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Development of one-pot benzylic amination reactions of azine *N*-oxides

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ABSTRACT

An efficient one-pot synthetic methodology has been developed for the benzylic amination reactions of methyl-substituted azine *N*-oxides that operate under mild conditions. The reaction was found to tolerate quinoline and isoquinoline *N*-oxides with electron donating and withdrawing substituents as the electrophilic reaction partners as well as a broad range of nucleophilic primary, secondary and aromatic amines, affording the benzylic amination products in up to 82% yield.

During the last decade, there has been a renaissance of interest in the chemistry of azine *N*-oxides, which enables efficient functionalization of a broad range of *N*-heteroaromatic compounds.[1] In this context, azine *N*-oxides were shown to react successfully with a variety of carbon,[2] nitrogen,[3] oxygen,[4] phosphorus[5] and sulfur[6]-based nucleophiles as well as halides,[7] generally in the presence of a suitable activating agent or a catalyst. Among various activating agents, PyBroP proved to be a particularly effective reagent for the activation of azine *N*-oxides in a plethora of applications.[8]

Whereas most of the recent synthetic efforts focused on the reactions of azines with nucleophiles at the 2-position, their functionalization at the benzylic position represents an equally important reaction class. In this regard, 2-(aminomethyl)azine derivatives are commonly encountered as ligands used in metal complexes,[9] natural products such as Aplidiopsamine A (**1**),[10] and many biologically active compounds such as BI 1356 (**2**),[11] VUF-K-8788 (**3**),[12] and **4** (Fig. 1).[13] One of the common methods for the functionalization of 2-methylazine compounds is via their radical bromination using NBS followed by nucleophilic substitution.[9a,14] However, this reaction sometimes gives multiple bromination products,[14] and may have selectivity issues in the presence of other functional groups. 2-Methylazines can also be oxidized to aldehydes at the benzylic position by SeO_2 for further functionalization.[15] One of the most widely employed methods for the derivatization of 2-methylazine *N*-oxides is the Boekelheide rearrangement[16] using acetic anhydride (Ac_2O)[17] and trifluoroacetic anhydride.[18] While highly effective, these reactions may require high reaction temperatures, and more importantly, the 2-(acetoxymethyl)azine products of the rearrangement have to be hydrolyzed to the corresponding alcohols and further activated with suitable activating agents for their subsequent reactions with nucleophiles, all of which increase the overall number of steps.[9d–f,13] In addition to acetic and trifluoroacetic anhydride, acyl chlorides,[19] sulfonyl chlorides and sulfonic anhydrides[20] and *in situ*-generated dialkylchlorophosphates[21] have occasionally been used in Boekelheide-type rearrangements for the activation of azine *N*-oxides.

In this work, we performed a systematic investigation on the activation of methyl-substituted azine *N*-oxides towards their reactions with amine nucleophiles, and developed an effective protocol for their one-pot benzylic amination reactions under mild conditions. Development of synthetic methodologies that operate in a one-pot manner has recently attracted significant attention from the synthetic community since such protocols eliminate the need for the purification of reaction intermediates and thus, lower the cost, reaction time, labour and waste generation.[22,23]

We initiated our study by screening a variety of activating agents for the targeted one-pot benzylic amination reaction (Table 1). Inspired by the recent successful utilization of PyBroP in a broad range of reactions as an activating agent for azine *N*-oxides,[8] we first tested this reagent in the reaction of quinaldine *N*-oxide (**5**) with morpholine (**6**) in acetonitrile at 80 °C. Disappointingly, the formation of the desired benzylic amination

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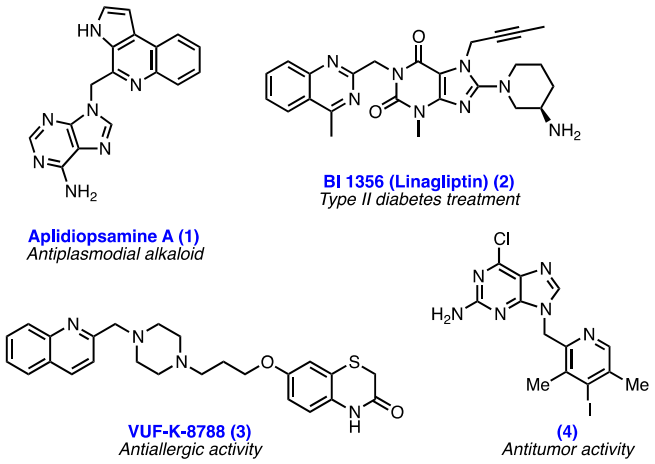
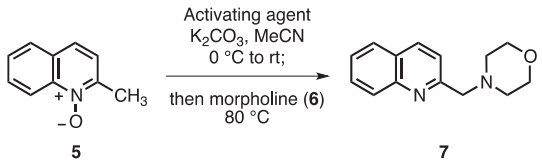


Fig. 1. Examples of biologically active 2-(aminomethyl)azine derivatives.

Table 1
Screening of activating agents for the one-pot benzylic amination reaction.[a]



5 **7**

Entry	Activating agent	Yield (%)[b]
1	PyBroP	<5
2	Ph_3PBr_2	<5
3	MsCl	71
4	TsCl	81
5	Ms_2O	67
6	Ts_2O	70
7	Tf_2O	7
8[c]	TsCl	80

[a] Reaction conditions: 0.31 mmol of quinaldine *N*-oxide (**5**), 0.37 mmol of activating agent, 0.68 mmol of K_2CO_3, 0.47 mmol of morpholine (**6**) and 2.0 ml of MeCN.
[b] Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.
[c] Activated 4 Å molecular sieves were used. *Abbreviations:* PyBroP, bromotripyrrolidinophosphonium hexafluorophosphate; Ms, methanesulfonyl; Ts, *p*-toluenesulfonyl; Tf, trifluoromethanesulfonyl.

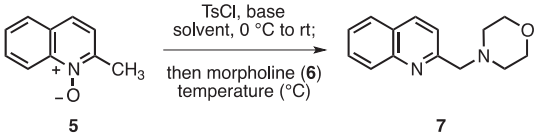
product **7** was not observed by the use of PyBroP (entry 1), and changing reaction parameters (solvent, temperature and base) did not provide any improvement. The use of another phosphonium salt, Ph_3PBr_2,[24] which is structurally related to PyBroP, gave a similar result and did not lead to the formation of **7** (entry 2). It should be noted that in these experiments, *N*-oxide **5** was observed to remain almost completely unreacted at the end of the reactions. Based on these observations, we turned our attention to the use of sulfonyl chlorides and sulfonic anhydrides as activating agents for the desired transformation. Pleasingly, methanesulfonyl chloride (MsCl) was found to be an effective promoter of the reaction providing the benzylic amination product **7** in 71% yield (entry 3). Switching to *p*-toluenesulfonyl chloride (TsCl) led to a further increase in reaction yield (81%, entry 4). Next, we tested sulfonic anhydrides Ms_2O and Ts_2O in order to observe the effect of the counter anion (Cl^-, MsO^- and TsO^-) formed upon the activation of the *N*-oxide reactant. While still active, Ms_2O and Ts_2O gave slightly lower yields (67 and 70% yields, respectively) compared to their Cl-containing counterparts, MsCl and TsCl (entries 5 and 6). The more reactive activating agent Tf_2O gave rise to a complex mixture of products and afforded the amination product **7** in only 7% yield (entry 7). Finally, the addition of 4 Å molecular sieves did not provide an increase in the reaction yield when TsCl was used (80% yield, entry 8).

With the identification of TsCl as the optimal activating agent for the investigated one-pot benzylic amination reaction, we next performed a base, solvent and temperature screening (Table 2). When the reaction was run in acetonitrile at 80 °C, Na_2CO_3 and K_3PO_4 gave inferior results compared to K_2CO_3 (entries 1–3). To our delight, switching the solvent to CH_2Cl_2 not only increased the yield to 90% but also demonstrated that the reaction operated well at a much lower temperature, 35 °C (entry 4). In a control experiment, the yield of the amination product **7** was found to be 74% when the reaction was conducted in MeCN at 35 °C (entry 5). Lower reaction yields were observed when THF and toluene were tested as solvents (64 and 27%, respectively; entries 6 and 7). Benzotrifluoride ($PhCF_3$) was introduced by Curran and coworkers in 1997 as an alternative solvent to CH_2Cl_2 with a comparable polarity but higher boiling point.[25] However, amination product **7** was obtained in 62 and 53% yields, when the reaction was run in $PhCF_3$ at 35 and 60 °C, respectively (entries 8 and 9). The use of 2-MeTHF as a biorenewable, green solvent[26] and TBME did not provide an improvement (entries 10 and 11). Finally, we focused on the effect of using organic amine bases instead of K_2CO_3 as an inorganic base. In this respect, Et_3N, Hunig's base (iPr_2-NEt) and DBU were tested in CH_2Cl_2 at 35 °C, but lower reaction yields were observed in each case (entries 12–14).

We next investigated the substrate scope of the developed benzylic amination reaction using the optimized conditions (Table 3). Initially, the performance of a variety of amines as the nucleophilic component of the reaction was tested systematically. Under the optimized reaction conditions, amination product **7** was obtained in 82% isolated yield after purification by column chromatography. Other cyclic secondary amines piperidine and pyrrolidine were found to be competent reaction partners giving the amination products **8** and **9** in 76% and 62% yields, respectively. Medicinally important piperazine moiety was incorporated to the amination reaction via the use of *N*-Boc-piperazine, and the amination product **10** was isolated in 72% yield. The use of diethylamine amine as an acyclic secondary amine afforded product **11** in good yield (73%). Cyclohexylamine and α-methylbenzylamine were tested as primary amine nucleophiles, and were found to be successful reaction partners (46 and 64% yields, respectively). Finally, we investigated pyrazole and imidazole as nitrogen-containing aromatic amine nucleophiles. While benzylic amination product **14** was obtained in 50% yield, the utilization of imidazole afforded the amination product **15** in a higher yield (61%). These results demonstrate that a broad range of cyclic and acyclic secondary, primary and aromatic amines are successful nucleophilic reaction partners in the developed one-pot benzylic amination protocol.

Afterwards, we turned our attention to the investigation of various methyl-substituted azine *N*-oxides in the amination reaction (Table 3). All the *N*-oxide derivatives tested in this study were prepared from the corresponding azine compounds through their oxidation by *m*-CPBA.[28] The use of 6-bromoquinaldine *N*-oxide gave product **16** in 66% isolated yield. The Ar-Br moiety in this product has the potential to be utilized as a functional handle for further functionalization via a variety of cross-coupling reactions. The reaction tolerates the presence of the electron-donating –OMe group on the *N*-oxide component, and the amination product was obtained in 47% yield. The use of 4-chloroquinaldine *N*-oxide substrate afforded product **18** in good yield (69%). We next opted to test the reactivity of a substrate containing an amino group at the 4-position because of the importance of 4-dimethylaminopyridine (DMAP) analogues in organic chemistry. With this aim, the

Table 2
Optimization of the one-pot benzylic amination reaction.[a]



5 7

Entry	Base	Solvent	Temperature (°C)	Yield (%)[b]
1	K_2CO_3	MeCN	80	81
2	Na_2CO_3	MeCN	80	61
3	K_3PO_4	MeCN	80	76
4	K_2CO_3	CH_2Cl_2	35	90
5	K_2CO_3	MeCN	35	74
6	K_2CO_3	THF	35	64
7	K_2CO_3	Toluene	35	27
8	K_2CO_3	$PhCF_3$	35	62
9	K_2CO_3	$PhCF_3$	60	53
10	K_2CO_3	2-MeTHF	60	34
11	K_2CO_3	TBME	35	27
12	Et_3N	CH_2Cl_2	35	60
13	*i*Pr_2NEt	CH_2Cl_2	35	<5
14	DBU	CH_2Cl_2	35	13

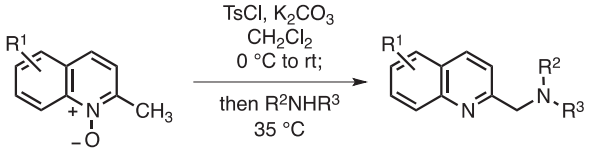
[a] Reaction conditions: 0.31 mmol of quinaldine *N*-oxide (**5**), 0.37 mmol of TsCl, 0.68 mmol of base, 0.47 mmol of morpholine (**6**) and 2.0 ml of solvent.
[b] Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. *Abbreviations:* DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene.

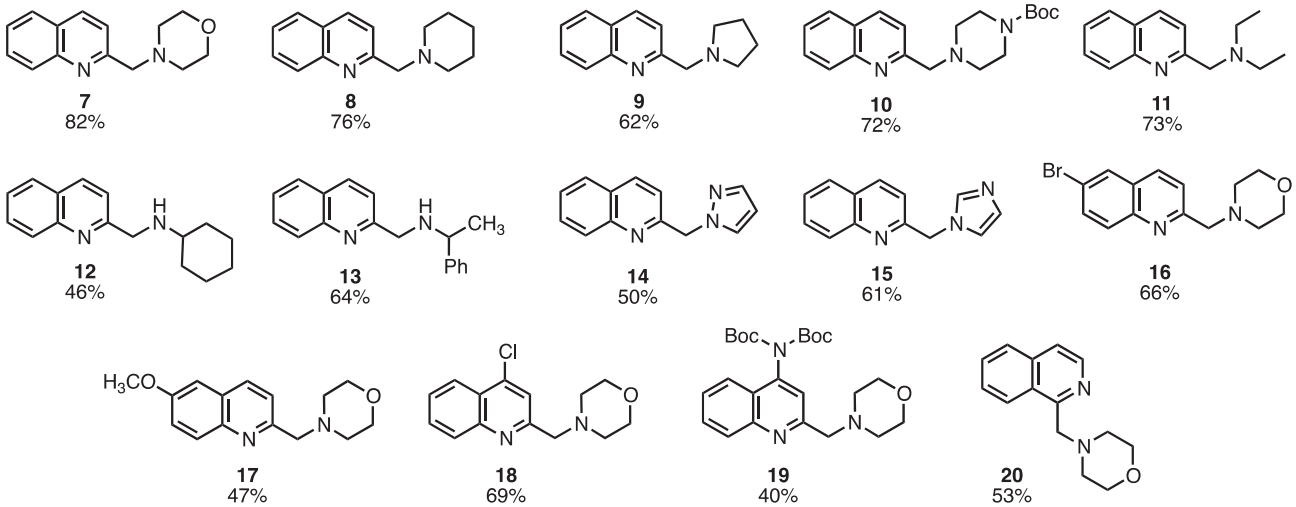
amination product **19** that possesses the doubly Boc-protected amino substituent was prepared successfully, albeit in a lower yield (40%). Finally, 1-methylisoquinoline *N*-oxide was found to be a compatible reaction partner affording the benzylic amination product **20** in 53% yield, which demonstrates that the methodology can be extended to the synthesis of functionalized isoquinolines as well.

In order to assess the scalability of the one-pot protocol developed in this study, we next performed the benzylic amination reaction of quinaldine *N*-oxide (**5**) on 10 mmol scale (1.59 g), and the amination product **7** was isolated in 64 and 63% yields on two trials (Scheme 1a). Even though there is a slight decrease in yield, these gram-scale experiments showcase the scalability and reproducibility of this one-pot method. When treated with TsCl, a methyl-substituted azine *N*–oxide first undergoes a Boekelheide-type rearrangement to give a (tosyloxymethyl)azine intermediate (**21**), which, without isolation, reacts subsequently with the nucleophilic amine component (Scheme 1b). When the reaction of quinaldine *N*-oxide (**5**) was performed without the addition of an amine, 2-(tosyloxymethyl)quinoline (**22**) was isolated in 72% yield.[28,29] It was reported that this reaction gave an imidazoquinoline side product with the incorporation of acetonitrile which was used as the reaction solvent.[20c] During the optimization studies, we also observed the formation of this side product in 6–25% yield depending on the activating agent used when MeCN was the reaction solvent.[28] The higher yields that we obtained with CH_2Cl_2 may be attributed to the lack of the formation of this side product. In another control experiment, the reaction between quinaldine *N*-oxide and morpholine, performed under the optimized conditions but without K_2CO_3, gave product **7** in only 19% yield along with unreacted *N*-oxide **5**.[30] Finally, 2-picoline *N*-oxide was found to be unreactive towards the Boekelheide-type rearrangement under the standard reaction conditions and did not provide the corresponding benzylic amination product.

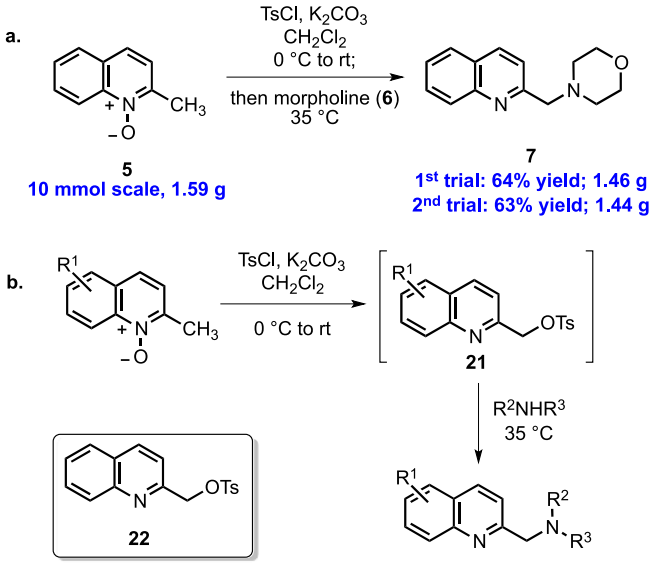
In summary, we have developed a one-pot synthetic protocol that allows efficient benzylic amination reactions of methyl-substituted azine *N*-oxides. This method is operationally simple, proceeds under mild reaction conditions and does not require the isolation of reaction intermediates. A broad range of cyclic and acyclic secondary, primary and aromatic amines as well as electron rich and deficient quinoline and isoquinoline *N*-oxides are well tol-

Table 3
Substrate scope of the one-pot benzylic amination reaction[27].[a]





[a] Reactions were carried out using azine *N*-oxide (1.0 equiv), TsCl (1.4 equiv), K_2CO_3 (2.5 equiv) and amine base (2.0 equiv) in anhydrous CH_2Cl_2. Yields refer to isolated yields after purification by column chromatography.



Scheme 1. Gram-scale example and description of the benzylic amination reaction.

erated in the reaction affording the benzylic amination products in up to 82% yield. Scalability of the method has been demonstrated through a gram-scale reaction. Given the importance of 2-(aminomethyl)azine derivatives as ligands and biologically active molecules, this one-pot protocol is expected to find widespread use in synthetic applications.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.03.062.

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27. *Representative procedure for the benzylic amination reaction:* Quinaldine *N*-oxide **5** (200 mg, 1.26 mmol) was dissolved in anhydrous CH_2Cl_2 (8.0 mL) at rt under nitrogen. After the addition of K_2CO_3 (428 mg, 3.10 mmol), the reaction mixture was cooled down to 0 °C in an ice-water bath. After five minutes, TsCl (332 mg, 1.74 mmol) was added, and it was stirred for five more minutes at this temperature. The cooling bath was removed, and the reaction mixture was stirred at rt for 5 h. Morpholine (224 μL, 2.52 mmol) was then added, and the reaction mixture was stirred at 35 °C for 18 h. After the mixture was cooled down to rt, water was added, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, MeOH:EtOAc = 1:19) gave pure product **7** as a yellow oil (234 mg, 82%). R_f = 0.39 (MeOH: EtOAc = 1:19); ^{1}H NMR (400 MHz; $CDCl_3$) δ: 8.11 (1H, d, *J* = 8.5 Hz), 8.07 (1H, d, *J* = 8.5 Hz), 7.78 (1H, d, *J* = 8.1 Hz), 7.68 (1H,

ddd, J = 8.4, 6.9 and 1.4 Hz), 7.62 (1H, d, J = 8.4 Hz), 7.50 (1H, ddd, J = 8.1, 7.0 and 1.0 Hz), 3.83 (2H, s), 3.73 (4H, t, J = 4.7 Hz), 2.55 (4H, t, J = 4.6 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ: 159.2, 147.8, 136.5, 129.5, 129.2, 127.6, 127.5, 126.3, 121.2, 67.1, 65.7, 54.0; IR ν_{max} (ATR, oil)/cm^{-1} 2957, 2852, 2808, 1618, 1599, 1503, 1453, 1425, 1349, 1327, 1265; HRMS: Calculated for $C_{14}H_{17}N_2O$ $[M+H]^+$ 229.1335, observed 229.1332.

28. Please see the Supplementary Information for details.
29. This observation is in accordance with the result obtained by Sledeski and coworkers (Ref. 20c).
30. 4.5 equivalents of morpholine was used in this control experiment in order to have an equal total amount of base as in the standard conditions.