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Amine-cation-driven heteroannulation of halomaleimides with C–N cleavage: metal-free access to heterobicyclic frameworks

Luka Ciber, Helena Brodnik, Nejc Petek, Jurij Svete, Uroš Grošelj * and Bogdan Štefane *

Maleimides and their derivatives are highly versatile scaffolds with broad applications in synthetic chemistry, medicinal chemistry, and materials science; however, methods to expand their structural diversity remain limited. Here, we present a so far undescribed, metal-free, and mild strategy for the rapid construction of functionalized maleimides from readily available dihalomaleimide derivatives. The reaction is initiated by tertiary amine-mediated formation of an ammonium cation, which directs heteroannulation to efficiently generate heterobicyclic scaffolds. This modular approach also enables the synthesis of 3,4-diamino-substituted maleimides, including challenging second halogen substitutions with weak nucleophiles. Mechanistic studies indicate that a quaternary enamine intermediate plays a central role in steering the transformation, providing broad functional group tolerance and synthetically useful yields. Overall, this strategy offers a versatile platform for accessing structurally diverse maleimides, unlocking new opportunities in bioconjugation, medicinal chemistry, and materials science.

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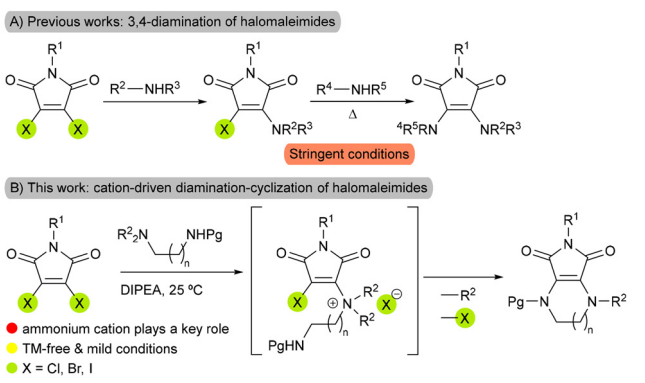
Introduction

Maleimides are an exceptional scaffold widely used in natural products and pharmaceuticals, serving as a versatile building block for synthesizing bioactive molecules and advanced materials.[1–5] Because of their efficiency, mild reaction conditions, and chemoselectivity, maleimides provide robust methods for protein conjugation and material modification.[6,7] Their widespread use is partly due to their ability to undergo two highly efficient reactions: Michael addition with nucleophiles and Diels–Alder cycloaddition with dienes.[8–12] Annulated[13,14] and spirocyclic[15] maleimide products can be prepared by various methods, including metal-catalyzed reactions,[16–18] cycloadditions,[19–22] photochemical processes,[23–25] and oxidant-based approaches.[26–28] Compared to single substitution, double substitution offers improved functionalization, allowing both symmetric and asymmetric substitution patterns. A notable example is the addition–elimination reaction with halogenated maleimide derivatives.[29] Incorporating halogens into the maleimide scaffold creates predefined reactive sites.[30,31] This synthetic approach enables efficient halide anion loss, yielding substituted maleimides while retaining the synthetically valuable C=C bond. The singly substituted maleimide scaffold allows further manipulations for improved functionalization, enabling asymmetric disubstituted or (hetero)bicyclic structures, for example, by cross-coupling, Diels–Alder reaction, or reaction with nucleophiles such as alcohols, thiols, and amines. While substitution of the second halogen with thiols can be achieved under relatively mild conditions,[32] reactions with alcohol or amino functionalities often require harsh conditions (Scheme 1A),[33–38] such as an excess of amine, high temperatures up to 140 °C, microwave irradiation or strong bases, as the initially incorporated amino group significantly reduces the electrophilicity of the maleimide.[39–43]



Scheme 1 Diamination of halogenated maleimide derivatives.

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Večna pot 113, 1000 Ljubljana, Slovenia.
E-mail: Uros.Groselj@fkkt.uni-lj.si, Bogdan.Stefane@fkkt.uni-lj.si

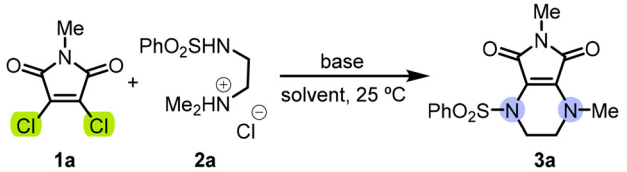
During our studies on the functionalization of dihalogenated maleimides, we serendipitously discovered an addition–elimination reaction of halogenated maleimides with functionalized primary–tertiary diamines, which also enables double halogen substitution under mild conditions (Scheme 1B). Considering that this five-membered imide heterocycle has been identified in various families of natural products, synthetic pharmaceuticals, biochemistry,[44] and technological applications,[45] and represents a valuable building block, we wanted to explore the mechanism and develop a practical synthetic protocol for preparing heterobicyclic maleimide derivatives. As part of our design, we postulated that the tertiary amine functionality could initially generate a quaternary enammonium salt of maleimide, a potent electrophile, facilitating the second addition–elimination step and providing a promising route to construct structurally more diverse enaminone compounds.

Results and discussion

Dichloromaleimide **1a** and *N*-(2-(dimethylamino)ethyl)benzenesulfonamide hydrochloride (**2a**) were selected as model substrates to test the feasibility of double amination of the electron-deficient substrate **1a** (Table 1). After thoroughly optimizing the reaction conditions – including reaction temperature, choice of base, and amount of functionalized diamine to achieve maximum yield and optimal reaction time – the reaction was carried out using 1.5 equivalents of amine hydrochloride **2a**, NMP as the solvent, and 2 equivalents of DIPEA as the optimal base at 25 °C, yielding the desired product **3a** in a synthetically useful 93% yield (Table 1).

Different combinations of solvents and bases yielded the desired product **3a**, but with inferior results compared to NMP/DIPEA (entries 2–14). Using protic methanol as a solvent or pyridine as a base (see entries 7 and 12) resulted in complex product mixtures. Using free amine **2a** led to 48% conversion after 24 hours (entry 15), while no reaction occurred in the absence of base (entry 16).

Table 1 Optimization of the reaction conditions[a]



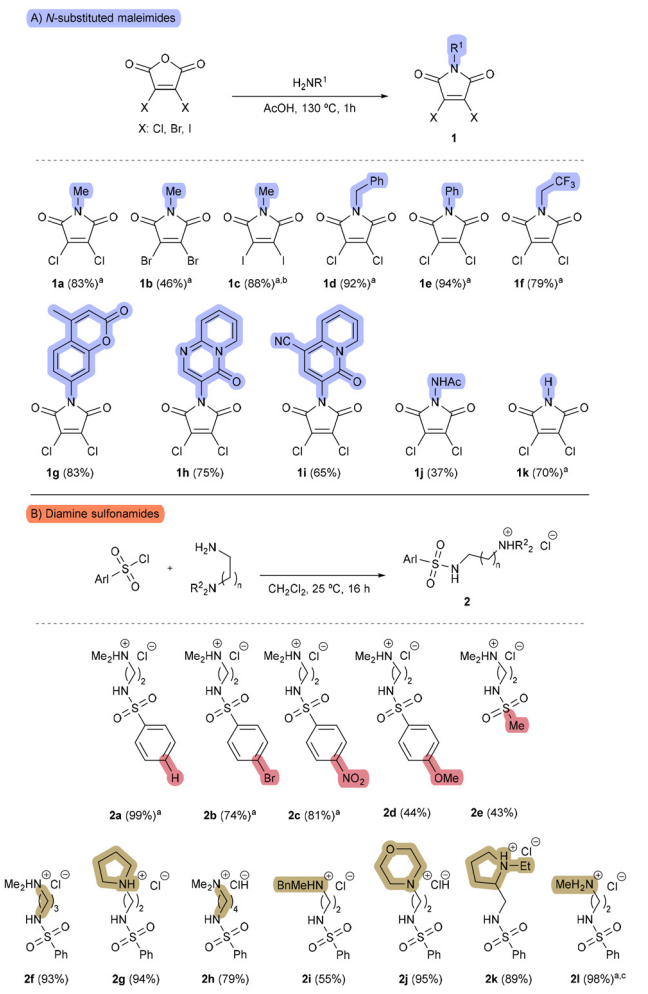
1a 2a 3a

Entry	Deviation from optimal conditions[a]	Yield[b] (%)
1	None	93
2	MeCN, Cs_2CO_3, 16 h	57
3	DMF, Cs_2CO_3, 16 h	65
4	DMSO, Cs_2CO_3, 24 h	72
5	NMP, Cs_2CO_3, 16 h	90
6	EtOAc, Cs_2CO_3, 96 h	34
7	MeOH, Cs_2CO_3, 16 h	—[c]
8	DCM, Cs_2CO_3, 96 h	31
9	THF, Cs_2CO_3, 48 h	40
10	NMP, K_2CO_3, 16 h	90
11	NMP, $KHCO_3$, 48 h	75
12	NMP, pyridine, 16 h	—[c]
13	NMP, NaOH or KOH, 16 h	44
14	NMP, K_3PO_4, 48 h	65
15	NMP, without base, free amin, 24 h	48[d]
16	NMP, without base, 96 h	0[e]

[a] Optimal reaction conditions unless specified otherwise: **1a** (0.1 mmol), amine hydrochloride (0.11 mmol), DIPEA (0.22 mmol), NMP (1.0 mL), 25 °C, 16 h, reactions were performed using undried solvents under ambient atmosphere. [b] Isolated yields are reported. [c] A mixture of products was formed. [d] NMR conversion. [e] No conversion.

Scope

To study the scope of our transformation, a series of 3,4-dihalomaleimide derivatives **1** was prepared from 3,4-dihalofuran-2,5-dione and the corresponding aliphatic and (hetero)aromatic amines, ammonia, and acetohydrazide in acetic acid at elevated temperature, with yields of 37–92% (Scheme 2A).[46]

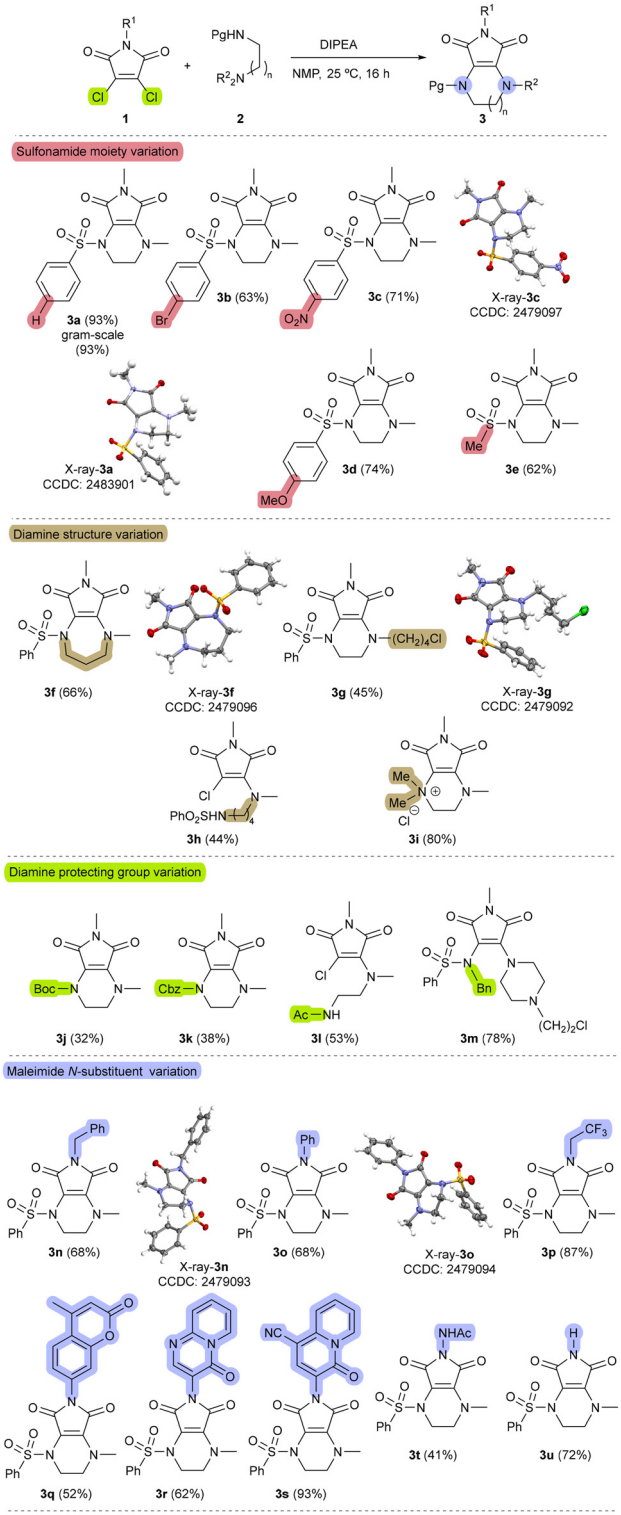


Scheme 2 (A) Synthesis of 3,4-dihalomaleimide **1**; (B) synthesis of amino-sulfonamide hydrochlorides **2**. [a]Known compound; see SI. [b]Synthesized from 3,4-dichloro-1-methyl-1*H*-pyrrole-2,5-dione (**1a**) by chloride-iodide substitution with NaI. [c]Synthesized by acid deprotection of *tert*-butyl methyl(2-(phenylsulfonamido)ethyl)carbamate using 2 M HCl in ethyl acetate.

The iodo analogue **1c** was prepared by transhalogenation of dichloromaleimide **1a** with excess sodium iodide (see SI). Similarly, a library of twelve amino-sulfonamide hydrochlorides **2** was synthesized from the corresponding sulfonyl chlorides and tertiary-primary diamines, with yields of 43–99% (Scheme 2B). Compound **2l** was prepared by HCl-catalyzed deprotection of the corresponding Boc-protected amino-sulfonamide (see SI).

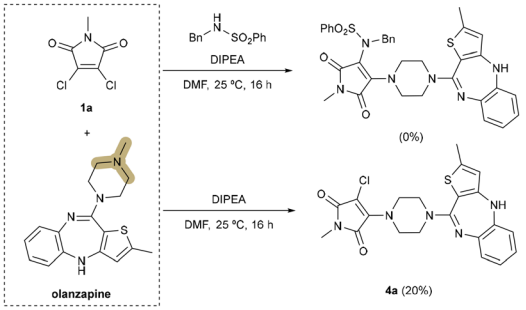
Next, the reactivity of the bromo analog **1b** and the iodo analog **1c** with diamine **2a** was examined, yielding the corresponding bicyclic product **3a** in 72% and 56% yield, respectively. The differences in reaction rates among the chloro analog **1a**, bromo analog **1b**, and iodo analog **1c** are notable, with the iodo analog exhibiting the slowest rate. These trends correlate well with the isolated yields and reflect the reactivity of the carbon–halogen bond in nucleophilic aromatic substitution reactions[47] (see SI, Fig. S6).

Scheme 3 illustrates the reaction scope of functionalized diamines **2** with dichloromaleimide derivatives **1** under optimized conditions. Varying the benzensulfonamide moiety from neutral to electron-poor and electron-rich analogs yielded the corresponding bicyclic products **3b–3d** in 63–74% yields. *N*-(2-(dimethylamino)ethyl)methanesulfonamide (**2e**) reacted equally well, affording the corresponding bicyclic maleimide **3e** in 62% yield. The impact of the diamine structure on the cyclization reaction showed that, in general, the reaction was compatible with a range of structurally diverse diamine derivatives, including 1,3-diamine **2f**, *N*-(2-(pyrrolidin-1-yl)ethyl)benzenesulfonamide hydrochloride (**2g**), and 1,2-tertiary diamine (Scheme 3, examples **3f–3i**). Attempts to position the diamine functionality beyond the 1,3-position, such as by reacting *N*-(4-(dimethylamino)butyl)benzenesulfonamide (**2h**) with **1a**, were unsuccessful and did not produce the corresponding eight-membered bicyclic structure. Instead, the monosubstituted maleimide analog **3h** was isolated in 44% yield. Notably, when N^1,N^1,N^2,N^2-tetramethylethane-1,2-diamine was reacted with **1a** under optimized conditions, the corresponding bicyclic ammonium chloride **3i** was isolated in 80% yield. The reaction of the *N*-(2-(benzyl(methyl)amino)ethyl)benzenesulfonamide (**2i**) with dichloromaleimide **1a** was not regioselective and produced an inseparable mixture of dealkylated products. The transformation was not compatible with the electron-deficient morpholine scaffold exemplified by *N*-(2-morpholinoethyl)benzenesulfonamide (**2j**) and the α-branched pyrrolidine-based diamine derivative *N*-((1-ethylpyrrolidin-2-yl)methyl)benzenesulfonamide (**2k**), as these did not produce the desired products. Various amine protecting groups, such as Boc, Cbz, and Ac, were introduced to expand the synthetic utility of the transformation. Diamines with Boc and Cbz protecting groups on the vicinal amine afforded the desired bicyclic products **3j** and **3k** in 32% and 38% yield, respectively, while the acetamido group was unreactive toward cyclization, resulting in the isolation of the corresponding substituted maleimide **3l** in 53% yield. The follow-up three-component reaction of dichloromaleimide **1a**, *N*-benzylbenzenesulfonamide, and DABCO yielded the doubly substituted maleimide **3m** in 78% yield. Finally,



Scheme 3 Scope and limitations of the reaction of diamine derivatives with 3,4-dichloromaleimide.

the *N*-substituent at the maleimide core was varied. As shown in Scheme 3, various dichloromaleimides **1** successfully undergo a double addition–elimination reaction under mild, optimized conditions to afford the corresponding bicyclic pro-



Scheme 4 Reaction of Olanzapine with *N*-methyl-3,4-dichloromaleimide.

ducts **3n–3u** in synthetically useful yields (52–93%), including the *N*-acetylamino-substituted maleimide product **3t** in 41% yield. To test the influence of scalability on the yield, a gram-scale reaction of **1a** (1.980 g, 11.0 mmol) with **2b** was performed under optimized conditions, yielding pure compound **3a** in an excellent 93% yield (3.280 g).

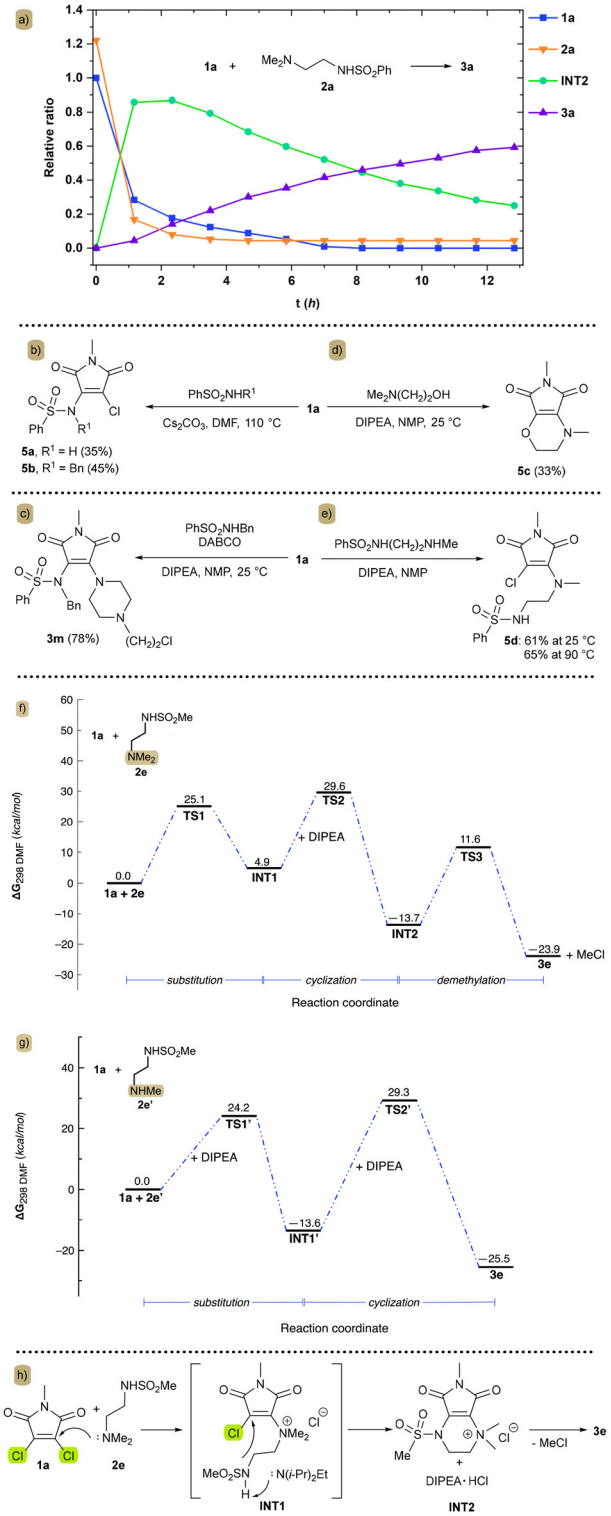
The structures of several products **3** were unambiguously confirmed by X-ray diffraction analysis, and the corresponding ORTEP structures are shown in Scheme 3. Diaminated products **3** exhibit characteristic yellow fluorescence under UV-A light (see SI for optical data for **3a**, **3e**, **3f**, **3h**, and **3k**).

The mild conditions developed for this double or single substitution process suggest that it can serve as a precise tool for late-stage modification of more complex, biologically relevant substrates. As shown in Scheme 4, the maleimide scaffold was successfully incorporated into olanzapine, yielding derivative **4a** in 20%. The corresponding three-component reaction with *N*-benzylbenzenesulfonamide did not produce the desired product, presumably due to steric reasons.

Mechanistic studies

We performed key control experiments (Scheme 5) and DFT calculations to elucidate the sequential reaction pathway of cyclization. First, we monitored the reaction progress of **1a** with *N*-(2-(dimethylamino)ethyl)benzenesulfonamide (**2a**) over time by ^{1}H NMR in DMSO-d_6 under standard reaction conditions for 14 hours. The proton NMR analysis revealed rapid consumption of the starting material within the first hour, with significant formation of the intermediate **INT2** before the demethylation step. The identity of intermediate **INT2** was confirmed by ESI-HRMS. Intermediate **INT2** reached its maximum concentration after approximately 2 hours and was then consumed to form the neutral end product **3a**. These results indicate that the demethylation step is rate-determining for the formation of product **3a** (Scheme 5a and h).

Key control experiments were performed to elucidate the relative reactivity of sulfonamide (RSO_2NH–) and tertiary amine (Me_2RN) groups in *N*-(2-(dimethylamino)ethyl)sulfonamide reagents and to provide insight into the role



Scheme 5 Mechanistic studies. (a) Time-course monitoring of the reaction **1a** + **2a** → **3a**. (b–e) Key control experiments for the heteroannulation reaction cascade of diamine derivatives **2** with dichloromaleimide **1a**. (f) and (g) Computational DFT study (M06-2X/Def2-TZVPP//wB97X-D/Def2-TZVP, SMD(DMF) at 298 K, free energies in kcal mol^{-1}) for the reactions **1a** + **2e** → **3e** and **1a** + **2e'** → **3e'**, respectively. (h) Proposed reaction pathway for the cation-driven heteroannulation of diamine **2a** with dichloromaleimide **1a**.

of the quaternary ammonium functionality formed during the cyclization reaction. When benzenesulfonamide and *N*-benzylbenzenesulfonamide were used as reagents under standard reaction conditions with **1a**, only the starting material was recovered. The corresponding substitution products **5a** and **5b** (Scheme 5b) were obtained only when the reaction mixture was heated at 110 °C for 24 hours, indicating low reactivity of the sulfonamide nucleophile toward substitution with **1a**. In contrast, treatment of maleimide **1a** with *N*-benzylbenzenesulfonamide and DABCO as the tertiary amine under optimized reaction conditions gave the monocyclic, doubly substituted product **3m** in 78% yield (Scheme 5c). When **1a** was dissolved in ethanol in the presence of a base, no substitution occurred under standard reaction conditions, whereas reaction of **1a** with 2-(dimethylamino)ethan-1-ol led to the formation of a bicyclic product **5c**, albeit in a modest yield of 33% (Scheme 5d). When the secondary amine *N*-(2-(methylamino)ethyl)benzenesulfonamide was used, the corresponding substituted maleimide **5d** was isolated in 61% yield, with no detection of bicyclic product **3a**. Repeating the reaction in the presence of DIPEA at 90 °C gave product **5d** in 65% yield (Scheme 5e). Heating substituted maleimide **5d** above 90 °C resulted in thermal decomposition of **5d** (see SI, Table S3), with no detection of bicyclic product **3a**. This result confirms that the heteroannulation leading to the bicyclic maleimide products **3** proceeds *via* a crucial ammonium intermediate **INT2** that facilitates the second vinylic substitution under milder reaction conditions.

Density functional theory (DFT) calculations were performed to provide deeper insight into the underlying reaction mechanism. The calculated Gibbs free energy profile in DMF for the proposed reaction pathway is shown in Scheme 5 (see SI for computational details). The reaction pathway was examined starting from substrate **1a** and the functionalized diamine **2e**, as illustrated in Scheme 5f. Initially, **1a** undergoes nucleophilic substitution with the tertiary amine moiety (R–NMe_2) *via* transition state **TS1**, with an activation free energy of 25.1 kcal mol^{-1}, to afford the cationic intermediate **INT1**. This step is endergonic and reversible. The resulting quaternary ammonium group in **INT1** facilitates the subsequent base-catalyzed addition–elimination–cyclization sequence involving the relatively weak sulfonamide nucleophile (–SO_2NH–), which proceeds through **TS2** with an activation barrier of 24.7 kcal mol^{-1} and is overall exergonic, yielding intermediate **INT2**. In the final step, energetically favorable demethylation of the quaternary ammonium moiety in **INT2** by chloride anion occurs *via* **TS3**, with an activation barrier of 25.3 kcal mol^{-1}, furnishing the bicyclic product **3e**.

To elucidate the role of the ammonium moiety in **INT1** during the cyclization step, a comparative reaction profile was calculated for an analogous system with an amino nucleophile containing a secondary amine functionality (R–NHMe, **2e′**; see Scheme 5g). Under the investigated conditions, reaction with the secondary amine *N*-(2-(methylamino)ethyl)benzenesulfonamide does not produce the cyclized product; instead, the monosubstituted product **5d** is observed experimentally (see Scheme 5e). As shown in Scheme 5g, substrate **1a** undergoes a favorable, exergonic base-catalyzed substitution with the secondary amine of **2e′** to form the neutral intermediate **INT1′**. In contrast to the ammonium containing system, the subsequent cyclization step *via* **TS2′** has a much higher activation barrier (42.9 kcal mol^{-1}) leading to the bicyclic product **3e**, making this pathway kinetically inaccessible at ambient temperature. Overall, these results indicate that cyclization to bicyclic products **3** is significantly facilitated by the involvement of ammonium cationic intermediates, which, due to their limited thermodynamic stabilization, readily undergo a second substitution at the vinylic position under relatively mild reaction conditions.

Based on experimental observations and DFT analysis, a plausible reaction mechanism for the heteroannulation cascade between diamine derivatives **2** and dihalogenated maleimides **1** is proposed, as shown in Scheme 5h. The transformation is initiated by an elementary addition–elimination step involving the tertiary amine nucleophile, leading to the formation of the key quaternary ammonium intermediate **INT1**. Under mild reaction conditions, this intermediate undergoes a second addition–elimination event with the intrinsically electron-deficient sulfonamide nucleophile; this transformation proceeds *via* a general base-catalyzed pathway to yield the cyclized cationic intermediate **INT2**. In the final stage, **INT2** undergoes demethylation by a chloride anion, producing the heteroannulated product **3**.

Conclusions

In summary, we have developed a novel and synthetically feasible strategy for the rapid construction of functionalized maleimides under metal-free, mild conditions, starting from inexpensive bulk dihalomaleimide derivatives. This modular approach enables efficient access to heterobicyclic and 3,4-diamino-substituted maleimides in synthetically useful yields. The protocol demonstrates broad functional group tolerance and uniquely allows a second halogen substitution with relatively weak nucleophiles – an otherwise challenging transformation with 3-amino-4-halomaleimide substrates. Both experimental and theoretical studies indicate that the formation of a quaternary enamine intermediate plays a central role in directing the reaction toward 3,4-diaminomaleimide derivatives. Taken together, these results provide a new and versatile platform for accessing structurally diverse maleimides with potential applications in bioconjugation, medicinal chemistry, and materials science.

Author contributions

Conceptualization, B. Š., L.C. and U. G.; methodology, H. B., L. C., and N. P.; software, B. Š.; validation, B. Š., N. P., and J. S.; formal analysis, B. Š. and L. C.; investigation, H. B., N. P., and L. C.; data curation, B. Š., N. P., L. C., and U. G.; writing – orig-

inal draft preparation, B. Š.; writing – review and editing, J. S., U. G., L. C., and N. P.; visualization, B. Š.; supervision, B. Š. and U. G.; funding acquisition, J. S. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data that support the findings of this study are available in the supplementary information (SI). Supplementary information: all experimental data, characterization data (^{1}H NMR, ^{13}C NMR, HRMS spectra), and computational details. See DOI: **https://doi.org/10.1039/d6qo00010j**.

The authors have cited additional references within the SI.[46–68]

Raw data files are available from the corresponding author upon reasonable request.

CCDC 2483901 (**3a**), 2479097 (**3c**), 2479096 (**3f**), 2479092 (**3g**), 2479093 (**3n**) and 2479094 (**3o**) contain the supplementary crystallographic data for this paper.[69a–f]

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