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Radical-mediated remote migration of quinoxalinones†

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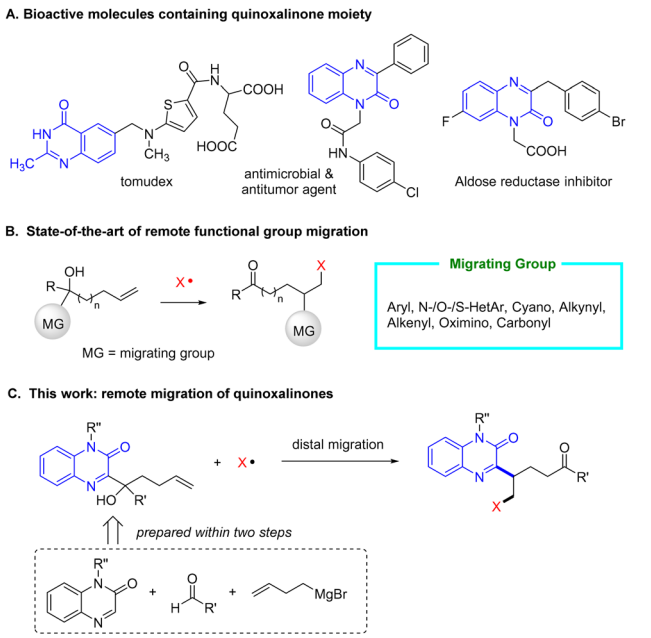
Disclosed herein is the first example of radical-mediated remote migration of quinoxalinones. The quinoxalinonyl-functionalization of alkenes employs the quinoxalinone-substituted tertiary bishomoallylic alcohols as substrates, proceeds through intramolecular 1,4-quinoxalinone migration, and gives rise to complex γ-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,[1] 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).[2] In view of broad prospects in application, the preparation of quinoxalinone derivatives has attracted great attention over the past few years.[3] The most common approaches rely on the Minisci reaction by adding various alkyl radicals to the parent quinoxalinone.[4] Alkenes are easily available and can act as the precursor of alkyl radicals that engage in the Minisci reaction.[5] 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.[6] We and others have comprehensively investigated the FGM reactions, where a portfolio of functional groups including aryls,[7] heteroaryls,[8] cyano,[9] alkynyl,[10] alkenyl,[11] oximino,[12] and carbonyl,[12a,13] 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



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

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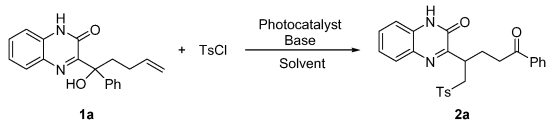
Table 1 Reaction parameter survey[a]



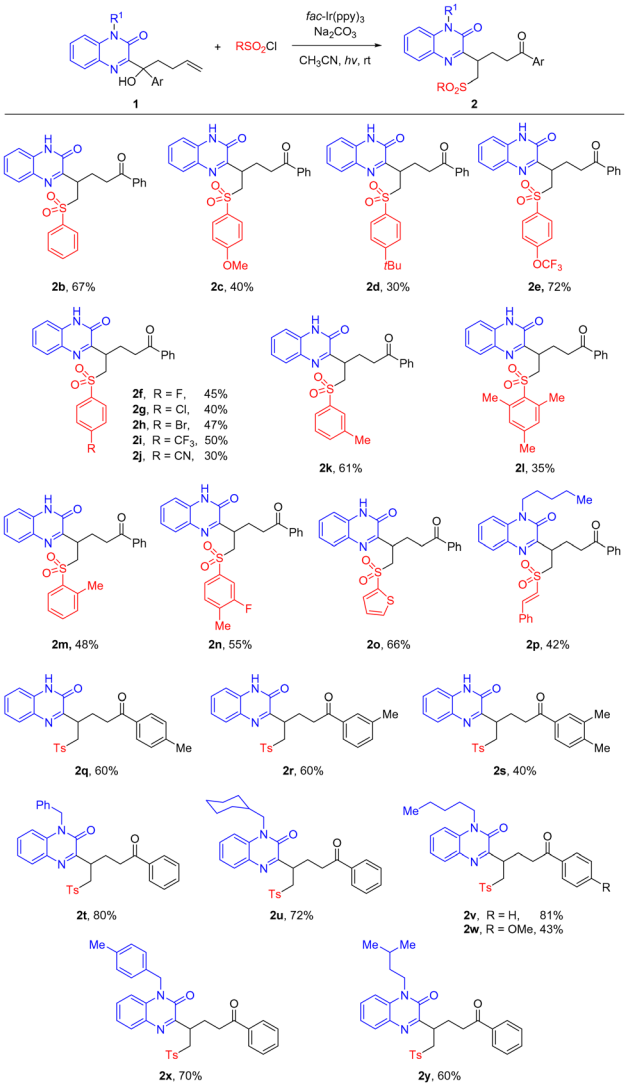
Entry	Base	Photocatalyst	Solvent	Yield[b] (%)
1	Na_2CO_3	*fac*-Ir(ppy)$_3$	CH_3CN	70
2	Na_2CO_3	*fac*-Ir(ppy)$_3$	EtOAc	30
3	Na_2CO_3	*fac*-Ir(ppy)$_3$	DCM	18
4	Na_2CO_3	*fac*-Ir(ppy)$_3$	THF	26
5	Na_2CO_3	*fac*-Ir(ppy)$_3$	DMF	15
6	Na_2CO_3	*fac*-Ir(ppy)$_3$	Acetone	22
7	K_2CO_3	*fac*-Ir(ppy)$_3$	CH_3CN	43
8	K_2HPO_4	*fac*-Ir(ppy)$_3$	CH_3CN	45
9	$NaHCO_3$	*fac*-Ir(ppy)$_3$	CH_3CN	55
10	$KHCO_3$	*fac*-Ir(ppy)$_3$	CH_3CN	64
11	NaOAc	*fac*-Ir(ppy)$_3$	CH_3CN	51
12	Na_2CO_3	[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$	CH_3CN	31
13	Na_2CO_3	Ir(ppy)$_2$(dtbbpy)PF$_6$	CH_3CN	38
14	Na_2CO_3	Ru(bpy)$_3$Cl$_2$·6H$_2$O	CH_3CN	28
15	Na_2CO_3	4CzIPN	CH_3CN	61
16	Na_2CO_3	Eosin Y	CH_3CN	24
17[c]	Na_2CO_3	*fac*-Ir(ppy)$_3$	CH_3CN	65
18[d]	Na_2CO_3	*fac*-Ir(ppy)$_3$	CH_3CN	74
19[e]	Na_2CO_3	—	CH_3CN	N.R.
20[f]	Na_2CO_3	*fac*-Ir(ppy)$_3$	CH_3CN	N.D.

[a] Reaction conditions: **1a** (0.2 mmol), TsCl (0.3 mmol, 1.5 equiv.), base (0.2 mmol, 1.0 equiv.) and photocatalyst (3 mol %) in solvent (2.0 mL) were irradiated with 30 W blue LEDs at rt under N_2. [b] Isolated yield. [c] 5 W blue LEDs. [d] 18 W blue LEDs (460 nm). [e] No photocatalyst. [f] In the dark.

of adding a carbonyl radical to quinoxalinone followed by the nucleophilic addition of Grignard reagent to the resulting ketone.[14] The reaction of the tertiary alcohols with various external radicals readily proceeds, leading to complex γ-quinoxalinone-substituted aliphatic ketones, otherwise difficult to synthesize, through radical difunctionalization of unactivated alkenes. Remarkably, this is the first example of radical-mediated quinoxalinone migration.

At the outset, a reaction parameters survey was implemented with the reaction of quinoxalinone-substituted tertiary alcohol **1a** and tosyl chloride (Table 1). The reaction proceeded with the use of *fac*-Ir(ppy)$_3$ as a photosensitizer, Na_2CO_3 as a base, and acetonitrile as a solvent under blue-light irradiation, leading to the desired product **2a.** Then various solvents were investigated (entries 1–6). Among those commonly used solvents, acetonitrile delivered the best yield. A set of bases was subsequently examined, in which no one delivered a better yield than Na_2CO_3 (entries 7–11). Photosensitizers were also briefly screened, showing that others were not as effective as the original one (entries 12–16). Finally, light intensity was evaluated and the yield was further improved to 74% under the irradiation of 18 W blue light (entry 18). Control experiments indicated that the reaction could not occur in the absence of either light or photosensitizer (entries 19 and 20).

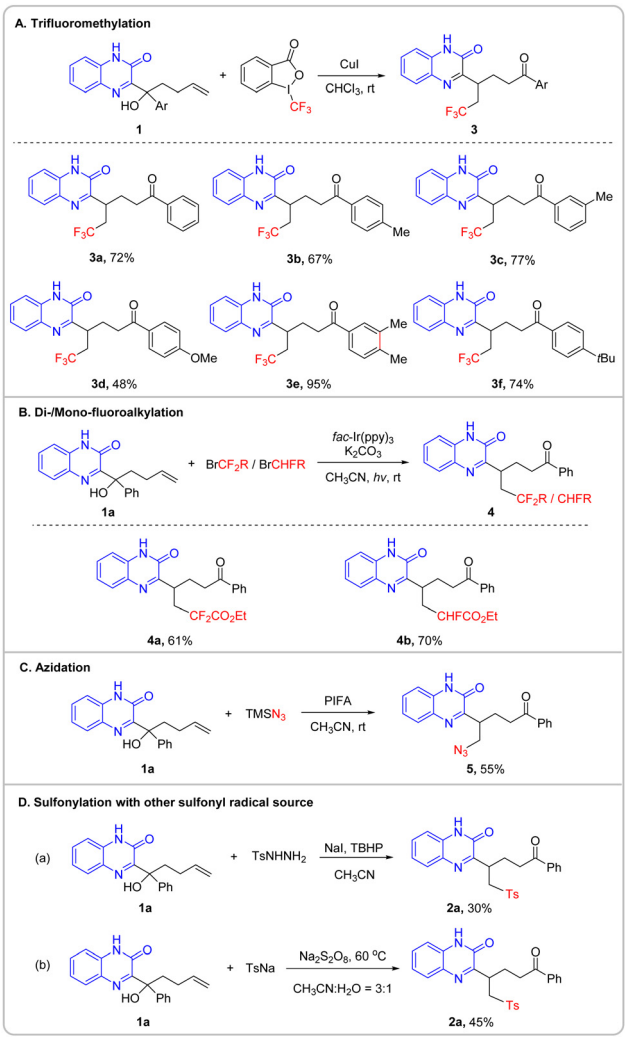
With the optimized reaction conditions in hand, we turned our attention to defining the scope of sulfonyl radicals and tertiary alcohol substrates (Scheme 2), in order to assess the compatibility of functional groups. Firstly, the substituent on



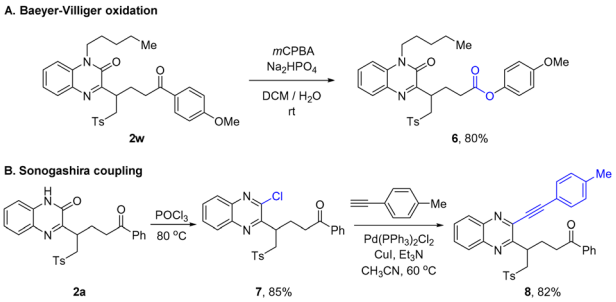
Scheme 2 Scope of different substituted free radicals. Reaction conditions: **1** (0.2 mmol), TsCl (0.3 mmol, 1.5 equiv.), Na_2CO_3 (0.2 mmol, 1.0 equiv.) and *fac*-Ir(ppy)$_3$ (3 mol%) in CH_3CN (2.0 mL) were irradiated with 18 W blue LEDs (460 nm) at rt under N_2. Yields of isolated products are given.

the aryl sulfonyl chlorides was investigated. The substrates bearing either electron-rich or deficient groups were apt to afford the corresponding products (**2b–2k**). Many common groups such as halides and cyano were tolerated in the reaction. Steric hindrance caused a decline in yield, as shown in the examples bearing an *ortho*-substituent (**2l** and **2m**). Heteroaryls such as thienyl sulfonyl radicals and vinyl sulfonyl radicals were amenable to the reaction, giving rise to the corresponding products **2o** and **2p** in useful yields. The substituent of tertiary alcohols **1** could also be varied. Adding extra functional groups on the aryl, such as methyl, did not interfere with the reaction (**2q–2s**). In addition to the parent quinoxalinone, the migration of functionalized quinoxalinones with protecting groups was investigated. The quinoxalinone bearing either a benzyl or alkyl protecting group readily migrated in the reaction, leading to the corresponding products within appreciably improved yields (**2t–2y**).

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 $CHCl_3$ (2.0 mL) at rt under N_2. Yields of isolated products are given. (B) **1a** (0.2 mmol), $BrCF_2CO_2Et$ or $BrCHFCO_2Et$ (0.4 mmol, 2.0 equiv.), *fac*-Ir(ppy)$_3$ (3 mol %) and K_2CO_3 (0.2 mmol, 1.0 equiv.) in CH_3CN (2.0 mL) were irradiated with 30 W blue LEDs at rt under N_2. (C) **1a** (0.2 mmol), $TMSN_3$ (0.8 mmol, 4.0 equiv.) and PIFA (0.4 mmol, 2 equiv.) in CH_3CN (2.0 mL) at rt under N_2. (D) (a) **1a** (0.2 mmol), $TsNHNH_2$ (0.3 mmol, 1.5 equiv.), NaI (0.1 mmol, 50 mol %), and TBHP (0.5 mmol, 2.5 equiv.) in CH_3CN (2.0 mL) at rt under N_2. (b) **1a** (0.2 mmol), TsNa (0.4 mmol, 2.0 equiv.) and $Na_2S_2O_8$ (0.6 mmol, 3.0 equiv.) in CH_3CN/H_2O (2.0/0.2 mL) at 60 °C under N_2.

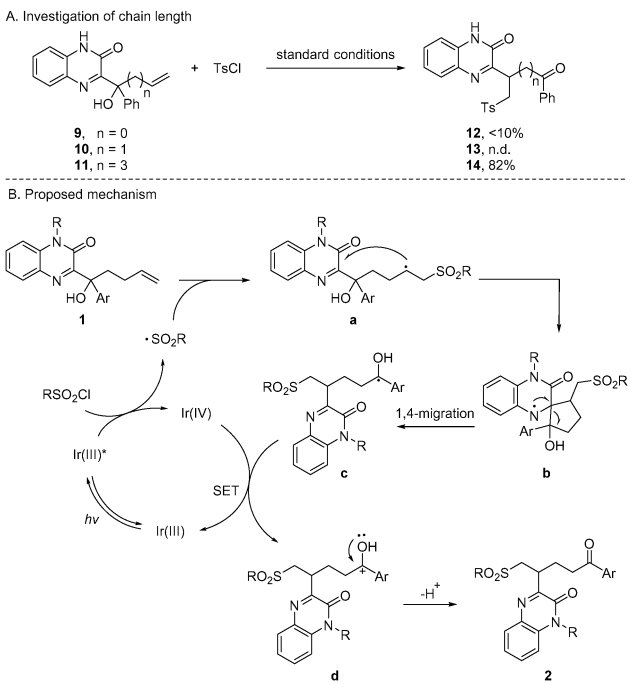


Scheme 4 Product transformations.

(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 $TsNHNH_2$ 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 $POCl_3$ 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 γ-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.

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