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Carbene-Catalyzed Aerobic Oxidation of Isoquinolinium Salts: Efficient Synthesis of Isoquinolinones

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A mild and environmentally friendly carbene-catalyzed aerobic oxidation of isoquinolinium salts was successfully realized. Accordingly, a diverse set of isoquinolinones and phenanthridinones was efficiently prepared in good to excellent yields. The mechanistic study indicates that the formation of aza-Breslow intermediate is the crucial step in this transformation. This reaction features ambient air as the sole oxidant and oxygen source, a broad substrate scope, excellent functional-group tolerance and proceeds under mild reaction conditions. Furthermore, the highly efficient synthesis of bioactive molecules and natural products including N-mehtylcrinasiadine, N-isopentylcrinasiadine, N-phenethylcrinasiadine, isoindolo [2,1-*b*]isoquinolin-5(*7H*)-one, PJ-34, rac-Gusanlung D, rosettacin, 8-oxopseudopalmatine and ilicifoline B, was accomplished.

Introduction

As an important family of N-heterocycles, isoquinolinone is often presented as a core structural scaffold in numerous biological natural products and pharmaceuticals (Figure 1).[1] For example, 8-oxopseudopalmatine which was isolated from *Guatteria hispida* by the Costa group,[2] exhibits cytotoxic activity towards MDA-MB-231 cells. Significantly, this type of isoquinolinones shows stronger biological activities than the related isoquinoline.[3] Accordingly, several methods have been well addressed for the synthesis of isoquinolinones.[4] Among them, the oxidation of isoquinolinium salts, which were easily prepared from a variety of widespread isoquinolines with alkyl halides, is a particularly reliable and straightforward strategy. However, traditional oxidative methods require the employment of excess $K_3Fe(CN)_6$ as a reagent and cannot avoid generation of equivalents of toxic byproducts.[5] In contrast, mild, environmentally friendly oxidative methods are highly desirable and urgent to be developed. A particularly attractive approach was recently reported by Fu and co-workers,[6] who described a visible light-mediated radical process to form isoquinolinones using an organic photocatalyst and air as the sole oxidant. Owning to the importance of isoquinolinones, the development of conceptually new environmentally friendly synthetic strategies is still highly desirable.

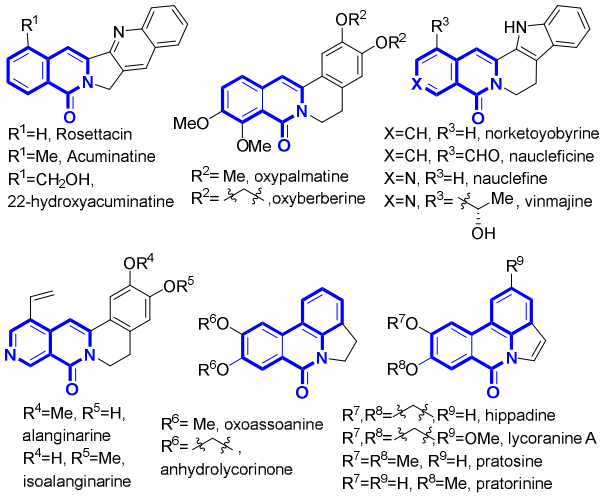

Figure 1 Some representative natural products containing isoquinolinones and phenanthridinones.

Over the past decade, N-heterocylic carbene (NHC) has been proven to be one of the most powerful organocatalysts in organic synthesis.[7] O_2 (or ambient air) is recognized as the ideal oxidant and oxygen source. Despite considerable advances heavily relying on transition metal catalysts, the use of O_2 in organocatalysis is still less explored.[8] Specifically, in organocatalysis by carbene, oxygenation of reactive substrates

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(such as aldehydes and enals) as the side reactions cannot be avoided when O_2 (or ambient air) was used as the oxidant, which significantly limited the use of O_2.[9] As a part of our ongoing interest in carbene catalysis,[10] we envisaged that a conceptually new aerobic oxidative strategy for isoquinolinones from new substrates isoquinolinium salts promoted by carbene might be achieved. The carbene should be able to attack the isoquinolinium salt to form an aza-Breslow intermediate[10a,11] via deprotonation. And following aerobic oxidation by ambient air might furnish isoquinonlinone and regenerate carbene. We herein firstly describe a mild, environmentally friendly carbene-catalyzed aerobic oxidation of isoquinolinium salts. Notably, ambient air was used as the sole oxidant and oxygen source under mild conditions in this organocatalyzed reaction. Accordingly, a diverse set of isoquinolinones and phenanthridinones was efficiently prepared. Furthermore, many related bioactive molecules and natural products, including N-mehtylcrinasiadine, N-isopentylcrinasiadine, N-phenethylcrinasiadine, isoindolo [2,1-*b*]isoquinolin-5(7*H*)-one, PJ-34, rosettacin, rac-Gusanlung D, 8-oxopseudopalmatine and ilicifoline B, could be efficiently constructed by this flexible strategy.

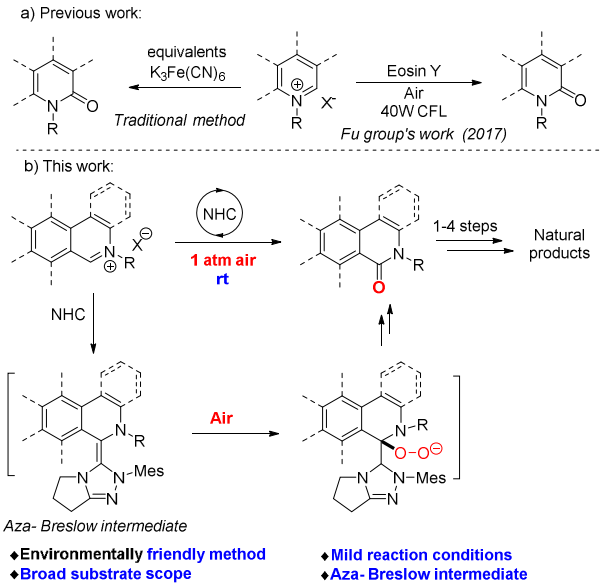
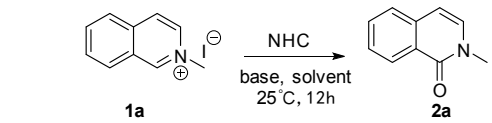


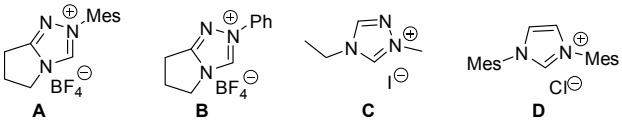
Figure 2 Some representative oxidative approaches.

Results and discussion

We began our investigation by selecting 2-methylisoquinolin-2-ium iodide **1a** as a model isoquinolinium salt. The key results of our initial studies and optimization of the reaction conditions are summarized in Table 1. To our delight, the desired isoquinolinone **2a** was obtained in nearly quantitative yield when the achiral triazolium N-Mes pre-catalyst **A** was used with DBU as a base in THF under an air atmosphere at room temperature (entry 1). Other NHC pre-catalyst (including triazolium N-Ph pre-catalyst **B**, triazolium pre-catalyst N-Me **C** and imidazolium pre-catalyst N-Mes **D**) could also realize this transformation, albeit with comparatively lower efficiency (entries 2-4). Several bases were next evaluated and DBU proved to be the most effective choice (entries 5-9). Subsequent solvent screening revealed that THF was the most effective (entries 10-14). Gratifyingly, lowering the catalyst loading to 10 mol % decreased the product yield only slightly (entry 15). Reducing the amount of base decreased the product yield considerably (entry 16). Without NHC, only 24% yield of **2a** was achieved when DBU was used as base (entry 17).

Table 1. Optimization of reaction conditions[a]





Entry[a]	NHC	base	solvent	Yield(%)[b]
1	A	DBU	THF	99
2	B	DBU	THF	56
3	C	DBU	THF	83
4	D	DBU	THF	43
5	A	K_2CO_3	THF	98
6	A	KO^{t}Bu	THF	79
7	A	Cs_2CO_3	THF	97
8	A	Et_3N	THF	N.R.
9	A	NaOAc	THF	N.R.
10	A	DBU	DMF	82
11	A	DBU	CH_3CN	88
12	A	DBU	MeOH	40
13	A	DBU	1,4-dioxane	95
14	A	DBU	toluene	89
15[c]	A	DBU	THF	96
16[d]	A	DBU	THF	61
17*e*	-	DBU	THF	24
18[e,f]	-	DBU	THF	N.R.
19[c,f]	A	DBU	THF	97
20[e]	-	K_2CO_3	THF	N.R.
21[g]	A	DBU	THF	N.R.

[a] Reaction conditions: NHC (15 mol%), **1a** (0.2 mmol, 1.0 equiv), base (1.5 equiv), solvent (0.1 M), under air atmosphere, 25℃, 12 h. [b] Isolated yields after column chromatography. [c] 10 mol % of NHC was used. [d] 0.5 equiv of base was used. [e] Without NHC. [f] Under dark conditions. [g] Under nitrogen atmosphere.

Notably, no desired product was found under dark conditions (entry 18). These results indicate that sun light slightly influences this transformation when DBU was used as the base and in the absence of NHC. Comparatively, no desired product was found by using K_2CO_3 as the base and in the absence of NHC (entry 20). Further experiment was performed under the same conditions with entry 15 except in dark, the desired

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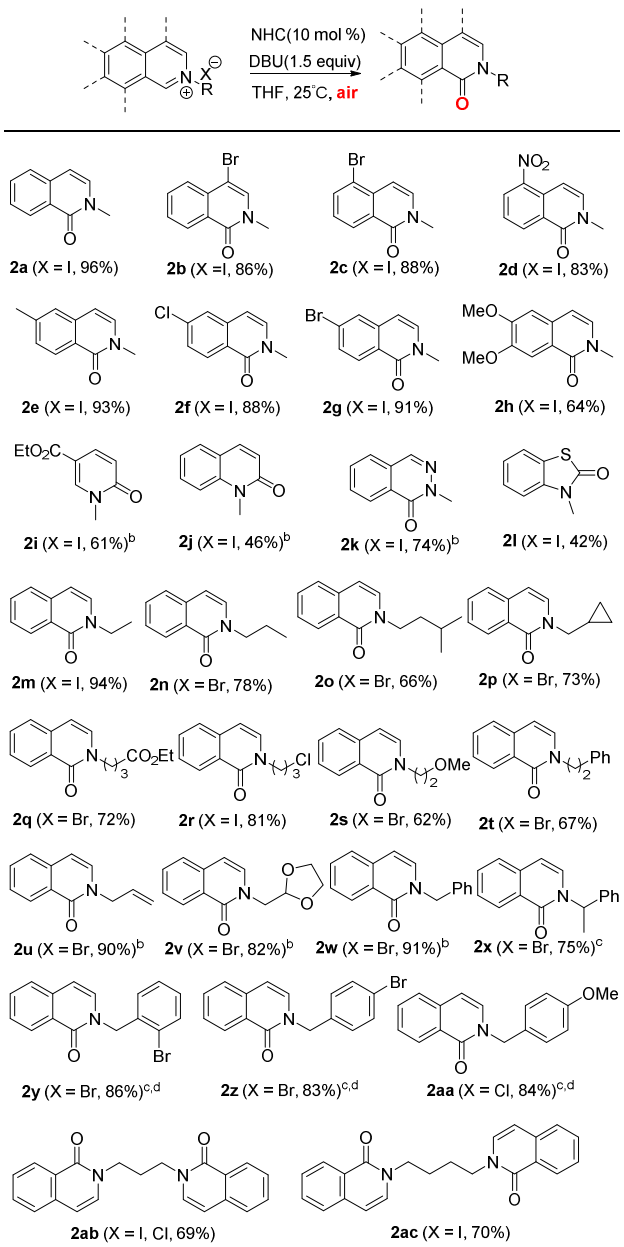
product **2a** was obtained without any loss yield (entry 19). When the reaction was performed under a nitrogen atmosphere, rather than air, none of the desired isoquinolinone **2a** was formed (entry 21).

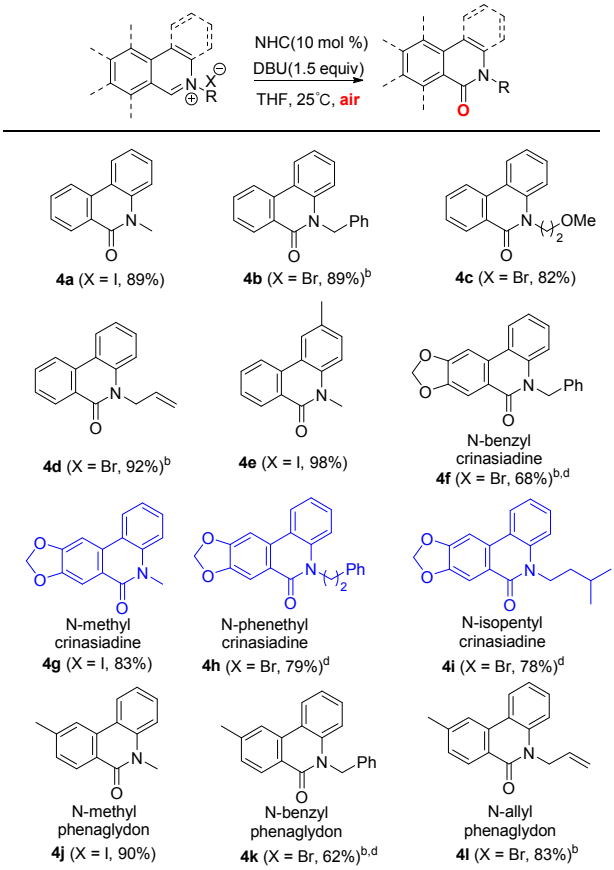
Table 2. Reaction Scope[a]



[a] Reaction conditions as in Table 1, entry15; yields (after SiO_2 chromatography purification) were based on imnium salts **1**. [b] Reaction temperature -10 ℃. [c] Reaction temperature -40 ℃. [d] 20 mol % NHC **A** was used.

With acceptable optimized conditions in hand (Table 1, entry 15), we next evaluated the scope of the reaction for isoquinolinium salts **1** as substrates (Table 2). For a range of substituents at the 4, 5, 6 and 7 positions on the isoquinoline ring, the reactions proceeded smoothly and led to the formation of the corresponding diverse isoquinolinone products (**2a-h**) in good to excellent yields. Phthalazine and benzo[d]thiazole-derived iminium salts were also tested and afforded the corresponding products (**2k** & **2l**) in acceptable yields. Pyridinium and quinolinium salts also are suitable substrates for this transformation (**2i** & **2j**). Isoquinolinium salts with a series of N-alkyl groups also worked efficiently as well (**2m**-**2aa**). Pleasingly, ether, NO_2, ester, halide, acetal group, three-membered rings, and double and triple bonds were well-tolerated. Two isoquinolinium moieties in one molecule also worked well (**2ab** & **2ac**).

Table 3. Reaction Scope[a]



Note: **4g**-**i** are natural products.

[a] Reaction conditions as in Table 1, entry15; yields (after SiO_2 chromatography purification) were based on imnium salts **3**. [b] Reaction temperature -10 ℃ [c] Reaction temperature -40 ℃ [d] 20 mol % NHC **A** was used.

We then extended our strategy to the synthesis of phenanthridinones **4**, which are widely found in natural products and bioactive molecules,[12] from the corresponding phenanthridinium salts. Not surprisingly, all reactions proceeded smoothly and led to formation of the desired phenanthridinones **4** in good to excellent yields under optimal conditions (Table 3). In particular, the natural products N-methyl crinasiadine **4g**, N-phenethyl crinasiadine **4h** and N-

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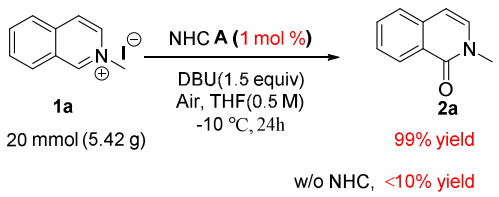
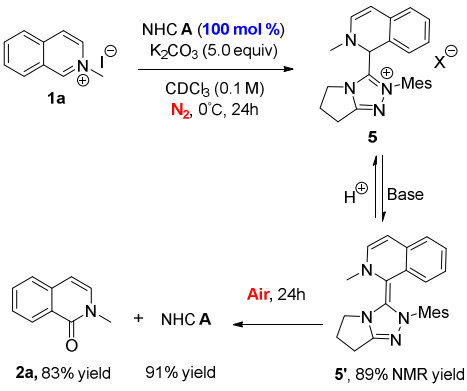
isopentyl crinasiadine **4i** could be easily constructed by our strategy under mild conditions.

To show the practicality of our method, a gram-scale reaction was carried out (Scheme 1). In the presence of only 1 mol % of NHC pre-catalyst **A**, a 5-gram scale reaction of 2-methylisoquinolin-2-ium iodide **1a** worked very well and afforded 2-methylisoquinolin-1(2H)-one **2a** in up to 99% yield. In contrast, without NHC, **2a** was obtained in less than 10% yield.



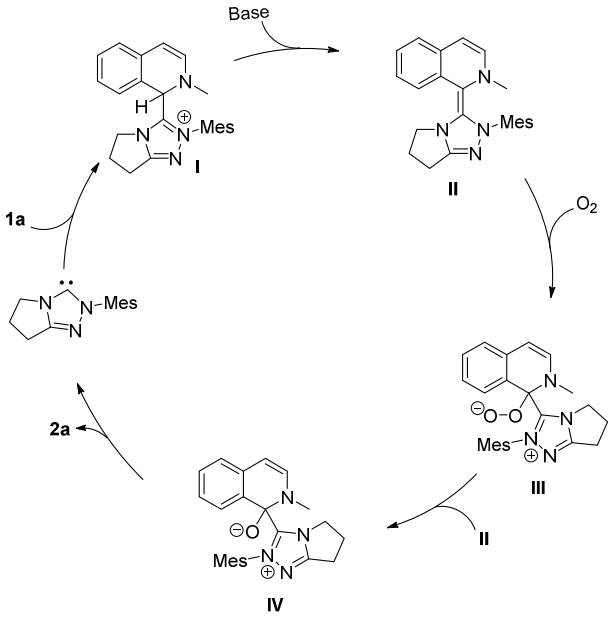
Scheme 1 Gram-scale reaction.

To probe the reaction pathway, the control experiments were performed as shown in Scheme 2. Gratifyingly, when the isoquinolinium salts **1a** was treated with 1 equivalent of NHC **A** in presence of K_2CO_3 in $CDCl_3$ under nitrogen atmosphere at room temperature, expected aza-Breslow intermediate **5'** via deprotonation of intermediate **5** was successfully captured in 89% NMR yield. And the structure of **5** was confirmed by ^1H NMR, ^{13}C NMR, HRMS and 2D NMR (for details, please see supporting information). Furthermore, in the presence of ambient air at room temperature, the aza-Breslow intermediate **5'** was converted to **2a** in 83% yield and regenerated NHC **A** in 91% yield. These results indicate that our transformation proceeded through an aza-Breslow intermediate.



Scheme 2 Mechanistic study. 1, 3, 5-trimethoxybenzene was used as internal standard.

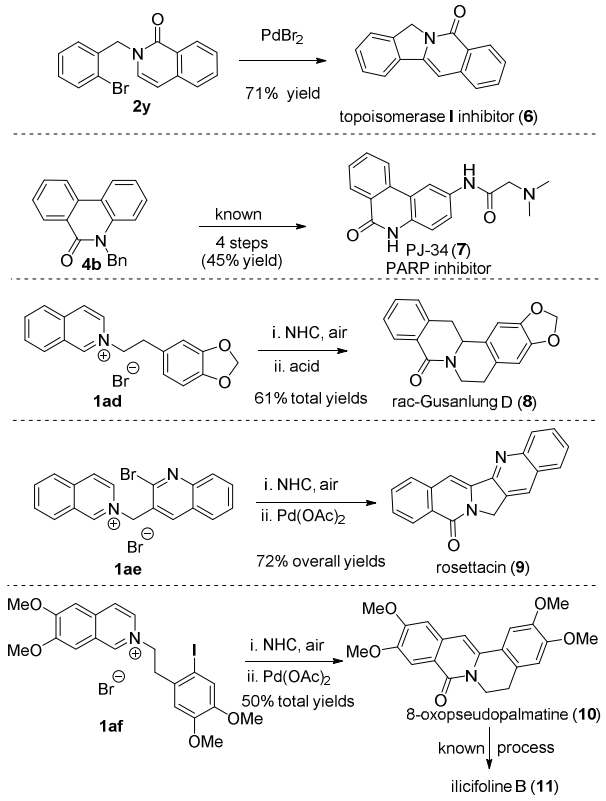
Based on previous work and the current results, a proposed reaction pathway for the formation of isoquinolinones from isoquinoline-derived iminium salts under aerobic oxidative NHC catalysis is illustrated in Scheme 3. The addition of NHC to 2-methylisoquinolin-2-ium iodide **1a** produces the NHC-bound intermediate **I**, which undergoes deprotonation to give the aza-Breslow intermediate **II** (Rovis group.).[12b] Single electron transfer of the aza-Breslow intermediate **II** with dioxygen, followed by radical recombination generates intermediate **III**.[13] Further another aza Breslow intermediate **II**, which might act as the reducing reagent, reacts with intermediate **III** to lead to the formation of intermediate **IV**.[14] Finally, intermediate **IV** forms two molecules **2a** and regenerates of the free carbene.



Scheme 3 Proposed mechanism.

With this efficient route to isoquinolinones in hand, we next turned our attention to the synthetic utility of these compounds (Scheme 4). Involving the carbene-catalyzed umpolung of iminium salts followed by ambient air oxidation as the key steps, several bioactive molecules and natural products were efficiently synthesized via 1-4 steps. Specifically, an obtained isoquinolinone **2y** was easily converted to the topoisomerase **I** inhibitor isoindolo [2,1-*b*]isoquinolin-5(*7H*)-one **6** in up to 82% yield (the highest yield so far)[15] via a Pd-catalzyed intramolecular cyclization. N-benzyl phenanthridinone **4b** was easily transformed to the PARP inhibitor PJ-34 **7** via a known process.[16] Rac-Gusanlung D **8** was also obtained from isoquinolinium salts **1ad** via our aerobic oxidative strategy and then acid-mediated intramolecular cyclization.[17] The natural product rosettacin **9** was synthesized from the isoquinolin-2-ium salt **1ae** via a two-step process in 72 total yields using our NHC-catalyzed aerobic oxidative reaction followed by a Pd-catalyzed intramolecular cyclization. 8-oxopseudopalmatine **10**, a natural product with promising biological activities, also could be formed in 50% overall yield via our NHC-catalyzed umpolung method followed a known Pd-catalyzed cyclization process.[18] Furthermore, oxidation of

8-oxopseudopalmatine **10** provided ilicifoline B **11** via a known process.[19]



Scheme 4 Synthetic transformations of isoquinolinones.

Conclusions

In summary, we have successfully developed a mild and environmentally friendly carbene-catalyzed aerobic oxidative method for the facile synthesis of a diverse set of isoquinolinones and phenanthridinones with good to excellent yields. The umpolung of isoquinolinium salts enabled by carbene as the crucial step was involved in this transformation and witnessed by mechanistic study. Significantly, ambient air as the sole oxidant and oxygen source was efficiently used in carbene-catalyzed reactions. This reaction features a broad substrate scope, excellent functional-group tolerance, and proceeds under mild conditions. And this transformation can be easily scaled-up. Furthermore, this strategy enabled the highly efficient synthesis of many bioactive molecules and natural products including N-mehtylcrinasiadine, N-isopentylcrinasiadine, N-phenethylcrinasiadine, isoindolo [2,1-*b*]isoquinolin-5(7*H*)-one, PJ-34, rosettacin, rac-Gusanlung D, 8-oxopseudopalmatine and ilicifoline B. This economical and environment-friendly approach may be applied to other types of NHC-activated iminium salt reactions and further investigations are ongoing in our laboratory.

Acknowledgements

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Notes and references

1 (a) M. C. Gonzalez, M. C. Zafra-Polo, A. Blazquez, A. Serrano and D. J. Cortes, *Nat. Prod.,* 1997, **60**, 108; (b) V. A. Glushkov and Y. V. Shklyaev, *Chem. Heterocycl. Compd.,* 2001, **37**, 663; (c) F. Coelho, D. Veronese, E. C. S. Lopes and R. C. Rossi, *Tetrahedron Lett.,* 2003, **44**, 5731; (d) M. Nagarajan, A. Morrell, B. C. Fort, M. R. Meckley, S. Antony, G. Kohlhagen, Y. Pommier and M. Cushman, *J. Med. Chem.,* 2004, **47**, 5651; (e) A. Cappelli, G. Pericot Mohr, G. Giuliani, S. Galeazzi, M. Anzini, L. Mennuni, F. Ferrari, F. Makovec, E. M. Kleinrath, T. Langer, M. Valoti, G. Giorgi and S. Vomero, *J. Med. Chem.,* 2006, **49**, 6451; (f) A. Saeed and Z. Ashraf, *Pharm. Chem. J.,* 2008, **42**, 277; (g) G. R. Pettit, S. Ducki, S. A. Eastham and N. J. Melody, *J. Nat. Prod.,* 2009, **72**, 1279; (h) D. B. Khadka and W.-J. Cho, *Bioorg. Med. Chem.*, 2011, **19**, 724; (i) D. B. Khadka, S. H. Yang, S. H. Cho, C. Zhao and W. -J. Cho, *Tetrahedron,* 2012, **68**, 250; (j) Z. Jin, *Nat. Prod. Rep.,* 2013, **30**, 849.

2 E. V. Costa, M. L. B. Pinheiro, A. Barison, F. R. Campos, M. J. Salvador, B. H. L. N. S. Maia, E. C. Cabral and M. N. Eberlin, *J. Nat. Prod.,* 2010, **73**, 1180.

3 D. Stubba, G. Lahm, M. Geffe, J. W. Runyon, A. J. Arduengo III and T. Opatz, *Angew. Chem. Int. Ed.,* 2015, **54**, 14187.

4 For selected examples, see: (a) G. Song, F. Wang and X. Li, *Chem. Soc. Rev.,* 2012, **41**, 3651; (b) F. W. Patureau, J. Wencel-Delord and F. Glorius, *Aldrichimica Acta.,* 2012, **45**, 31; (c) P. G. Jagtap, E. Baloglu, G. Southan, W. Williams, A. Roy, A. Nivorozhkin, N. Landrau, K. Desisto, A. L. Salzman and C. Szabo, *Org. Lett.,* 2005, **7**, 1753; (d) J. F. Guastavino, S. M. Barolo and R. A. Rossi, *Eur. J. Org. Chem.,* 2006, **2006**, 3898; (e) Z. Zheng and H. Alper, *Org. Lett.,* 2008, **10**, 4903; (f) J. Lu, X. Gong, H. Yang and H. Fu, *Chem. Commun.,* 2010, **46**, 4172; (g) C. C. Liu, K. Parthasarathy and C. H. Cheng, *Org. Lett.,* 2010, **12**, 3518; (h) N. Guimond, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.,* 2011, **133**, 6449; (i) K. Li, J. J. Ou and S. H. Gao, *Angew. Chem. Int. Ed.,* 2016, **55**, 14778.

5 For selected examples, see: (a)T. Ishi-i, R. Hirashima, N. Tsutsumi, S. Amemori, S. Matsuki, Y. Teshima, R. Kuwahara and S. Mataka, *J. Org. Chem.,* 2010, **75**, 6858; (b) I. M. Khalil, D. Barker and B. R. Copp, *J. Org. Chem.,* 2016, **81**, 282; (c) T. -T. Fan-Chiang, H. -K. Wang and J. -C. Hsieh, *Tetrahedron*, 2016, **72**, 5640.

6 Y. Jin, L. Ou, H. Yang and H. Fu, *J. Am. Chem. Soc.,* 2017, **139**, 14237.

7 For selected reviews on NHC asymmetric catalysis, see: (a) D. Enders and T. Balensiefer, *Acc. Chem. Res.,* 2004, **37**, 534; (b) K. Zeitler, *Angew. Chem. Int. Ed.,* 2005, **44**, 7506; (c) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.,* 2007, **107**, 5606; (d) J. L. Moore and T. Rovis, *Top. Curr. Chem.,* 2010,

View Article Online
DOI: 10.1039/C8GC01488D

291, 77; (e) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose and V. Sreekumar, *Chem. Soc. Rev.,* 2011, **40**, 5336; (f) J. Douglas, G. Churchill and A. D. Smith, *Synthesis.,* 2012, **44**, 2295; (g) S. J. Ryan, L. Candish and D. W. Lupton, *Chem. Soc. Rev.,* 2013, **42**, 4906; (h) S. D. Sarkar, A. Biswas, R. C. Samanta and A. Studer, *Chem. Eur. J.,* 2013, **19**, 4664; (i) M. N. Hopkinson, C. Richter, M. Schedler and F. Glorius, *Nature*, 2014, **510**, 485; (j) D. M. Flanigan, F. RomanovMichailidis, N. A. White and T. Rovis, *Chem. Rev.,* 2015, **115**, 9307; (k) M. H. Wang and K. A. Scheidt, *Angew. Chem. Int. Ed.,* 2016, **55**, 14912; (l) C. Zhang, J. F. Hooper and D. W. Lupton, *ACS Catal.,* 2017, **7**, 2583.

8 For selected examples, see: (a) S. -J. Jeon and P. J. Walsh, *J. Am. Chem. Soc.,* 2003, **125**, 9544; (b) D. R. Jensen, M. J. Schultz, J. A. Mueller and M. S. Sigman, *Angew. Chem. Int. Ed.,* 2003, **42**, 3810; (c) A. E. Lurain, A. Maestri, A. R. Kelli, P. J. Carroll and P. J. Walsh, *J. Am. Chem. Soc.,* 2004, **126**, 13608; (d) T. Punniyamurthy, S. Velusamy and J. Iqbal, *Chem. Rev.,* 2005, **105**, 2329; (e) M. S. Sigman and D. R. Jensen, *Acc. Chem. Res*., 2006, **39**, 221; (f) T. Hamada, X. Ye and S. S. Stahl, *J. Am. Chem. Soc.,* 2008, **130**, 833; (g) K. M. Gligorich and M. S. Sigman, *Chem. Commun.,* 2009, 3854; (h) C. Zhang, and N. Jiao, *J. Am. Chem. Soc.,* 2010, **132**, 28; (i) Y. Izawa, D. Pun and S. S. Stahl, *Science*, 2011, **333**, 209; (j) Y. Wei, I. Deb and N. Yoshikai, *J. Am. Chem. Soc.,* 2012, **134**, 9098; (k) Z. Shi, C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.,* 2012, **41**, 3381; (l) Z. Chen, B. Lu, Z. Ding, K. Gao and N. Yoshikai, *Org. Lett.,* 2013, **15**, 1966; (m) X. Huang, X. Li, M. Zou, S. Song, C. Tang, Y. Yuan and N. Jiao, *J. Am. Chem. Soc.,* 2014, **136**, 14858; (n) T.-S. Mei, E. W. Werner, A. J. Burckle and M. S. Sigman, *J. Am. Chem. Soc.,* 2013, **135**, 6830; (o) A. E. Wendlandt and S. S. Stahl, *J. Am. Chem. Soc.,* 2014, **136**, 11910; (p) S. Song, Y. Zhang, A. Yeerlan, B. Zhu, J. Liu and N. Jiao, *Angew. Chem. Int. Ed.,* 2017, **56**, 2487; (q) D. S. Mannel, M. S. Ahmed, T. W. Root and S. S. Stahl, *J. Am. Chem. Soc.,* 2017, **139**, 1690.

9 (a) R. S. Reddy, J. N. Rosa, L. F. Veiros, S. Caddick and P. M. P. Gois, *Org. Biomol. Chem.,* 2011, **9**, 3126; (b) J. Zhao, C. MückLichtenfeld and A. Studer, *Adv. Synth. Catal.,* 2013, **355**, 1098; (c) I. N. C. Kiran, K. Lalwani and A. Sudalai, *RSC Adv.,* 2013, **3**, 1695; (d) R. N. Reddi, P. V. Malekar and A. Sudalai, *Tetrahedron Lett.,* 2013, **54**, 2679; (e) E. G. Delany, C.-L. Fagan, S. Gundala, A. Mari, T. Broja, K. Zeitler and S. J. Connon, *Chem. Commun*., 2013. **49**, 6510; (f) E. G. Delany, C.-L. Fagan, S. Gundala, K. Zeitler and S. J. Connon, *Chem. Commun.,* 2013, **49**, 6513; (g) L. Ta, A. Axelsson and H. Sundén, *Green Chem.,* 2016, **18**, 686; (h) D. Xie, D. Shen, Q. Chen, J. Zhou, X. Zeng and G. Zhong, *J. Org. Chem.,* 2016, **81**, 6136.

10 (a) G. J. Wang, Z. Q. Fu and W. Huang, *Org. Lett.,* 2017, **19**, 3362; (b) Y. R. Gao, Y. F. Ma, C. Xu, L. Li, T. J. Yang, G. Q. Sima, Z. Q. Fu and W. Huang, *Adv. Synth. Catal.,* 2018, **360**, 479; (c) Y. X. Zhang, J. Huang, Y. Y. Guo, L. Li, Z. Q. Fu and W. Huang, *Angew. Chem. Int. Ed.,* 2018, **57**, 4594.

11 (a) S. Simonovic, J. C. Frison, H. Koyuncu, H. Koyuncu, A. C. Whitwoodand and R. E. Douthwaite, *Org. Lett.,* 2009, **11**, 245; (b) D. A. DiRocco, K. M. Oberg and T. Rovis, *J. Am. Chem. Soc.,* 2012, **134**, 6143; (c) A. Patra, S. Mukherjee, T. K. Das, S. Jain, R. G. Gonnade and A. T. Biju, *Angew. Chem. Int. Ed.;* 2017, **56**, 2730; (d) A. atra, F. Gelat, X. Pannecoucke, T. Poisson, T. Besset and A. T. Biju, *Org. Lett.,* 2018, **20**, 1086.

12 For selected examples, see: (a) S. Patil, S. Kamath, T. Sanchez, N. Neamati, R. F. Schinazi and J. K. Buolamwini, *Bioorg. Med. Chem.,* 2007, **15**, 1212; (b) A. Aldinucci, G. Gerlini, S. Fossati, C. Cipriani, T. Ballerini, N. Biagioli, L. Pimpinelli, L. Borgognoni, G. Massacesi, F. Moroni and A. Chiarugi, *J. Immunol.,* 2007, **179**, 305; (c) Z. Jin, *Nat. Prod. Rep.,* 2009, **26**, 363; (d) D. C. Hegan, Y. -H. Lu, G. C. Stachelek, M. E. Crosby, R. S. Bindra and P. M. Glazer, *Proc. Natl. Acad. Sci. U. S. A.,* 2010, **107**, 2201; (e) S. E. Nasrabady, A. Kuzhandaivel, M. Mladinic and A. Nistri, *Cell. Mol. Neurobiol.,* 2011, **31**, 503.

13 O. Bortolini, C. Chiappe, M. Fogagnolo, A. Massi and C. S. Pomelli, *J. Org. Chem.,* 2017, **82**, 302.

14 Y. K. Liu, R. Li, L. Yue, B. J. Li, Y. C. Chen, Y. Wu and L. S. Ding, *Org. Lett.,* 2006, **8** , 1521.

15 For selected examples, see: (a) J. C. Godfrey, *J. Org. Chem.,* 1959, **24**, 581; (b) H. T. M. Van and W. -J. Cho, *Bioorg. Med. Chem. Lett.;* 2009, **19**, 2551; (c) L. El Blidi, A. Namoune, A. Bridoux, V. D. Nimbarte, A. M. Lawson, S. Comesse and A. Daich, *Synthesis,* 2015, **47**, 3583.

16 (a) R. Bernini, S. Cacchi, G. Fabrizi, A. Sferrazza, *Synthesis,* 2008, **2008**, 729; (b) Z. Liang, J. Zhang, Z. Liu, K. Wang, Y. Zhang, *Tetrahedron*, 2013, **69**, 6519.

17 P. B. Wakchaure, S. Easwar, N. P. Argade, *Synthesis,* 2009, **2009**, 1667.

18 A. Chen, K. Zhao, H. Zhang, X. Gan, M. Lei and L. Hu, *Monatsh. Chem.,* 2012, **143**, 825.

19 H. Tohma, M. Iwata, T. Maegawa and Y. Kita, *Tetrahedron Lett.,* 2002, **43**, 9241.

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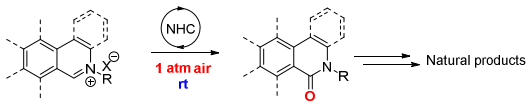
Graphic Abstract



♦Environmentally friendly method ♦Mild reaction conditions
♦Broad substrate scope ♦Aza- Breslow intermediate

A mild and environmentally friendly carbene-catalyzed aerobic oxidation of isoquinolinium salts was successfully realized.