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## Radical-mediated remote migration of quinoxalinones†

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Disclosed herein is the first example of radical-mediated remote migration of quinoxalinones. The quinoxalinonyl-functionalization of alkenes employs the quinoxalinone-substituted tertiary bishomoallylic alcohols as substrates, proceeds through intramolecular 1,4-quinoxalinone migration, and gives rise to complex  $\gamma$ -quinoxalinone-substituted aliphatic ketones. A set of external radicals is compatible with this method. The protocol features broad tolerance of functional groups, good adaptability to various external radicals and high product diversity, and opens a new door for the synthesis of quinoxalinone derivatives.

Nitrogen-containing heteroarenes are extensively present in natural products and drug molecules,<sup>1</sup> among which quinoxalinone often serves as the pharmacophore of bioactive compounds. For instance, they are widely exploited in anti-tumour and anti-bacteria agents, HIV-1 reverse transcriptase inhibitors, anticoagulants, and hypoglycaemic agents (Scheme 1A).<sup>2</sup> In view of broad prospects in application, the preparation of quinoxalinone derivatives has attracted great attention over the past few years.<sup>3</sup> The most common approaches rely on the Minisci reaction by adding various alkyl radicals to the parent quinoxalinone.<sup>4</sup> Alkenes are easily available and can act as the precursor of alkyl radicals that engage in the Minisci reaction.<sup>5</sup> Nevertheless, this approach is generally limited to activated alkenes, in particular styrene derivatives which only generate benzyl radicals in the reaction.

Remote functional group migration (FGM) provides an efficient strategy for the transformations of unactivated alkenes.<sup>6</sup> We

and others have comprehensively investigated the FGM reactions, where a portfolio of functional groups including aryls,<sup>7</sup> heteroaryls,<sup>8</sup> cyano,<sup>9</sup> alkynyl,<sup>10</sup> alkenyl,<sup>11</sup> oximino,<sup>12</sup> and carbonyl,<sup>12a,13</sup> showcase excellent migratory aptitudes (Scheme 1B). We conceive to study the migration of quinoxalinones and apply it to the construction of complex quinoxalinone derivatives. While the migration of several azaarenes, such as (benzo)thiazole, (benz)oxazole, (benz)imidazole, pyridine, quinoline, and pyrimidine, has been well established, the migrating behavior of quinoxalinone remains unaddressed.

Herein, we provide proof-of-principle studies for radical-mediated remote migration of quinoxalinones (Scheme 1C). The transformation employs strategically designed quinoxalinone-substituted tertiary bishomoallylic alcohols as substrates, which are conveniently accessed in two steps, the Minisci-type reaction

### A. Bioactive molecules containing quinoxalinone moiety



### B. State-of-the-art of remote functional group migration



### C. This work: remote migration of quinoxalinones



**Scheme 1** Importance of quinoxalinone derivatives and the preparation via remote migration of quinoxalinone.

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Other types of external radicals instead of sulfonyl radicals that triggered the migration reaction were explored, to assess the generality of the protocol (Scheme 3). Trifluoromethyl radicals derived from Togni's reagent in the presence of catalytic CuI readily added to the substrates, leading to the trifluoromethylation products in modest to high yields (Schemes 3A, 3a–3f). Likewise, changing the substitution of tertiary alcohols **1** did not impede the desired transformations. The reaction of **1a** with difluoroalkyl and monofluoroalkyl radicals generated under photochemical conditions smoothly proceeded to give the corresponding products in good yields



**Scheme 3** Assessment of external radicals. (A) Reaction conditions: **1** (0.2 mmol), Togni's reagent II (0.4 mmol, 2.0 equiv.), CuI (20 mol %) in CHCl<sub>3</sub> (2.0 mL) at rt under N<sub>2</sub>. Yields of isolated products are given. (B) **1a** (0.2 mmol), BrCF<sub>2</sub>CO<sub>2</sub>Et or BrCHFCO<sub>2</sub>Et (0.4 mmol, 2.0 equiv.), *fac*-Ir(ppy)<sub>3</sub> (3 mol %) and K<sub>2</sub>CO<sub>3</sub> (0.2 mmol, 1.0 equiv.) in CH<sub>3</sub>CN (2.0 mL) were irradiated with 30 W blue LEDs at rt under N<sub>2</sub>. (C) **1a** (0.2 mmol), TMSN<sub>3</sub> (0.8 mmol, 4.0 equiv.) and PIFA (0.4 mmol, 2 equiv.) in CH<sub>3</sub>CN (2.0 mL) at rt under N<sub>2</sub>. (D) (a) **1a** (0.2 mmol), TsNHNH<sub>2</sub> (0.3 mmol, 1.5 equiv.), NaI (0.1 mmol, 50 mol %), and TBHP (0.5 mmol, 2.5 equiv.) in CH<sub>3</sub>CN (2.0 mL) at rt under N<sub>2</sub>. (b) **1a** (0.2 mmol), TsNa (0.4 mmol, 2.0 equiv.) and Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (0.6 mmol, 3.0 equiv.) in CH<sub>3</sub>CN/H<sub>2</sub>O (2.0/0.2 mL) at 60 °C under N<sub>2</sub>.



**Scheme 4** Product transformations.

(Schemes 3B, 4a and 4b). Moreover, the reaction of **1a** with azido radicals furnished the azidation product in a useful yield (Scheme 3C, 5). Other sulfonyl radical precursors such as TsNHNH<sub>2</sub> and TsNa were also suitable for the radical sulfonylation, giving rise to product **2a**, respectively (Scheme 3D).

The utility of this method was further manifested by converting the product to other valuable molecules. For instance, ketone product **2w** could be transformed into ester **6** by Baeyer-Villiger oxidation (Scheme 4A). The treatment of quinoxalinone with POCl<sub>3</sub> resulted in 2-chloroquinoxaline **7**, which was subject to Sonogashira coupling to afford the complex alkyne product **8** (Scheme 4B).

The chain length of tertiary alcohols was investigated to probe the preferable transition state of the migrating step (Scheme 5A). While the reaction of **9** (*n* = 0) and **10** (*n* = 1) did not provide satisfactory outcomes, the conversion of **11** (*n* = 3) to product **14** delivered a high yield similar to that of **1a**. These results suggested that 1,4- or 1,5-migration of quinoxalinones



**Scheme 5** Proposed reaction mechanism.

readily proceeded *via* a kinetically favored five- or six-membered transition state.

On the basis of the experimental results, a plausible mechanism is depicted in Scheme 5B. Firstly, the transition of Ir(III) species to the excited state is enabled by visible-light irradiation, and generates a sulfonyl radical from sulfonyl chloride and Ir(IV) species *via* SET. Adding the sulfonyl radical to **1** gives rise to alkyl radical **a**, which undergoes intramolecular cyclization of quinoxalinone to generate a spiro intermediate **b**. The subsequent *N*-centered radical promoted ring opening accomplishes the 1,4-migration of quinoxalinone, and results in ketyl radical **d**. Single-electron oxidation of **c** to cation **d** by Ir(IV) species followed by deprotonation furnishes final product **2**, and regenerates Ir(III) species to perpetuate the photoredox catalytic cycle.

In summary, we have disclosed the radical-mediated remote migration of quinoxalinones for the first time. It presents a new supplement to the precedent examples of functional group migration. The reaction proceeds through intramolecular 1,4-quinoxalinone migration, leading to a variety of complex  $\gamma$ -quinoxalinone-substituted aliphatic ketones in synthetically useful yields. The protocol features wide tolerance of functional groups, good adaptability to external radicals and high product diversity, and opens a new door for the synthesis of quinoxalinone derivatives.

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## Conflicts of interest

There are no conflicts to declare.

## Notes and references

- For selected reviews: (a) J. P. Michael, *Nat. Prod. Rep.*, 1999, **16**, 675; (b) A. A. Kalinin and V. A. Mamedov, *Chem. Heterocycl. Compd.*, 2011, **46**, 1423; (c) L. Zhang, X. Peng, G. L. V. Damu, R. Geng and C.-H. Zhou, *Med. Res. Rev.*, 2014, **34**, 340; (d) M. D. Matveeva, R. Purgatorio, L. G. Voskressensky and C. D. Altomare, *Future Med. Chem.*, 2019, **11**, 2735.
- For selected reviews: (a) A. Carta, S. Piras, G. Loriga and G. Paglietti, *Mini-Rev. Med. Chem.*, 2006, **6**, 1179; (b) X. Li, K.-H. Yang, W.-L. Li and W.-F. Xu, *Drugs Future*, 2006, **31**, 979; (c) M. Demeunynck and I. Baussanne, *Curr. Med. Chem.*, 2013, **20**, 794; (d) L. Shi, W. Hu, J. Wu, H. Zhou, H. Zhou and X. Li, *Mini-Rev. Med. Chem.*, 2018, **18**, 392.
- For selected reviews: (a) X. Jiang, K. Wu, R. Bai, P. Zhang and Y. Zhang, *Eur. J. Med. Chem.*, 2022, **229**, 114085; (b) V. Mamedov, *RSC Adv.*, 2016, **6**, 42132; (c) Q. Ke, G. Yan, J. Yu and X. Wu, *Org. Biomol. Chem.*, 2019, **17**, 5863; (d) J. Berenguer, G. Blay, J. Pedro and C. Vila, *Eur. J. Org. Chem.*, 2020, 6148.
- For selected examples: (a) Y. Gao, Z. Wu, L. Yu, Y. Wang and Y. Pan, *Angew. Chem., Int. Ed.*, 2020, **59**, 10859; (b) J. Yang, S. Zhu, F. Wang, F. Qing and L. Chu, *Angew. Chem., Int. Ed.*, 2021, **60**, 4300; (c) P. Ghosh, N. Kown, S. Kim, S. Han, S. Lee, W. An, N. Mishra, S. Han and I. Kim, *Angew. Chem., Int. Ed.*, 2021, **60**, 191; (d) J. Yu, X. Zhang, X. Wu, T. Liu, Z.-Q. Zhang, J. Wu and C. Zhu, *Chem*, 2023, **9**, 472.
- For selected examples: (a) X. Li, J. Grokopf, C. Jandl and T. Bach, *Angew. Chem., Int. Ed.*, 2021, **60**, 2684; (b) M. Bhuyan, S. Sharma and G. Baishya, *Org. Biomol. Chem.*, 2022, **20**, 1462; (c) D. Zheng and A. Studer, *Org. Lett.*, 2019, **21**, 325.
- For selected reviews on FGM, see: (a) X. Wu, S. Wu and C. Zhu, *Tetrahedron Lett.*, 2018, **59**, 1328; (b) X. Wu and C. Zhu, *Acc. Chem. Res.*, 2020, **53**, 1620; (c) X. Wu, Z. Ma, T. Feng and C. Zhu, *Chem. Soc. Rev.*, 2021, **50**, 11577; (d) Y. Wei, X. Wu and C. Zhu, *Synlett*, 2022, 1017.
- For selected examples: (a) D. Wu, M. Christian, C. Daniliuc and A. Studer, *J. Am. Chem. Soc.*, 2021, **143**, 9320; (b) T. Zhou, F. Luo, M. Yang and Z. Shi, *J. Am. Chem. Soc.*, 2015, **137**, 14586; (c) W. Kong, M. Casimiro, E. Merino and C. Nevado, *J. Am. Chem. Soc.*, 2013, **135**, 14480; (d) N. Fuentes, W. Kong, F.-S. Luis, E. Merino and C. Nevado, *J. Am. Chem. Soc.*, 2015, **137**, 964; (e) X. Xiong, X. Huang, P. Li and X. Wu, *Angew. Chem., Int. Ed.*, 2013, **52**, 6962; (f) P. Gao, Y. Shen, R. Fang, X. Hao, Z. Qiu, F. Yang, X. Yan, Q. Wang, X. Gong, X. Liu and Y. Liang, *Angew. Chem., Int. Ed.*, 2014, **53**, 7629; (g) Z. Li, M. Wang and Z. Shi, *Angew. Chem., Int. Ed.*, 2021, **60**, 186.
- For selected examples: (a) Z. Wu, D. Wang, Y. Liu, L. Huan and C. Zhu, *J. Am. Chem. Soc.*, 2017, **139**, 1388; (b) H. Zhang, L. Kuo, D. Chen, M. Ji, X. Bao, X. Wu and C. Zhu, *Org. Lett.*, 2020, **22**, 5947; (c) J. Yu, Z. Wu and C. Zhu, *Angew. Chem., Int. Ed.*, 2018, **57**, 17156; (d) J. Liu, S. Wu, J. Yu, C. Lu, Z. Wu, X. Wu, X.-S. Xue and C. Zhu, *Angew. Chem., Int. Ed.*, 2020, **59**, 8195; (e) J. Jeon, Y.-T. He, S. Shin and S. Hong, *Angew. Chem., Int. Ed.*, 2020, **59**, 281; (f) M. Ji, X. Wang, J. Liu, X. Wu and C. Zhu, *Sci. China: Chem.*, 2021, **64**, 1703; (g) M. Ji, C. Chang, X. Wu and C. Zhu, *Chem. Commun.*, 2021, **57**, 9240.
- For selected examples: (a) Z. Wu, R. Ren and C. Zhu, *Angew. Chem., Int. Ed.*, 2016, **55**, 10821; (b) R. Ren, L. Huan and C. Zhu, *Adv. Synth. Catal.*, 2017, **359**, 3052; (c) M. Ji, Z. Wu, J. Yu, X. Wan and C. Zhu, *Adv. Synth. Catal.*, 2017, **359**, 1959; (d) M. Ji, Z. Wu and C. Zhu, *Chem. Commun.*, 2019, **55**, 2368; (e) C. Chang, H. Zhang, X. Wu and C. Zhu, *Chem. Commun.*, 2022, **58**, 1005.
- For selected examples: (a) Y. Xu, Z. Wu, J. Jiang, Z. Ke and C. Zhu, *Angew. Chem., Int. Ed.*, 2017, **56**, 4545; (b) X. Tang and A. Studer, *Chem. Sci.*, 2017, **8**, 6888; (c) J. Liu, W. Li, J. Xie and C. Zhu, *Org. Chem. Front.*, 2018, **5**, 797; (d) M. Wang, H. Zhang, J. Liu, X. Wu and C. Zhu, *Angew. Chem., Int. Ed.*, 2019, **58**, 17646.
- For selected examples: (a) X. Tang and A. Studer, *Angew. Chem., Int. Ed.*, 2018, **57**, 814; (b) A. Hossay, M. Josep, M. Mostafa, J. Derek, R. Robin, F. Natalie and C. Jonathan, *Angew. Chem., Int. Ed.*, 2019, **58**, 2418; (c) J. Yu, H. Zhang, X. Wu and C. Zhu, *CCS Chem.*, 2021, **3**, 1426; (d) Y. Wei, H. Zhang, X. Wu and C. Zhu, *Angew. Chem., Int. Ed.*, 2021, **60**, 20215.
- For selected examples: (a) J. Yu, D. Wang, Y. Xu, Z. Wu and C. Zhu, *Adv. Synth. Catal.*, 2018, **360**, 744; (b) N. Wang, J. Wang, Y. Guo, L. Li, Y. Sun, Z. Li, H. Zhang, Z. Guo, Z. Li and X. Liu, *Chem. Commun.*, 2018, **54**, 8885.
- For selected examples: (a) Z.-L. Li, X.-H. Li, N. Wang, N.-Y. Yang and X.-Y. Liu, *Angew. Chem., Int. Ed.*, 2016, **55**, 15100; (b) C. Morrill, A. Peter, I. Amalina, E. Pye, G. Crisenza, N. Kaltsoyannis and D. Procter, *J. Am. Chem. Soc.*, 2022, **144**, 13946; (c) W. Yao, G. Zhao, Y. Wu, L. Zhou, U. Mukherjee, P. Liu and M. Ngai, *J. Am. Chem. Soc.*, 2022, **144**, 3353; (d) G. Zhao, W. Yao, I. Kevlishvili, J. Mauro, P. Liu and M. Ngai, *J. Am. Chem. Soc.*, 2021, **143**, 8590.
- (a) X. Zeng, C. Liu, X. Wang, J. Zhang, X. Wang and Y. Hu, *Org. Biomol. Chem.*, 2017, **15**, 8929; (b) J.-W. Yuan, J.-H. Fu, S.-N. Liu, Y.-M. Xiao, P. Mao and L.-B. Qu, *Org. Biomol. Chem.*, 2018, **16**, 3203; (c) J. Lu, X.-K. He, X. Cheng, A.-J. Zhang, G.-Y. Xu and J. Xuan, *Adv. Synth. Catal.*, 2020, **362**, 2178; (d) L.-Y. Xie, Y.-S. Bai, X.-Q. Xu, X. Peng, H.-S. Tang, Y. Huang, Y.-W. Lin, Z. Cao and W.-M. He, *Green Chem.*, 2020, **22**, 1720.