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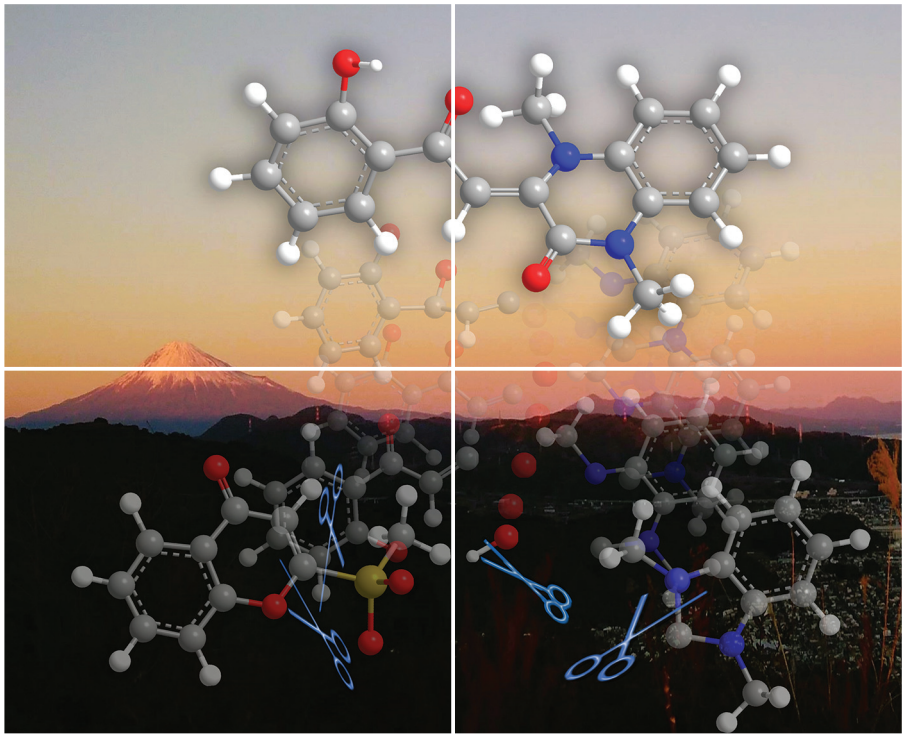

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Carbon atom insertion into *N*-heterocyclic carbenes to yield 3,4-dihydroquinoxalin-2(1*H*)-ones†

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Carbon atom insertion into a cyclic framework is an attractive form of molecular editing since it can modify the core skeleton of a molecule, allowing for controlled increases in molecular size and complexity. We have discovered that when benzimidazoliums and 2-(methylsulfonyl)chromones were mixed under basic conditions, followed by the addition of a basic aqueous solution/mixture, the carbon atom located at position 2 of the chromone could be inserted into the *in situ*-generated *N*-heterocyclic carbenes (NHCs) to afford (*Z*)-3-(2-phenyl-2-oxoethylidene)-3,4-dihydroquinoxalin-2(1*H*)-ones, a scaffold found in numbers of bioactive compounds. Under the same conditions, 1-methyl-3-phenylbenzimidazolium iodide provided an unexpected pentacyclic product with a [1]benzopyrano[2,3-*b*]phenazine framework in an excellent yield presumably *via* a pathway involving a single-carbon transfer from the NHC.

Introduction

Molecular editing is a powerful strategy for accessing new areas of chemical space.[1] Unlike peripheral editing strategies such as C–H functionalization, it can directly alter the skeletal core of a molecule *via* the insertion,[2] deletion,[3] or exchange[4] of one or more atoms. The development of new molecular editing methods for highly functionalized molecules is of particular interest for drug discovery.[5]

Among the methods of molecular editing, single-atom insertion reactions hold the potential for the greatest leap in molecular complexity from the lead scaffold. Insertion of single atoms bearing substituents can expand both the skeletal and peripheral structures at the same time, reducing further synthetic steps. Despite the concept being commonly applied in reactions with carbonyl compounds, for instance in Beckmann rearrangement[2a] and Baeyer–Villiger oxidation,[2b] single-atom insertions into aromatic skeletal cores are still uncommon. Furthermore, in comparison to the introduction of heteroatoms, reports on the insertion of single carbon atoms are relatively scarce.

Carbon atom insertions with aromatic compounds can be traced back to 1881 with the Ciamician–Dennstedt rearrangement[2c] reaction. In this reaction, dichlorocarbene provides a carbon source for the introduction of a carbon atom into pyrroles to form 3-chloropyridines. Despite the potential synthetic utility of this method, the competing Reimer–Tiemann reaction leads to low yields and has hindered the widespread adoption of this method (Scheme 1).[6]

Recent work by Levin and coworkers has notably improved the classical Ciamician–Dennstedt reaction. In their work, they reported the use of chlorodiazirines as carbene precursors to synthesize 3-arylpyridines and 3-arylquinolines in typically moderate to good yields from pyrroles and indoles, respectively.[2d] The application of this named reaction in the total syntheses of complanadine A and lycodine by Dai and coworkers demonstrates the great synthetic utility of not only this reaction, but also of single-carbon atom insertion reactions in general.[2e]

While the majority of the reports on carbon atom insertion reactions into aromatic compounds has focused on pyrroles or indoles, several papers have been published which have expanded the substrate scope.[1] In 2019, Mancheño and coworkers provided, to the best of our knowledge, the only example of a ring expansion of a benzimidazolium through the insertion of a carbon atom from an external molecule.[2r] While their report is mostly dedicated to the synthesis of benzo[*b*]azepines from hydroquinolines through a carbon atom insertion reaction using $TMSCHN_2$ as the external carbon atom source, they demonstrated that an *in situ* generated benzimidazolium could also undergo ring expansion under the same conditions. This transformation is particularly notable as it stands in stark contrast to the typical ring expansion reactions of benzimidazoliums, where the introduced atom originates from the parent molecule and not from an external molecule.[7]

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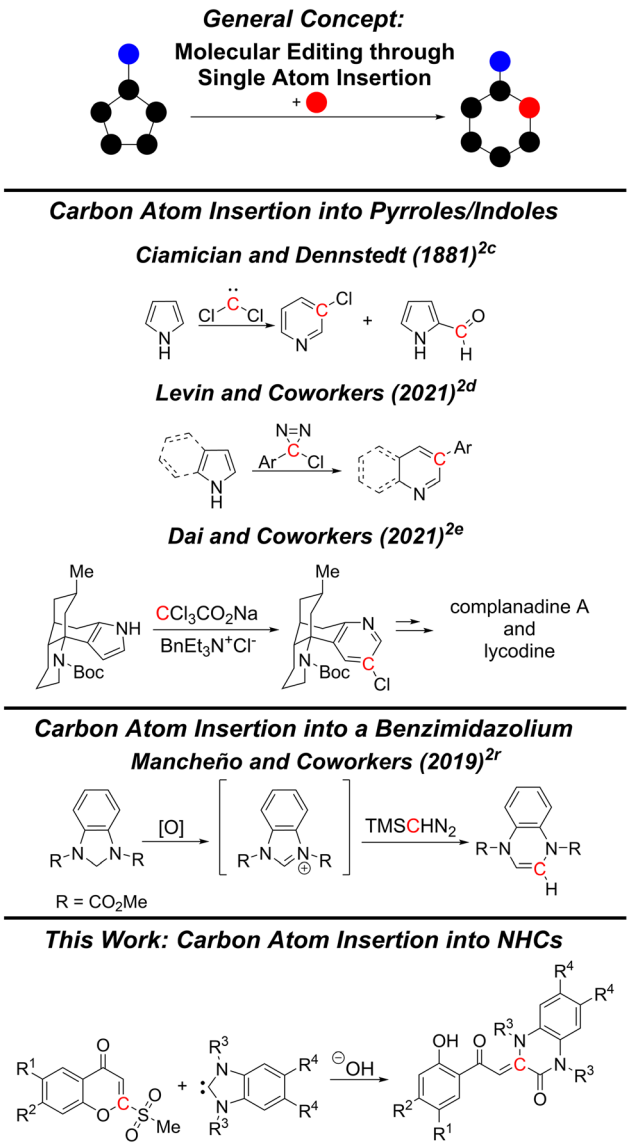


Scheme 1 Selected previous works and this work.

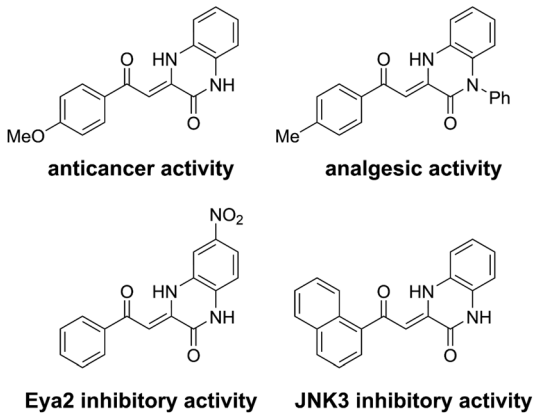


Fig. 1 Examples of biologically active compounds containing the 3-methylidene-3,4-dihydroquinoxalin-2(1*H*)-one motif.

Herein, we report a reaction between benzimidazolium-derived *N*-heterocyclic carbenes (NHCs) and 2-(methylsulfonyl) chromones where the carbon atom at position 2 of the chromone is inserted into the NHC to yield 3,4-dihydroquinoxalin-2(1*H*)-ones. This class of quinoxalinones is particularly attractive due to the range of biologically active derivatives which have been reported, including anticancer,[8] analgesic,[9] eyes absent homologue 2 (Eya2; promising therapeutic target for cancer) inhibitory,[10] and c-Jun N-terminal kinase 3 (JNK3; therapeutic target for Alzheimer's disease) inhibitory compounds[11] (Fig. 1).

Results and discussion

Over the course of our laboratory's research into NHC-catalyzed reactions, we observed an unexpected side product when 2-(methylsulfonyl)chromone **1a** and 1,3-dimethylbenzimidazolium iodide **2a** were applied in the same reaction. The X-ray structure of this side product showed it to be quinoxalinone **3a** (Fig. 2). It was observed that the carbon atom at position 2 of the chromone was inserted into the benzimidazolium and that there was an additional oxygen atom not from the original chromone structure.

Two key interpretations were made from this structure. First, the construction of the quinoxalinone is likely initiated by a direct substitution reaction between chromone **1a** and the NHC. Second, residual water in the solvent was likely necessary for this transformation to occur. Based on these interpretations, a reaction mechanism was postulated as follows (Scheme 2).

First, deprotonation of the benzimidazolium salt **2a** by a base (NaH in this case) leads to the formation of the NHC **2a′**, which undergoes a substitution reaction with chromone **1a** to generate the chromonylbenzimidazolium salt intermediate **int. A**. A hydroxide anion (generated *in situ* by deprotonation of the residual water by NaH) attacks **int. A** at the iminium moiety to form **int. B**. Deprotonation of the hydroxyl group on **int. B** leads to the formation of the amide moiety and the introduction of the carbon atom at position 2 of the chromone into the benzimidazole core to form the spiro intermediate **int. C**.

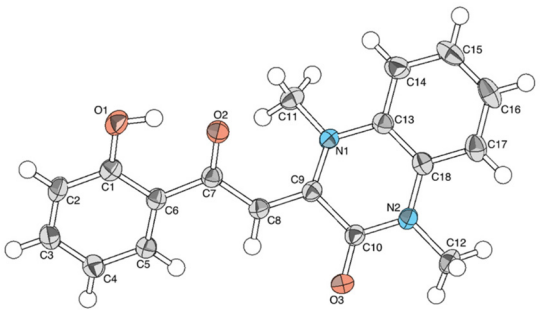
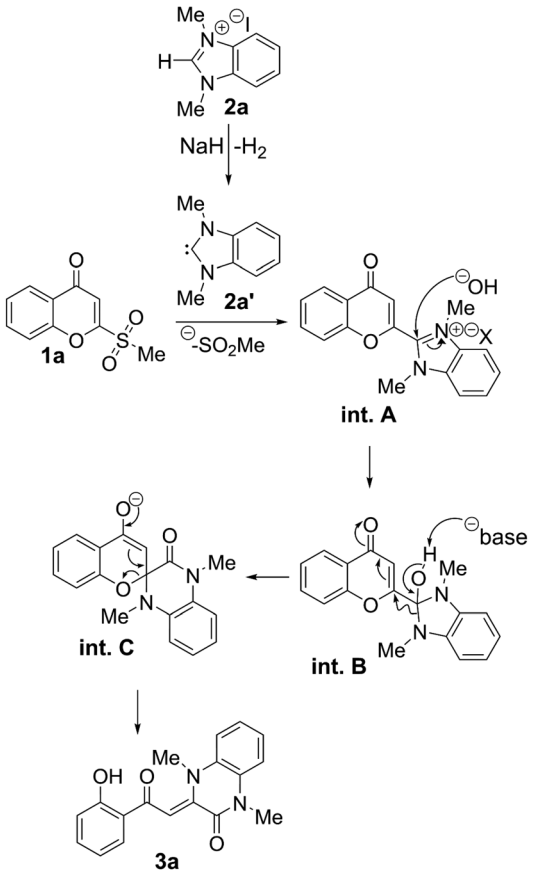


Fig. 2 X-ray crystallographic analysis of **3a**.



Scheme 2 Proposed mechanism.

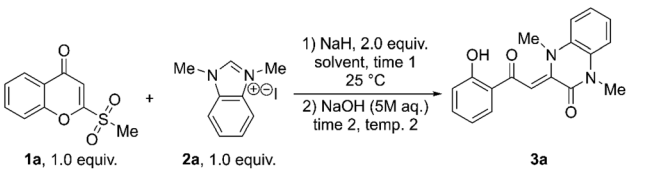
Reformation of the α,β-unsaturated structure opens the spiropyran ring in **int. C** to afford the final quinoxalinone **3a**.

Based on this mechanism, a two-step reaction to synthesize quinoxalinones from 2-(methylsulfonyl)chromones **1** and benzimidazoliums was designed. First, the chromone and benzimidazolium salt would be reacted together with 2 equivalents of NaH. After complete consumption of the starting chromone is observed by thin-layer chromatography, the reaction mixture would then be treated with an aqueous solution of NaOH in the second step to initiate the carbon atom insertion sequence, which would afford the desired quinoxalinones.

Chromone **1a** and NHC precursor **2a** were chosen as the substrates for the initial test reaction and optimization of the reaction conditions. The first experiment was performed in DMF at 25 °C at 0.3 mmol scale to afford quinoxalinone **3a** in 28% yield (Table 1, entry 1). Decreases in temperature of step 2 down to 5 °C improved yields up to 75% (entries 2–5). At 0 °C, a 54% yield was obtained (entry 6). An increase in the temperature of step 2 had a negative effect on the yield, providing **3a** in only 20% yield (entry 7).

Solvents other than DMF were then tested. **3a** was obtained in 61% yield when acetonitrile or 1,4-dioxane was used (entries 8 and 9). The use of NMP provided the best result with a 99% yield of **3a** (entry 10). An increased reaction scale from 0.3 mmol to 1.0 mmol had no significant effect on the yield,

Table 1 Screening of reaction conditions



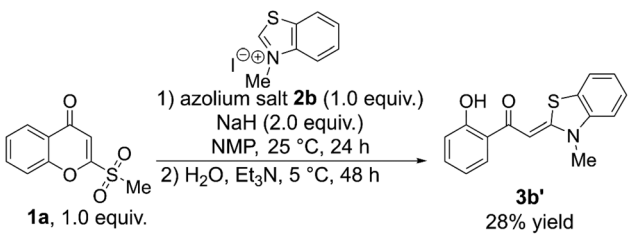
Entry[a]	Solvent	Time 1 (h)	Time 2 (h)	Temp. 2 (°C)	Yield (%)
1	DMF	3	18	25	28
2	DMF	3	18	20	42
3	DMF	3	18	15	54
4	DMF	3	18	10	72
5	DMF	3	23	5	75
6	DMF	3	24	0	54
7	DMF	3	18	50	20
8	MeCN	4	18	5	61
9	Dioxane	24	48	5	61
10	NMP[b]	24	48	5	99
11[c]	NMP	24	24	5	94
12[d]	NMP	1	18	5	44

[a] Entries 1–10 and 12: 0.3 mmol scale. [b] NMP = *N*-methyl-2-pyrrolidone. [c] 1.0 mmol scale. [d] Step 1 temp: 70 °C.

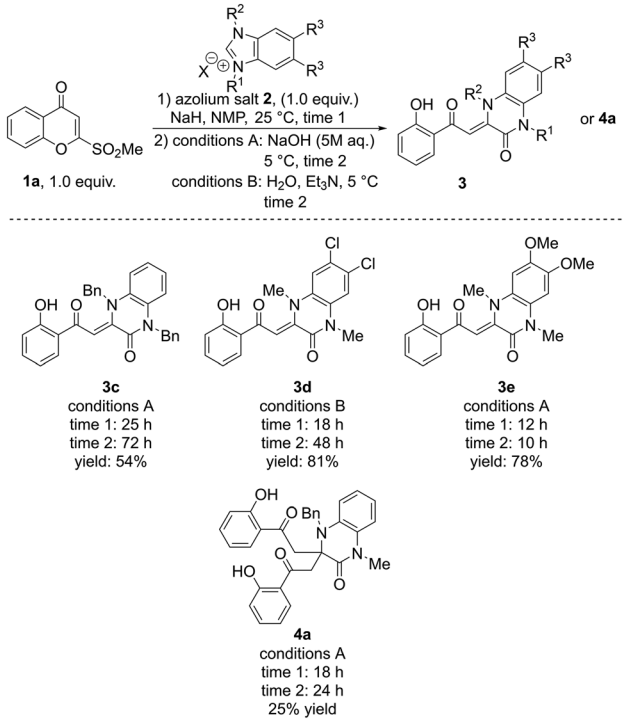
as **3a** was obtained in 94% yield (entry 11). An attempt to speed up the first step by heating at 70 °C resulted in a decreased yield (44%) of **3a** (entry 12).

Other substrates—imidazolium, triazolium, thiazolium, and benzothiazolium salts—were tested, however, no corresponding carbon-insertion products were detected. While the majority of the reactions generated complex mixtures, the use of 3-methylbenzothiazolium iodide **2b** provided the *S,N*-ketene-aceatal **3b′** in 28% yield (Scheme 3).

Other benzimidazolium salts were then tested (Scheme 4). 1,3-Dibenzylbenzimidazolium iodide provided the corresponding product **3c** in 54% yield. By contrast, more sterically demanding 1,3-diisopropylbenzimidazolium bromide had a significant negative impact on the reaction, as no corresponding product was observed. Both 5,6-dichloro-1,3-dimethylbenzimidazolium iodide and 5,6-dimethoxy-1,3-dimethylbenzimidazolium iodide provided the corresponding products **3d** and **3e** in high yields (81% and 78%, respectively). However, when 4,7-dimethoxy-1,3-dimethylbenzimidazolium iodide was tested in the reaction, a complex mixture of products was obtained. An unexpected quinoxalinone (**4a**), which bears two identical substituents at position 3, originating from



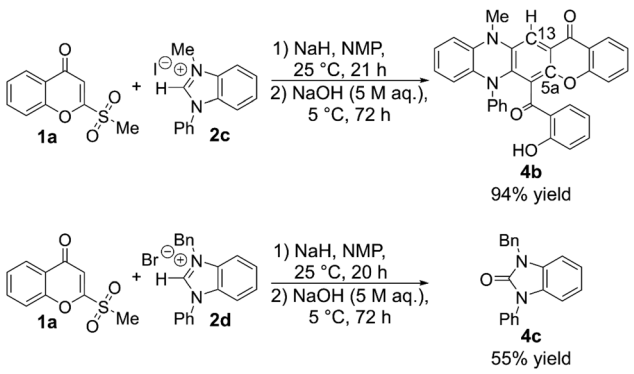
Scheme 3 Synthesis of the unexpected product **3b′**.



Scheme 4 Screening of benzimidazolium salts. Full screening scope can be viewed in the ESI.†

two molecules of **1a**, was isolated in 25% yield when 1-benzyl-3-methylbenzimidazolium iodide was used (a possible mechanism for the formation of **4a** is described in the ESI, Scheme S1†).

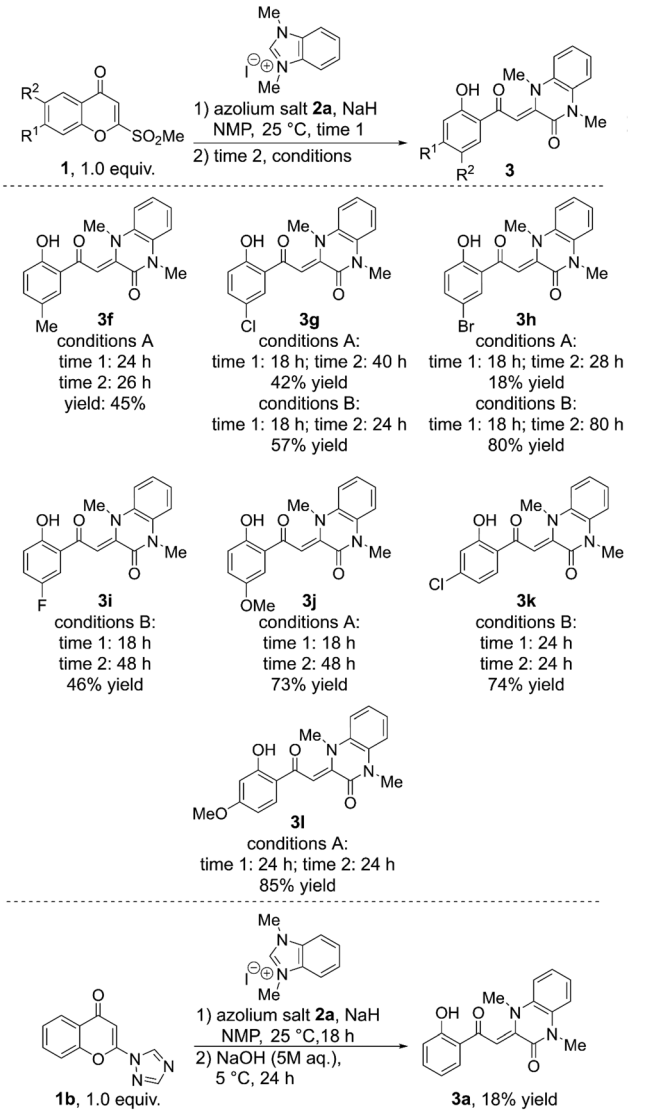
When *N*-phenyl-substituted benzimidazolium salts were applied in this reaction, no desired quinoxalinone products were detected. 1-Methyl-3-phenylbenzimidazolium iodide **2c** afforded chromeno[2,3-*b*]phenazine **4b** in 94% yield (Scheme 5). The structure of **4b** was confirmed by X-ray analysis. Although the mechanism is currently not elucidated, the C13 (or C5a) of **4b** is likely transferred from the C2 of the benzimidazolium (the carbene center),[12] indicating two molecules of each substrate are involved in the formation. It appears that



Scheme 5 Application of *N*-phenyl-substituted benzimidazolium salts.

the *N*-phenyl substituent changes the electronic properties of the desired quinoxalinone product, which leads to the occurrence of additional reactions. When 1-benzyl-3-phenylbenzimidazolium bromide **2d** was used, benzimidazol-2-one **4c** was obtained as the major product in 55% yield along with a complex mixture of products. The extra steric bulk of the benzyl group of **2d** in comparison with **2c** likely prevents the desired transformation from occurring.

Our attention next turned to the screening of chromone substrates in the reaction with **2a** (Scheme 6). Substituents at position 6 of the chromone were first tested. A chromone with a methyl group provided the corresponding product **3f** in 45% yield. With the introduction of halogen atoms, milder conditions were needed to obtain moderate to high yields. The use of a mixture of H_2O and Et_3N in the second step in place of NaOH allowed for the synthesis of chloro-, bromo-, and



Scheme 6 Screening of chromone substrates. Conditions A: NaOH, 5 °C; conditions B: H_2O, Et_3N (2 equivalents), 5 °C.

fluoro-substituted products (**3g**, **3h**, and **3i**, respectively) in moderate to high yields (57%, 80%, and 46%, respectively). An electron donating methoxy group at position 6 of the chromone was also well tolerated, with the corresponding product **3j** being obtained in 73% yield. Chromones with a chloro or methoxy group at position 7 could also be applied to this reaction affording quinoxalinones **3k** and **3l** in good yields (74% and 85%, respectively). The application of a naphthyl-fused chromone provided only a complex mixture of products.

To investigate the influence of the substituents at position 3, chromones with a 3-methyl or 3-chloro group were applied to the reaction, however, no desired quinoxalinones were isolated. Additionally, although the yield of **3a** was low (18%), a 1,2,4-triazolyl group[13] also functioned as a leaving group at position 2 instead of the methylsulfonyl group.

Conclusion

In summary, we have successfully developed a method of synthesizing 3,4-dihydroquinoxalin-2(1*H*)-ones *via* a carbon atom insertion reaction. *In situ* generated NHCs react with 2-(methylsulfonyl)chromones, which presumably generates the key chromonylbenzimidazolium intermediates. The subsequent addition of an aqueous NaOH solution or a H_2O/Et_3N mixture initiates a ring expansion where the carbon atom located at position 2 of the chromone is inserted into the imidazole ring to afford the quinoxalinones. The benzimidazole framework appeared to be a key to this reaction, since other NHC precursor salts provided no desired products. A novel heteropentacycle **4b** was unexpectedly, but efficiently, constructed in the reaction with 1-methyl-3-phenylbenzimidazolium iodide. The pentacycle was likely constructed from two molecules of the chromone and two molecules of the derived NHC. However, for one of the NHC molecules, only the C2 atom seems to be transferred into the product. Further studies into how this polycyclic compound was formed are currently underway. This work demonstrates the potential of NHCs as substrates to provide highly functionalized products in an atom-economic manner *via* carbon atom insertion reactions.

Author contributions

F. K. conducted the initial substrate scope experiments and collected the NMR data for compound **1c**. J. S. L. conducted the reaction optimization and additional substrate scope experiments, purification, and measurement of the characterization data (except X-ray). N. S. conducted the X-ray diffraction measurements and recrystallized compound **4b**. J. S. L. and Y. S. wrote the manuscript. Y. S. conceptualized the project.

Conflicts of interest

There are no conflicts to declare.

Note added after first publication

This article replaces the version published on 14th November 2023, which contained errors in the footnotes for Table 1.

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