X. Zheng, X. Wang and B. Li, *Ind. Eng. Chem. Res.*, 2013, **52**, 3600-3606.

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17 B. Li, M. Berliner, R. Buzon, C. K.-F. Chiu, S. T. Colgan, T. Kaneko, N. Keene, W. Kissel, T. Le, K. R. Leeman, B. Marquez, R. Morris, L. Newell, S. Wunderwald, M. Witt, J. Weaver, Z. Zhang, Z. Zhang, *J. Org. Chem.*, 2006, **71**, 9045-9050.
18 (a) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.*, 2014, **114**, 2432-2506; (b) K. Müller, C. Faeh, F. Diederich, *Science* 2007, **317**, 1881−1886; (c) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* 2011, **473**, 470−477.
19 Selected examples, see: (a) A. A. Nagel, J. Dibrino, L. A. Vincent, J. A. Retsema, *J. Med. Chem.* 1982, **25**, 881-884; (b) M. E. Kuehne, L. He, P. A. Jokiel, C. J. Pace, M. W. Fleck, I. M. Maisonneuve, S. D. Glick, J. M. Bidlack, *J. Med. Chem.* 2003, **46**, 2716-2730; (c) W. H. Jung, C. Harrison, Y. Shin, J.-H. Fournier, R. Balachandran, B. S. Raccor, R. P. Sikorski, A. Vogt, D. P. Curran, B. W. Day, *J. Med. Chem.* 2007, **50**, 2951-2966.
20 (a) H. Miyamura, A. Suzuki, T. Yasukawa and S. Kobayashi, *J. Am. Chem. Soc.*, 2018, **140**, 11325-11334; (b) A. K. Chakraborti, L. Sharma and M. K. Nayak, *J. Org. Chem.*, 2002, **67**, 2541-2547; (c) K. Yang, F. Zhou, Z. Kuang, G. Gao, T. G. Driver and Q. Song, *Org. Lett.*, 2016, **18**, 4088-4091.
21 (a) R. Coutts, D. Noble and D. Wibberley, *J. Pharm. Pharmacol.*, 1964, **16**, 773-778; (b) Y. Hashimoto, T. Ishizaki, K. Shudo and T. Okamoto, *Chem. Pharm. Bull.*, 1983, **31**, 3891-3896; (c) M. A. Cismesia, M. A. Ischay and T. P. Yoon, *Synthesis*, 2013, **45**, 2699-2705; (d) B. Egle, J. M. de Muñoz, N. Alonso, W. M. De Borggraeve, A. de la Hoz, A. Díaz-Ortiz and J. Alcázar, *J. Flow Chem.*, 2014, **4**, 22-25;
22 Selected synthetic utility of the nitro products, see: M. R. Yadav, M. Nagaoka, M. Kashihara, R.-L. Zhong, T. Miyazaki, S. Sakaki, Y. Nakao, *J. Am. Chem. Soc.* **2017**, *139*, 9423-9426.