Facile Access to Ring-Fused Aminals via Direct α-Amination of Secondary Amines with *o*-Aminobenzaldehydes: Synthesis of Vasicine, Deoxyvasicine, Deoxyvasicinone, Mackinazolinone, and Ruteacarpine

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Dedicated to Prof. Scott E. Denmark on the occasion of his 60th birthday

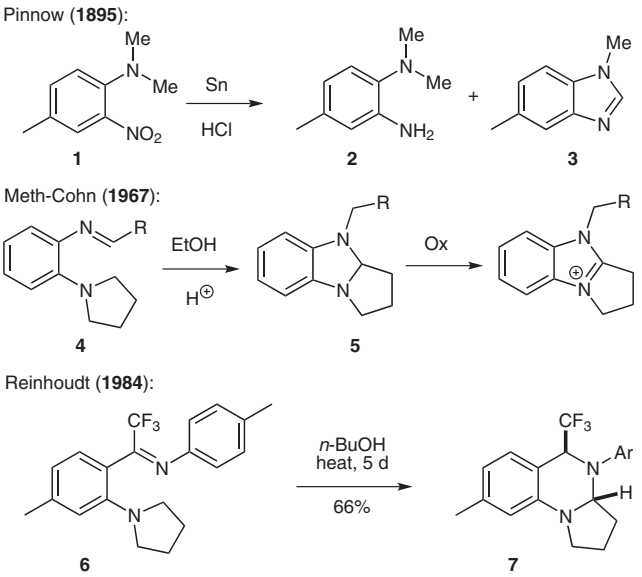
Abstract: Secondary amines undergo redox-neutral reactions with aminobenzaldehydes under conventional and microwave heating to furnish polycyclic aminals via amine α-amination/N-alkylation. This unique α-functionalization reaction proceeds without the involvement of transition metals or other additives. The resulting aminal products are precursors for various quinazolinone alkaloids and their analogues.

Key words: C–H bond functionalization, redox isomerization, aminals, quinazolinone alkaloids, Friedländer condensation

Introduction

The transformation of simple amines into value-added building blocks via α-C–H bond functionalization remains an active area of research.[1] While the majority of current approaches are oxidative in nature, redox-neutral[2] methods offer an attractive alternative. Perhaps the earliest example of a nonoxidative α-functionalization of an amine can be traced back to Pinnow who in 1895 reported the unusual reaction outlined in Scheme 1.[3] Exposure of nitroaniline **1** to reducing conditions provided benzimidazole **3** in addition to the expected diamine **2**. Product **3** results from the functionalization of a methyl group, presumably via intramolecular H-transfer to an intermediate nitroso compound.

Reactions of this type in which a tertiary amine undergoes functionalization in α-position were later classified under the term *tert*-amino effect. Several reviews on this topic have appeared.[4] Other classic examples of the *tert*-amino effect that lead to amine α-amination are shown in Scheme 1. Meth-Cohn et al. reported the acid-catalyzed isomerization of imines **4** to dihydrobenzimidazoles **5**, species that readily air-oxidize to the corresponding benzimidazolium salts.[5] This interesting rearrangement is thought to proceed via a 1,6-hydride transfer from an amine α-C–H bond to an iminium ion. Reinhoudt and coworkers, in addition to many other key contributions,[6] reported the thermal rearrangement of imine **6** to aminal **7**.[6b] This reactions involves a 1,5-hydride shift/ring closure sequence. Akiyama et al.[7] and our group[8] independently reported the Brønsted acid catalyzed formation of aminals related to **7** by employing a one-pot cascade strategy starting form primary amines and tertiary *o*-aminobenzaldehydes. In addition to standard condensation based approaches to aminals,[9] a number of oxidative amine α-aminations have also been reported.[10]



Scheme 1 Examples of amine α-amination via C–H bond functionalization

Our interest in the area of C–H functionalization was sparked by an unexpected discovery. In the course of performing Friedländer reactions[11] to prepare a number of quinolines, we observed the formation of an interesting pyrrolidine-containing by-product. Specifically, the supposedly innocent base pyrrolidine was found to undergo an unexpected reaction with *o*-aminobenzaldehyde **8a** to form aminal **9a** under mild conditions (Scheme 2). In this process, an amine α-C–H bond is replaced by a C–N bond, concomitant with a reductive N-alkylation of the amine.[12–14] Here we provide a full account of this process, along with the application to the synthesis of several quinazolinone alkaloids.

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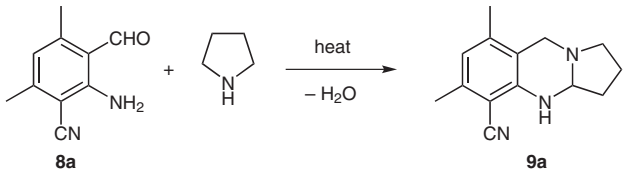
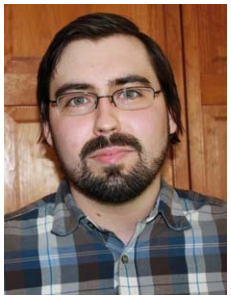


Scheme 2 Serendipitously discovered redox-neutral formation of aminals

Reaction Development

Following our initial discovery, the condensation of pyrrolidine and *o*-aminobenzaldehydes was evaluated under a range of conditions. Alcoholic solvents, in particular ethanol, provided better results than solvents such as toluene, DMF, THF, and acetonitrile. An excess amount of pyrrolidine proved beneficial to shorten reaction times while the use of pyrrolidine as solvent led to inferior re-

Biographical Sketches



Matthew T. Richers was born in Scotch Plains, NJ (USA) in 1987. In 2009, he obtained his B.Sc. in chemistry at The College of New Jersey. He is currently pursuing a Ph.D. in organic chemistry at Rutgers University in the laboratory of Prof. Daniel Seidel. His research focuses on the facile synthesis of nitrogen-containing heterocyclic compounds.

Indubhusan Deb was born in West Bengal (India). He obtained his B.Sc. (Honors in Chemistry) degree from the University of Calcutta and his M.Sc. degree from Banaras Hindu University in 2002. He performed his graduate work with Prof. I. N. N. Namboothiri at the Indian Institute of Technology Bombay and received his Ph.D. in 2008. He subsequently moved to Rutgers University where he carried out postdoctoral research with Prof. Daniel Seidel. Since 2011, he is pursuing postdoctoral research in Prof. Naohiko Yoshikai's research group at Nanyang Technological University, Singapore, where his research is focused on transition-metal-catalyzed C–H bond functionalization for the synthesis of heterocycles.

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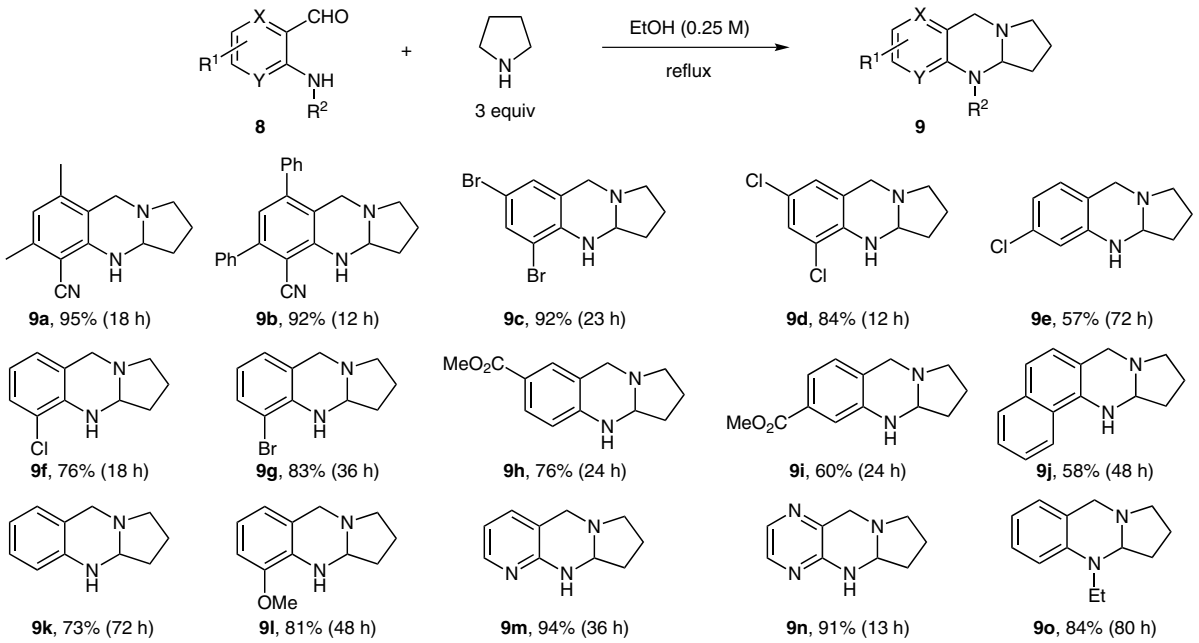
Chen Zhang was born in Fuzhou (P. R. of China) in 1982. He received his B.Sc. degree from the University of Science and Technology of China in 2005. In September of 2005, Chen joined the Seidel group at Rutgers University and received his Ph.D. in 2010. From 2010–2011, he performed his postdoctoral research in the group of Prof. Scott E. Denmark at the University of Illinois at Urbana-Champaign. Chen is currently conducting research in medicinal chemistry at Xizang Haisco Pharmaceutical Group Co., Ltd. in China.

Daniel Seidel was born in Mühlhausen, Thüringen (Germany) and studied chemistry at the Friedrich-Schiller-Universität Jena (Diplom 1998). His Ph.D. research at the University of Texas at Austin (1998–2002) under the supervision of Prof. Jonathan L. Sessler involved the development of new methods for the synthesis of expanded porphyrin analogues. From 2002–2005, Daniel was an Ernst Schering Postdoctoral Fellow in the group of Prof. David A. Evans at Harvard University. He started his independent career at Rutgers University in August 2005 and was promoted to Associate Professor with tenure in 2011. Research in his group is focused on new concepts for asymmetric catalysis and synthetic methodology.

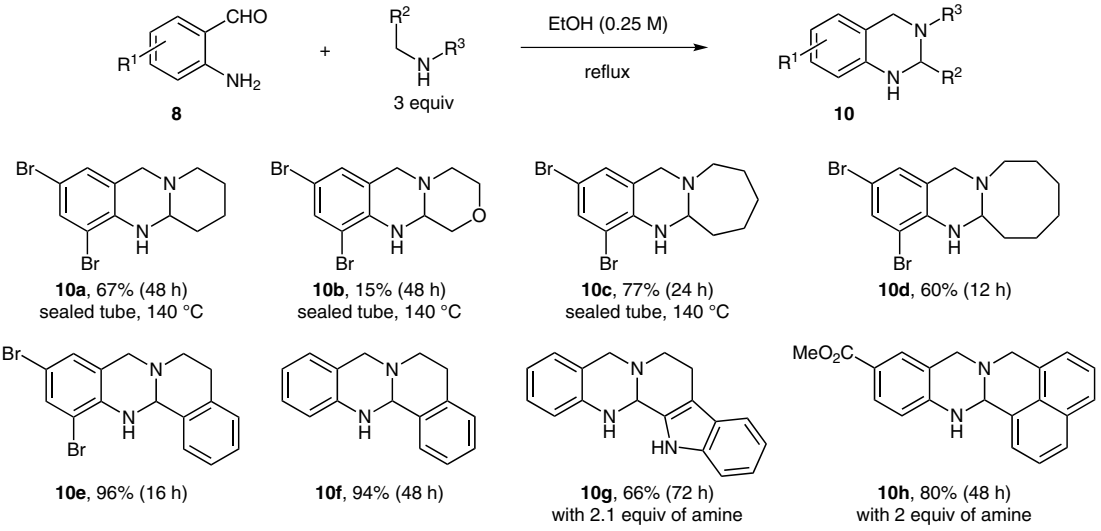


Scheme 3 Reactions of pyrrolidine with various *o*-aminobenzaldehydes

sults. Under optimized reaction conditions, a range of aminobenzaldehydes was allowed to react with three equivalents of pyrrolidine in ethanol under reflux (Scheme 3). Various aminobenzaldehydes with different substitution patterns and electronic properties proved to be suitable substrates, providing products in generally good yields. Electron-poor aminobenzaldehydes were found to be particularly reactive, whereas more electron-rich substrates furnished products in good yields after somewhat prolonged reaction times. Heterocyclic aminoaldehydes gave ring-fused aminals in excellent yields. An ethyl substituent on the nitrogen atom of the aminobenzaldehyde was tolerated.

The aminal formation was also explored with regard to amines other than pyrrolidine (Scheme 4). Interestingly, piperidine gave very little conversion under the original reaction conditions (reflux in ethanol). However, a reaction of piperidine and aminobenzaldehyde **8c** performed in a sealed tube at 140 °C led to a reasonable conversion to product. Even under these more forcing conditions, morpholine proved to be a poor substrate. Azepane showed a higher reactivity than piperidine, and azocane was found to be reactive enough to undergo the reaction under the original reflux conditions. Cyclic amines with benzylic α-C–H bonds such as tetrahydroisoquinoline (THIQ) were identified as highly reactive substrates, typically providing good yields of aminal products. Notably, shortly after our initial communication on these results, Dang and Bai independently reported a related procedure with *o*-phenylthio-*o*-aminopyrimidine aldehyde.[15]

Several of the aminal products were characterized by X-ray crystallography (Figure 1). Interestingly, the pyrro-



Scheme 4 Reactions of *o*-aminobenzaldehydes with various cyclic amines

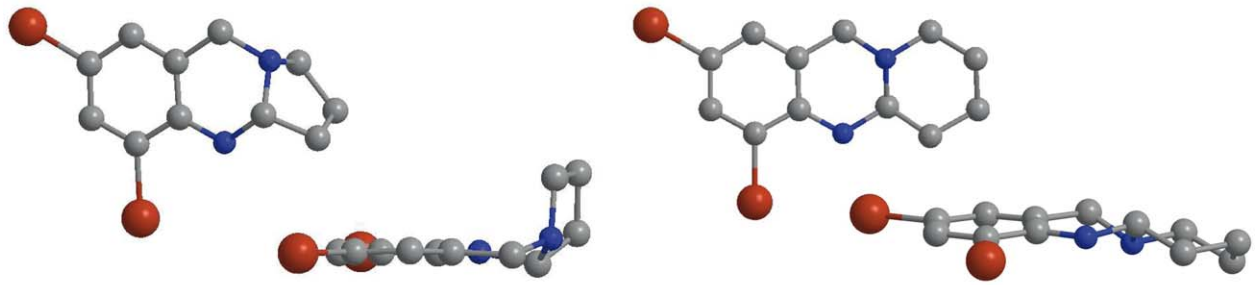


Figure 1 Top and side views of the X-ray crystal structures of **9c** (left) and **10a** (right)

lidine-derived aminal **9c** exhibits a bent structure whereas piperidine-based aminal **10a** adopts a relatively planar conformation.

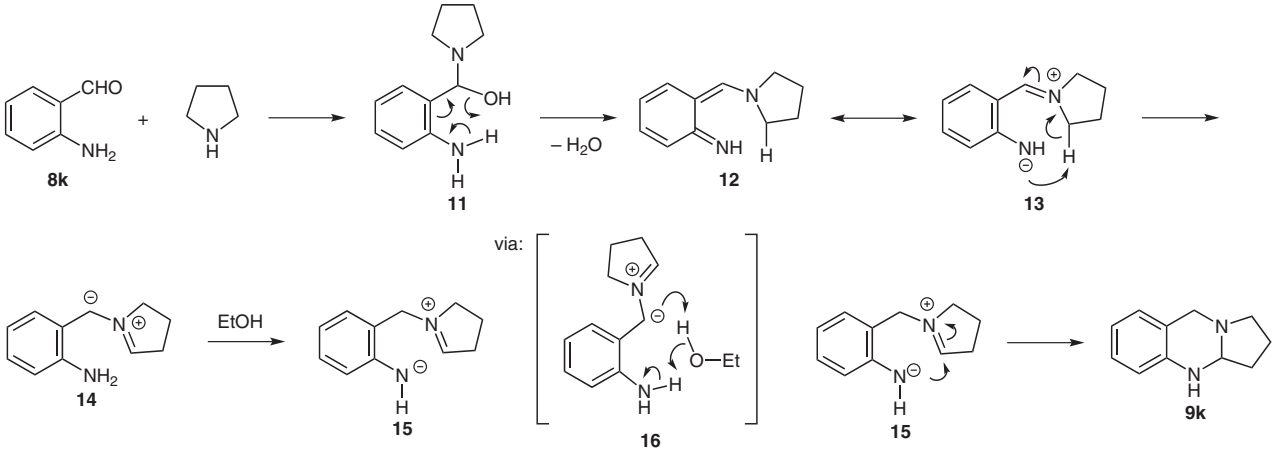
Reaction Mechanism

In collaboration with the Houk group, we have recently performed a combined computational and experimental study to delineate the mechanism of the aminal formation.[12c] Density functional theory calculations revealed a partially unexpected reaction pathway. Perhaps the most surprising finding is that simple iminium ions are most likely not involved in the overall process. The lowest energy pathway for aminal formation is outlined in Scheme 5, exemplified in the prototypical reaction of unsubstituted *o*-aminobenzaldehyde (**8k**) and pyrrolidine. In the first step, **8k** and pyrrolidine react to form *N*,*O*-acetal **11**. Rather than fragmenting into an iminium ion as originally assumed, **11** undergoes elimination of water via a six-membered transition state with participation of the NH_2 group to directly form *ortho*-azaquinonemethide **12**. Natural population analysis of **12** indicated a significant contribution from a zwitterionic resonance structure **13** with a negative charge on the aniline nitrogen and an iminium ion at the heterocycle, restoring the aromaticity of the system. The rate-determining step of the overall transformation is the rearrangement of azaquinonemethide **12**/**13** to azomethine ylide **14** via 1,6-proton abstraction. The alternative 1,6-hydride transfer process was ruled out. Another proton transfer step follows, converting azomethine ylide **14** to zwitterion **15**. Interestingly, ethanol acts as a proton-shuttle in this instance (via **16**). Ultimately, zwitterion **15** collapses into product **9k**. Support for this computationally derived mechanism was obtained from various deuterium-labeling studies and trapping of azaquinonemethide and azomethine ylide intermediates (*vide infra*).

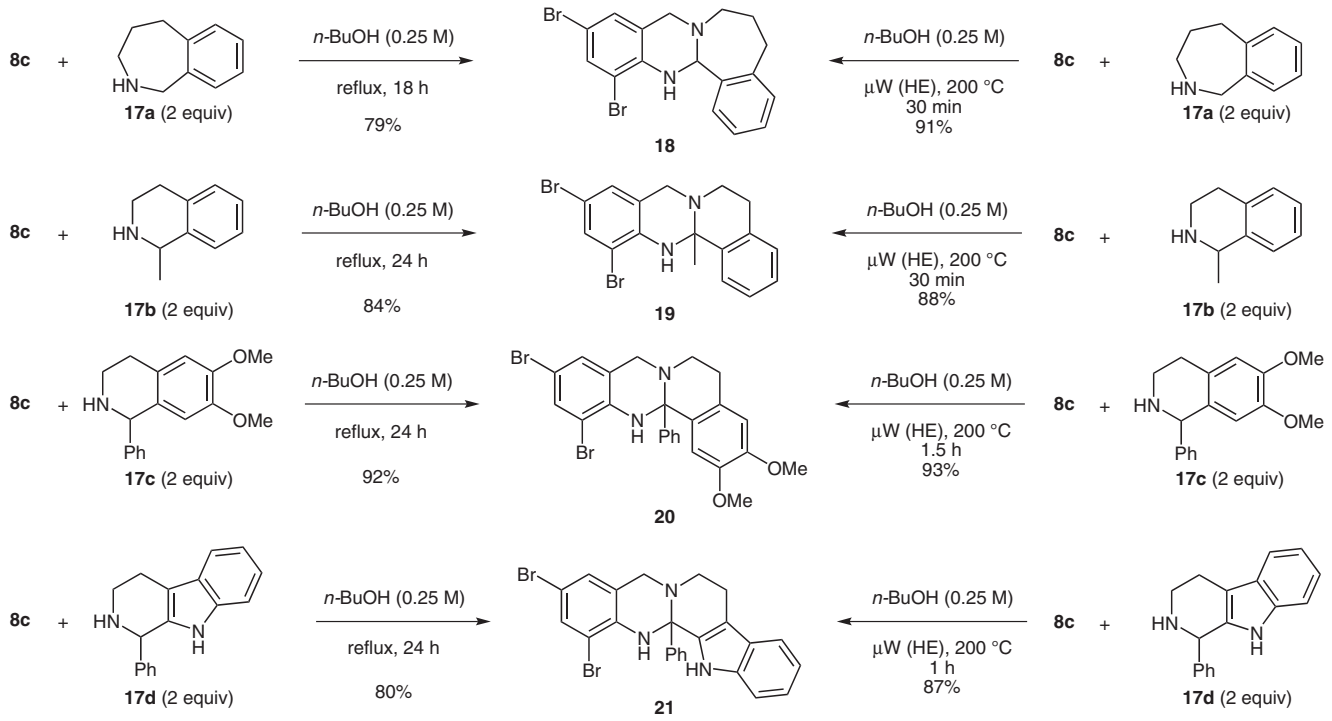
Reaction Optimization Under Microwave Conditions

Following our original publication,[12a] Polshettiwar and Varma reported the use of microwave irradiation to accelerate the formation of aminals from secondary amines and *ortho*-aminobenzaldehydes.[16] According to these authors, the reaction is best performed under solvent-free conditions with four equivalents of the cyclic amine. Specifically, reaction times between 40–60 minutes at 130 °C were reported to give good yields of products. Surprisingly, the same reaction conditions are purportedly applicable to a broad range of substrates, including cyclic amines such as pyrrolidine, piperidine, and morpholine – substrates that we had found to exhibit vastly different reactivities. In our hands, the findings by Polshettiwar and Varma were largely irreproducible. Our own efforts to identify efficient microwave conditions are the subject of the following discussion.

Morpholine, a substrate that was previously shown to exhibit poor reactivity under conventional heating conditions was selected for performance optimization under microwave irradiation. Specifically, the reaction of aminobenzaldehyde **8c** with morpholine to give aminal **10b**



Scheme 5 Mechanism of the aminal formation

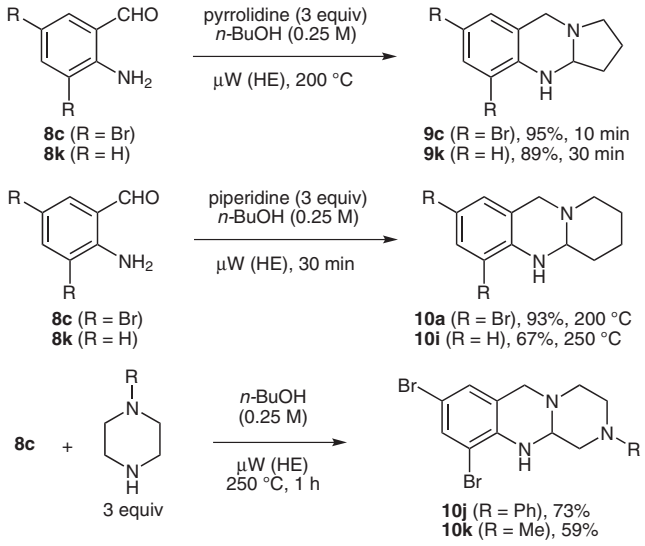


Scheme 7 Direct comparison of reflux vs microwave conditions for various amines

was investigated under a variety of conditions (Table 1). No reaction was observed when the reaction was conducted with four equivalents of morpholine under neat conditions at 130 °C (Table 1, entry 1). This reaction was also performed in the presence of a silicon carbide heating element (HE) under otherwise identical conditions (entry 2). While no change was observed in this instance, we have found previously that the presence of a HE can dramatically impact the outcome of related reactions.[13] Typically, improved substrate conversions are observed in the presence of a HE even at the same bulk temperature. Curiously, Polshettiwar and Varma reported the formation of **10b** in 65% yield under the conditions in entry 1, although it is not clear whether or not a HE was used. Microwave instrument calibration can certainly affect reaction outcomes and differences in yields are to be expected among different instruments, even when the exact same settings are used. However, we found that even when the title reaction was conducted under neat conditions at 200 °C for one hour in the presence of a HE, the conversion remained low and only 16% of aminal **10b** was formed (entry 3). A further increase in reaction temperature to 250 °C proved detrimental as decomposition was found to dominate under these conditions. As in conventional heating, the addition of alcoholic solvents led to superior results over the neat reaction conditions, a finding that is consistent with the reaction mechanism and the role of solvent as a proton shuttle (see structure **16** in Scheme 5). Relatively drastic reaction conditions were required to obtain a reasonable amount of morpholine-containing aminal **10b**. This product was obtained in 49% yield following a reaction time of 60 minutes at 270 °C. A HE was used in all subsequent reactions that were performed under microwave irradiation.

The optimized microwave conditions were applicable to a range of substrate combinations. For more reactive starting materials, microwave heating at 200 °C was sufficient. As outlined in Scheme 6, drastic rate accelerations were observed for the reaction of pyrrolidine with aminobenzaldehydes **8c** and **8k**. Products **9c** and **9k** were obtained in excellent yields in only 10 or 30 minutes, respectively. Applying the same reaction parameters to the substantially less reactive piperidine in a reaction with **8c** resulted in the formation of aminal **10a** in excellent yield (reaction time 30 min). Combining piperidine with the less reactive aminobenzaldehyde **8k** required for the reaction to be performed at 250 °C in order to obtain reasonable yields of aminal **10i**. The latter aminal was found not to be readily accessible using standard reflux conditions. Good yields of aminal products could also be obtained for *N*-methyl- and *N*-phenylpiperazine, substrates that previously failed to undergo the desired reactions.

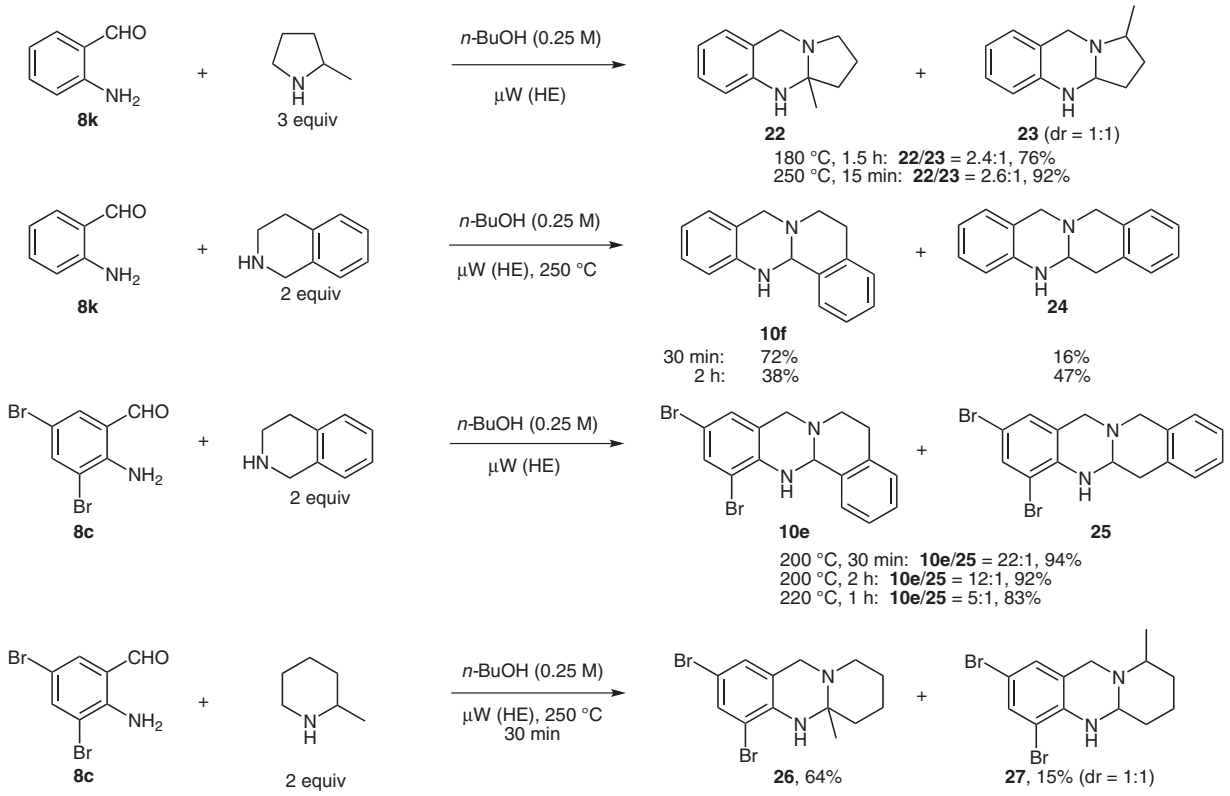
A range of other amines that had not previously been explored in the aminal formation were also evaluated, including sterically encumbered substrates. Shown in Scheme 7 is a side-by-side comparison for reactions conducted either at reflux or microwave heating in *n*-butanol. Tetrahydrobenzoazepine **17a** underwent the condensation cleanly to provide aminal **18** in high yield. Microwave heating proved superior not only in regard to reaction time but also yield. The same observation was made for 1-substituted tetrahydroisoquinolines **17b** and **17c** and 1-phenyltetrahydro-β-carboline **17d**. All corresponding aminal products were obtained in excellent yields.



Scheme 6 Optimized microwave conditions for other substrates

Regioselectivity of the Aminal Formation

An interesting situation arises for nonsymmetrical amines for which, at least in principle, different regioisomeric products may be formed (Scheme 8). In a reaction of *o*-aminobenzaldehyde (**8k**) and 2-methylpyrrolidine, conducted at 180 °C under microwave irradiation, products **22** and **23** were obtained in a 2.4:1 ratio. This reflects a preference for functionalization of a tertiary C–H bond over a secondary C–H bond. This electronic effect apparently outweighs any potential steric issues. The outcome of this reaction was essentially independent of the reaction temperature and is very similar to what was observed in a reaction of **8c** and 2-methylpyrrolidine, conducted under reflux in ethanol.[12a] As outlined previously in Scheme 4, THIQ leads to exclusive functionalization of a benzylic C–H bond when allowed to react with **8k** under reflux in ethanol. Aminal **10f** was formed as the only product in excellent yield. Based on the different available α-C–H bonds (benzylic vs aliphatic), this outcome is entirely expected. We were thus surprised to observe the formation of small amounts of the regioisomeric product **24** when the reaction was conducted under microwave irradiation. At a temperature of 250 °C, a substantial amount of **24** was obtained (16%) although **10f** was still formed as the major product. Extension of the reaction time from 30 minutes to two hours led to the isolation of **24** as the major product in 47% yield. In both cases, the combined yields of **10f** and **24** were essentially identical. These observations suggest that **10f** is the kinetic product of this transformation whereas **24** represents the thermodynamically more stable aminal. Furthermore, there appears to be a pathway for product isomerization. Computational results are consistent with the experimental findings.[12c] While the pathway leading to the formation of **24** was calculated to be higher in energy than that of **10f**, the free energy of **24** is lower than that of **10f**. Qualitatively similar observations were made in reactions of THIQ with **8c**, although product **10e** dominates in all cases. While this outcome is consistent with computational results (the difference in free energy between **10e** and **25** was found to be smaller than that of **10f** and **24**), the reaction of THIQ with **8c**



Scheme 8 Regioselectivity of the aminal formation

could not be performed at 250 °C as this resulted in substantial decomposition. A reaction of **8c** with 2-methylpiperidine led to the two expected regioisomeric products. Interestingly, the preference for functionalization of the tertiary C–H bond over a secondary C–H bond is more pronounced than was seen for 2-methylpyrrolidine.

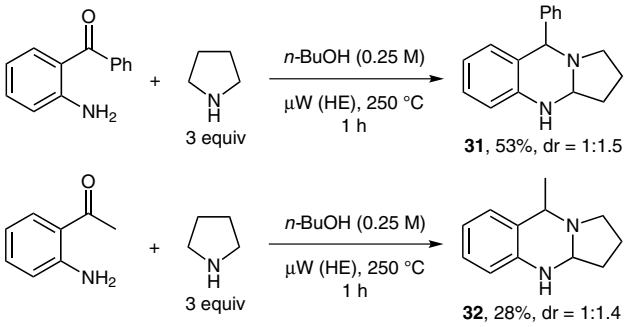
The impact of electronic factors on product distributions was evaluated next (Scheme 9). Three different 2-arylpyrrolidines were allowed to react with aminobenzaldehyde **8k** under identical conditions. The expected contra-steric preference for benzylic C–H bond over aliphatic C–H bond functionalization was observed in all instances. However, the electronics of the aryl ring exerted a marked influence on product distributions. Consistent with expectations, an electron-donating group placed in the *para*-position of the aromatic ring led to an increase in benzylic product, whereas an electron-withdrawing group in the same position resulted in a reduced ratio of benzylic to aliphatic functionalization. Notably, the overall product yields were excellent in all cases.

A related study was performed for three different methylbenzylamines, substrates that were previously found to resist aminal formation under reflux conditions. A clear trend was again observed with regard to electronics: the more electron-rich the substrate, the higher the yield of aminal product. However, any conclusions drawn from this should be considered tentative because aminal products **30a**–**c** might differ in their propensity to hydrolyze, potentially affecting product yields. Perhaps not surprisingly, no trace amounts of products were observed that would have been the result of methyl group functionalization.

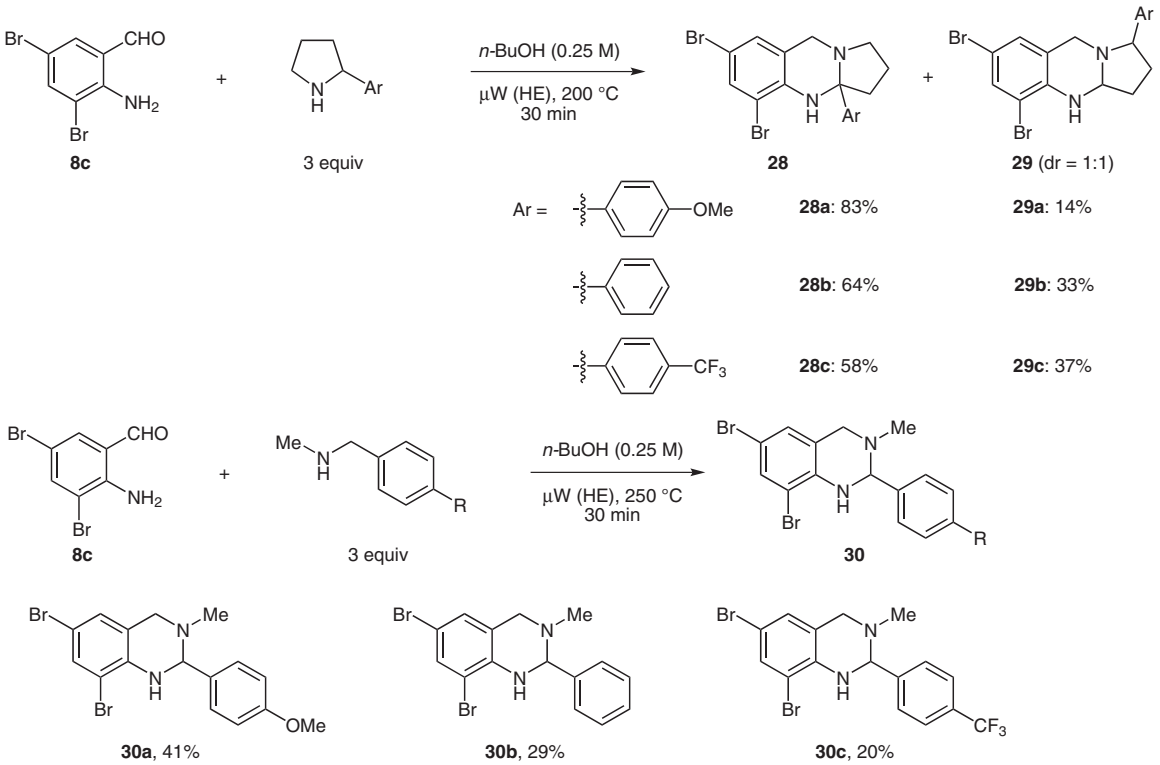
Reactions of Aminoketones

Previous attempts to expand the substrate scope from aminobenzaldehydes to related aminoketones had met with limited success. However, a reaction of aminobenzophenone with pyrrolidine, conducted under microwave irradiation at 250 °C, gave the corresponding aminal (Scheme 10). Product **31** was isolated as a 1:1.5 mixture of diastereomers in 53% yield, following a reaction time of one hour. Aminoacetophenone also underwent the corresponding reaction, albeit less efficiently. In this case, intermediate enamine formation might prevent higher yields. Polshettiwar and Varma reported the unlikely formation of **32** in 45% yield (reaction performed under neat conditions in a microwave reactor, 60 min at 130 °C).[16]

Competing Side Reactions



Scheme 10 Aminal formation with aminoketones

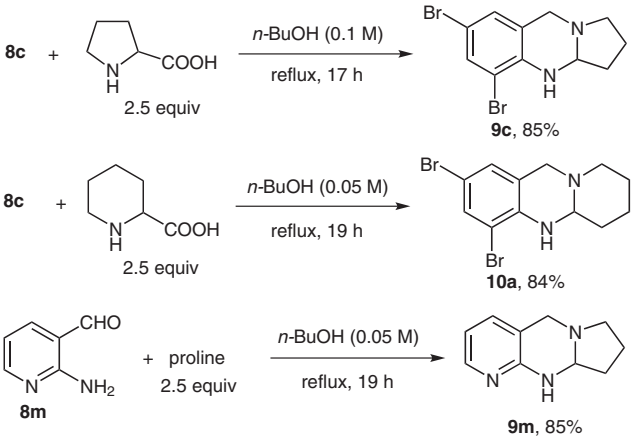


Scheme 9 Impact of electronic factors on the regioselectivity and yield of the aminal formation

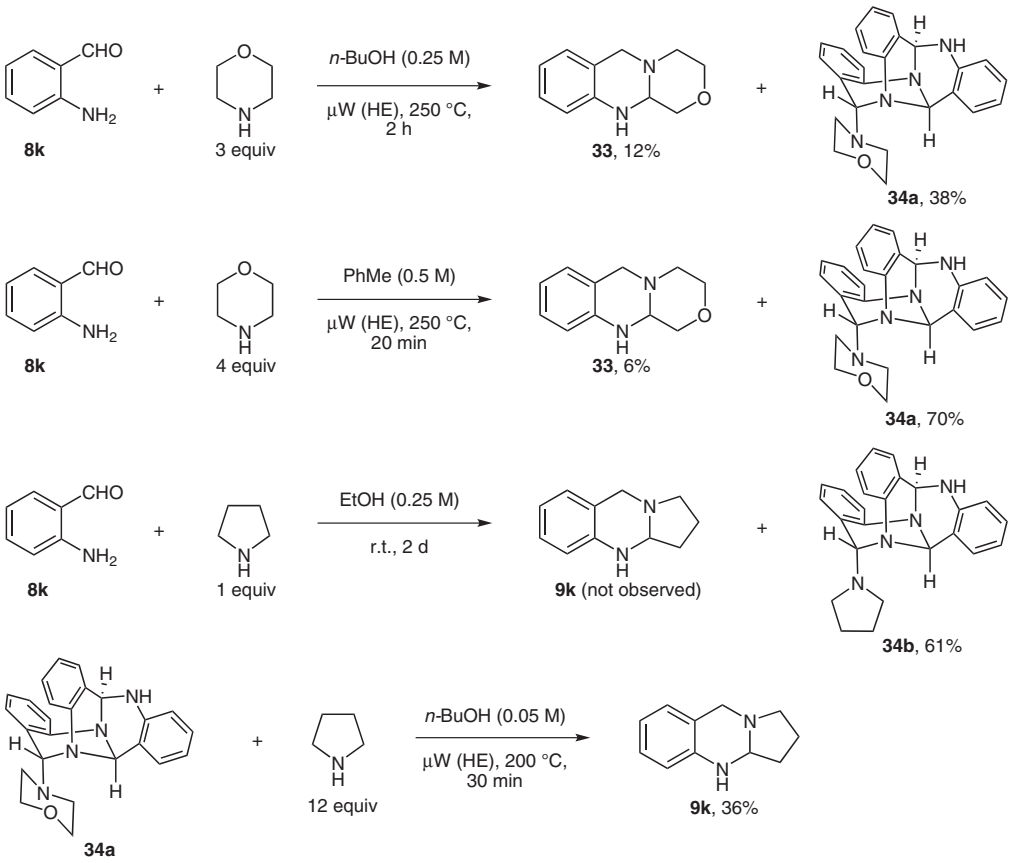
In the course of our studies, we made additional observations that outline the complexity of the overall process, including potentially competing, undesired reaction pathways (Scheme 11). As expected for this particularly challenging substrate combination, *o*-aminobenzaldehyde (**8k**) and morpholine underwent aminal formation only reluctantly (Scheme 11). Even a reaction conducted at 250 °C for two hours gave **33** in only 12% yield. Interestingly, in addition to **33**, the unexpected product **34a** was observed in 38% yield. A simple switch from *n*-butanol to toluene as the solvent and an increase in substrate concentration allowed for the isolation of **34a** in 70% yield. Related aminobenzaldehyde self-condensation products are well known.[17] In particular, products in which the morpholine subunit is replaced with simple alkoxy groups have been well characterized. In order to establish whether compounds such as **34a** could intervene in other aminal forming reactions, a solution of *o*-aminobenzaldehyde (**8k**) in ethanol was exposed to one equivalent of pyrrolidine at room temperature for two days. No trace of aminal **9k** was observed under these conditions. However, pyrrolidine-containing aminobenzaldehyde self-condensation product **34b** was obtained in 61% yield. Notably, corresponding reactions conducted with piperidine or morpholine at room temperature gave none of the trimeric condensation products. In order to establish whether aminobenzaldehyde self-condensation products can still participate in aminal formation, **34a** was exposed to 12 equivalents of pyrrolidine (200 °C, 30 min). Indeed, aminal **9k** was obtained as a product, albeit in only 36% yield, establishing the reversibility of aminobenzaldehyde self-condensation.

Aminal Formation under Decarboxylative Conditions

As part of our initial study, we established that substitution of pyrrolidine for proline in a reaction with aminobenzaldehyde **8c** gave rise to the identical aminal product **9c** although the reaction was less efficient than that with pyrrolidine.[12a] However, upon further optimization, effi-

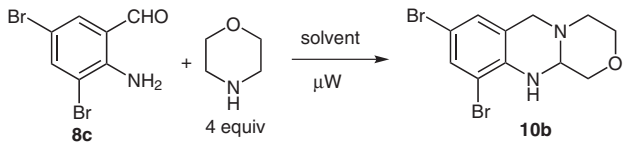


Scheme 12 Decarboxylative formation of aminals



Scheme 11 Formation of aminobenzaldehyde self-condensation products

Table 1 Optimization of Reaction Conditions for Morpholine, a Relatively Unreactive Amine



Entry	Solvent (conc)	HE[a]	Temp (°C)	Time (min)	Yield (%)
1	–	no	130	45	NR
2	–	yes	130	45	NR
3[b]	–	yes	200	60	16
4	–	yes	250	60	traces[c]
5	EtOH (2 M)	no	130	60	NR
6	*n*-BuOH (2 M)	yes	130	60	NR
7	*n*-BuOH (0.5 M)	yes	130	60	NR
8[b]	toluene (2 M)	no	200	45	6
9[b]	*n*-BuOH (0.5 M)	yes	200	45	20
10[b]	*n*-BuOH (0.25 M)	no	200	45	14
11[b]	*n*-BuOH (0.25 M)	yes	200	60	21
12[d]	*n*-BuOH (0.25 M)	yes	250	60	29
13	*n*-BuOH (0.25 M)	yes	250	60	26
14	*n*-BuOH (0.25 M)	yes	270	60	49

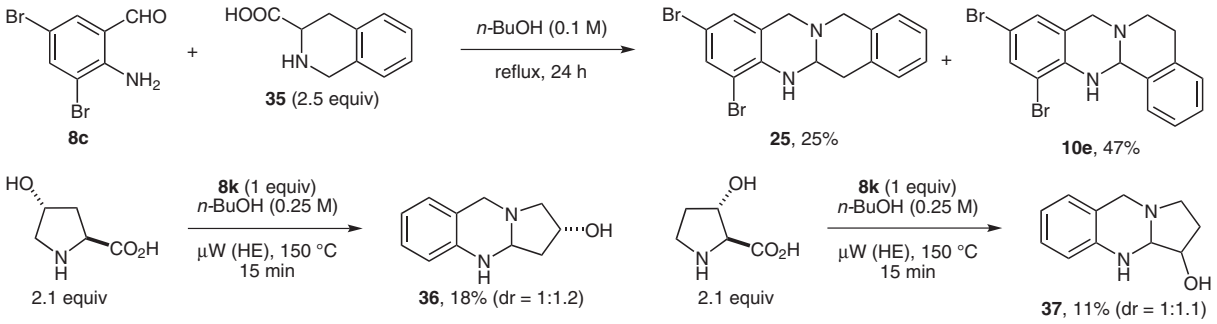
[a] HE: Silicon carbide heating element.
[b] The reaction was incomplete.
[c] Decomposition was observed.
[d] With 3 equiv of morpholine.

cient formation of **9c** was achieved in 85% yield for a reaction conducted under reflux in *n*-butanol at slightly lower concentration (Scheme 12). These conditions were applicable to other decarboxylative aminal formations such as the reaction of **8c** with pipecolic acid to give **10a** in 84% yield, and the reaction of **8m** with proline to give aminal **9m** in 85% yield. The ability of α-amino acids with a secondary amine to undergo the aminal formations is perfectly consistent with the intermediacy of azomethine ylides, as the latter species are known to be readily formed upon decarboxylative condensation of an α-amino acid with an aldehyde.[18,19]

Driven by the notion that the decarboxylative formation of aminals based on amino acids might enable control over product regioselectivity, this approach was tested in the formation of aminals that might otherwise be difficult to prepare in regioselective fashion (Scheme 13). A reaction of aminobenzaldehyde **8c** and amino acid **35** led to the expected product **25**, albeit in only 25% yield. In addition, aminal **10e** was isolated as the main product in 47% yield. Apparently, isomerization of the initially formed azomethine ylide is competitive with the direct pathway leading to aminal **25**, possibly involving intermediate formation of THIQ that can engage **8c** to form **10e**. In contrast to what was seen for **35**, the reactions of *trans*-4-hydroxyproline and *trans*-3-hydroxyproline with aminobenzaldehyde **8k** were fully regioselective. Unfortunately, the efficiency of these processes was poor and the results shown in Scheme 13 represent the best yields that could be obtained under a variety of conditions (including reactions conducted under reflux). Our group[13h] and others[20] have previously shown that *trans*-4-hydroxyproline forms *N*-alkylpyrroles when allowed to react with aldehydes at elevated temperatures. This process becomes competitive with aminal formation when the reaction is conducted at higher temperatures.

Interception of Reactive Intermediates

Various studies were performed in an effort to obtain experimental evidence for the intermediacy of azomethine ylides and *o*-azaquinonemethides.[18,21] Since aldehydes are known to be potent dipolarophiles, we speculated that [3+2] cycloaddition products such as **38** may be isolated under appropriate conditions (Scheme 14). We further reasoned that a reduction in the amount of pyrrolidine in combination with an increased reaction molarity might render the [3+2] pathway competitive with aminal formation. Indeed, a reaction conducted with aminobenzaldehyde **8c** and pyrrolidine in a 2:1 ratio and one molar concentration resulted in the formation of aminal **9c** in 74% yield, in addition to [3+2] cycloaddition product **38**. The latter was recovered as a single diastereomer in 18% yield. The yield of **38** was increased to 27% at the expense of aminal formation when the reaction was conducted in toluene under otherwise identical conditions. It was subsequently established that the [3+2] cycloaddition is re-



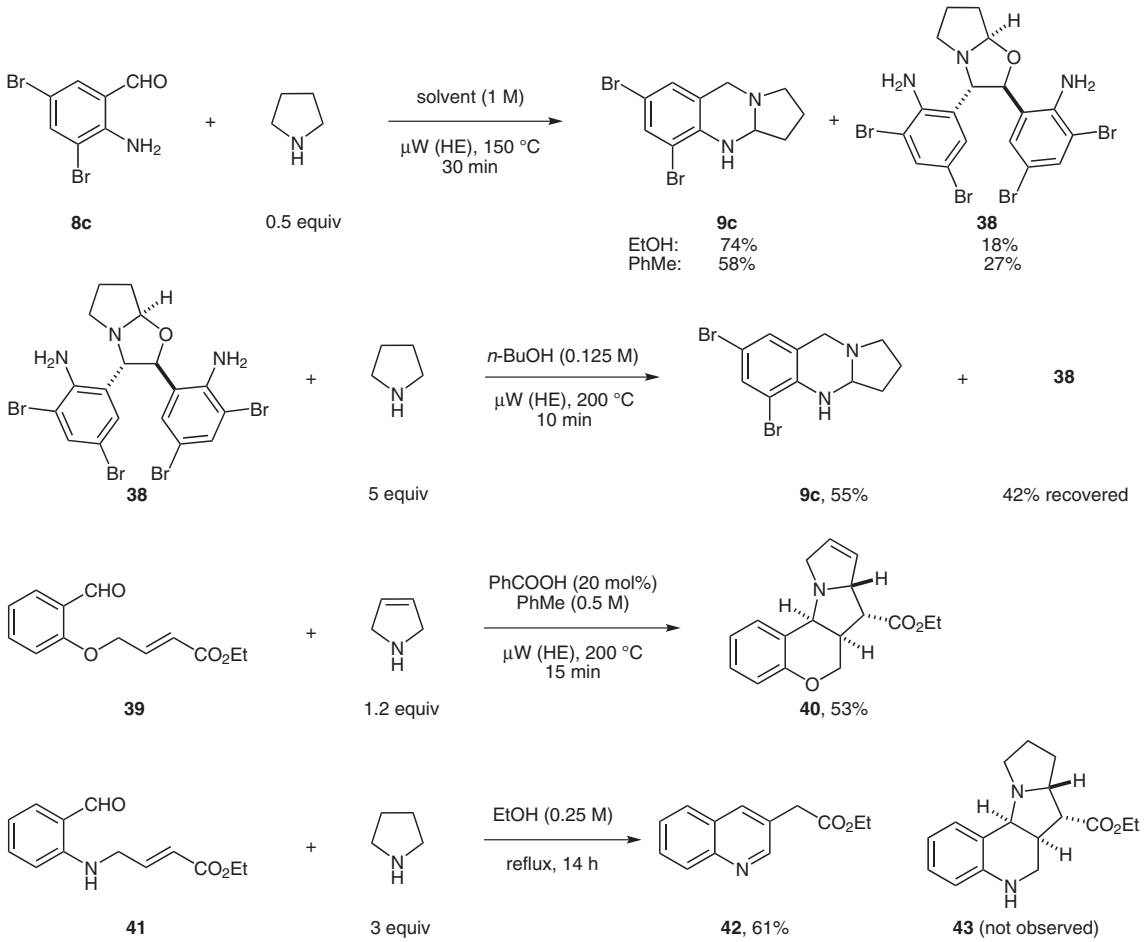
Scheme 13 Regioselectivity in the decarboxylative aminal formation

versible under certain conditions. Exposure of **38** to five equivalents of pyrrolidine for 10 minutes at 200 °C led to the isolation of aminal **9c** in 55% yield. Starting material **38** was recovered in 42% yield.

Other efforts were aimed at trapping an azomethine ylide in an intramolecular process. In previous work on another project, we have successfully demonstrated the formation of azomethine ylide intermediates upon benzoic acid catalyzed condensation of 3-pyrroline with aldehydes, a process that ultimately leads to the formation of *N*-alkylpyrroles.[13g] Specifically, a reaction of substituted salicylaldehyde **39** and 3-pyrroline resulted in the formation of [3+2] cycloaddition product **40** as a single diastereomer in 53% yield (Scheme 14). Based on this precedent, we prepared aminobenzaldehyde **41** bearing a pendant dipolarophile. Surprisingly, a reaction of **41** with pyrrolidine, conducted under the typical aminal-forming conditions gave neither aminal nor the expected cycloaddition product **43**. Instead, quinoline **42** was generated in 61% yield. The formation of **42** most likely involves the initial isomerization of **41** to the corresponding enamine, presumably by conjugate addition of pyrrolidine and subsequent elimination. Alternatively, the requisite enamine could be formed via a dienolate intermediate. No formation of **42** was observed when **41** was heated in the absence of pyrrolidine.

Support for the intermediacy of *o*-azaquinonemethides was obtained from a reaction of aminobenzaldehyde **44** and pyrrolidine, conducted under reflux in ethanol (Scheme 15). The expected product **45** was obtained in 7% yield, in addition to **47** (7%), conjugate addition product **48** (42%), aminal **49** (20%), and recovered starting material **44** (9%). The formation of **45** is fully consistent with an *o*-azaquinonemethide undergoing an *endo*-selective hetero-Diels–Alder reaction (via **46**). Given the mostly zwitterionic nature of the *o*-azaquinonemethide, the cycloaddition may not be fully concerted. Importantly, we could show that **45** does not form via an alternate pathway involving **47**. Exposure of **47** to pyrrolidine under reflux in ethanol did not result in the formation of any trace of **45** within 48 hours. An aza-Baylis–Hillman-type pathway was ruled out on the basis that this would have to involve an iminium ion, species that are unlikely to exist under these conditions. An intramolecular Baylis–Hillman-type pathway to the formation of **47** (conjugate addition of pyrrolidine to **44** with simultaneous attack of the aldehyde) was ruled out since this would involve the unlikely formation of an intermediate with a ten-membered ring. Moreover, heating **44** by itself or in the presence of Hünig's base or *N*-methylpyrrolidine led to no reaction.

In another attempt to capture an *o*-azaquinonemethide intermediate, we decided to evaluate an amine containing a

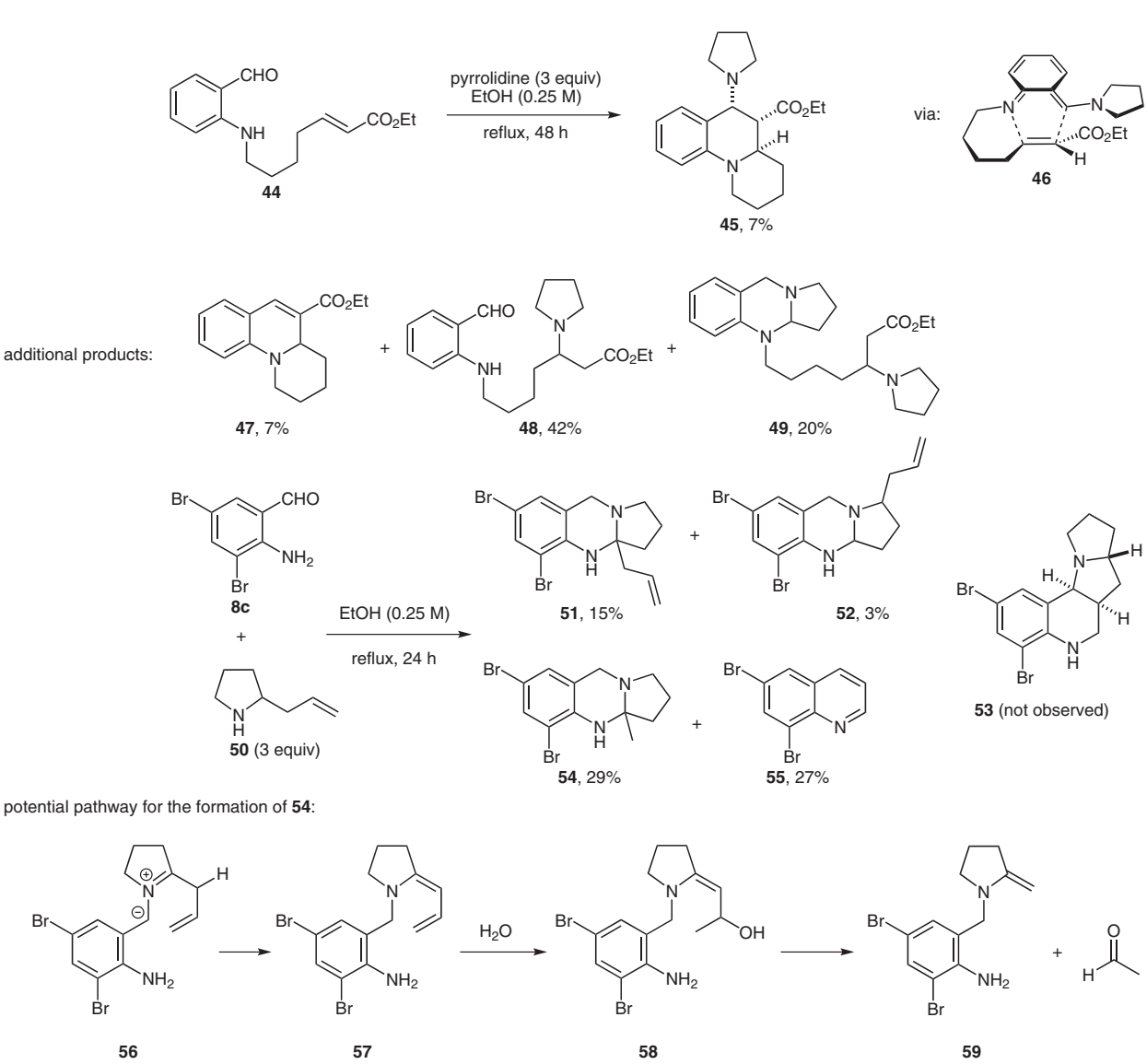


Scheme 14 Attempted capture of azomethine ylide intermediates

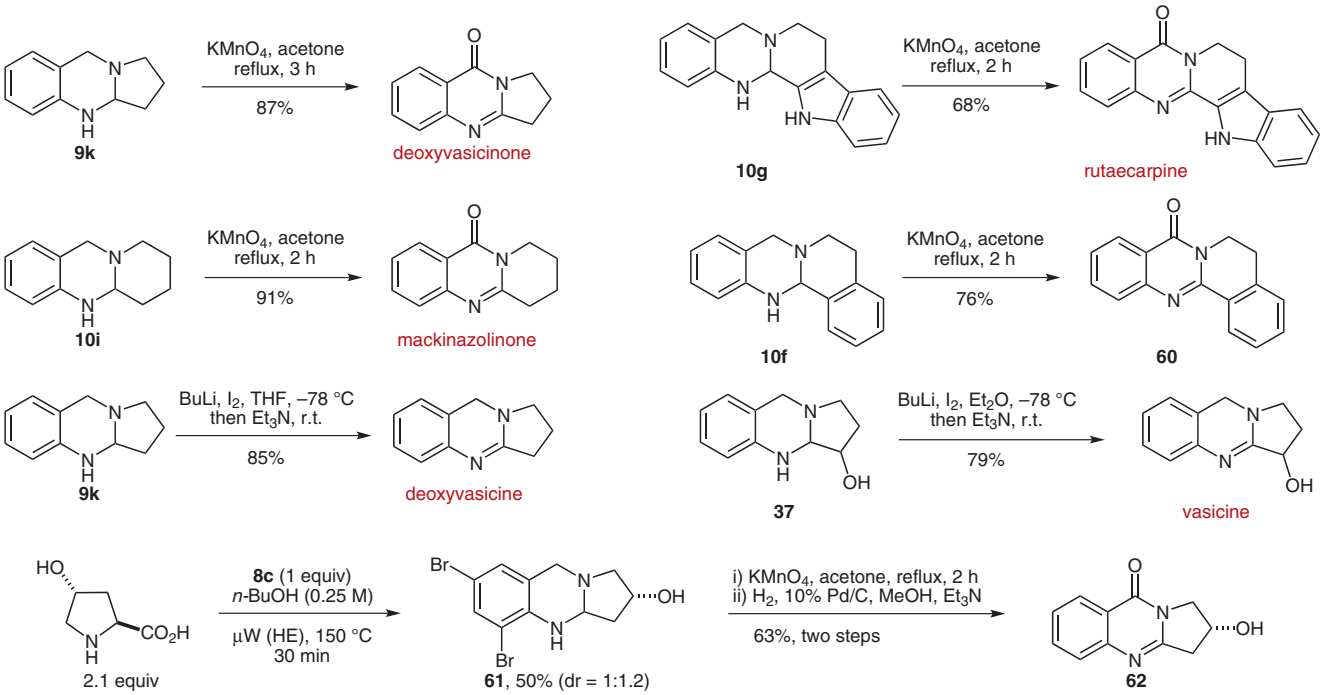
pendant dieneophile. However, a reaction of aminobenzaldehyde **8c** with pyrrolidine **50** did not give any of the desired cycloaddition product **53**. Interestingly, in addition to the expected aminal products **51** (15%) and **52** (3%), the formation of aminal **54** (29%) and quinoline **55** (27%) as the major products was observed. A plausible pathway for the formation of **54** and **55** is outlined in Scheme 15. Upon reaction of **8c** with **50** to give the typical azomethine ylide intermediate **56**, the latter could undergo a transformation to dienamine **57**, either by a concerted proton transfer or a protonation/deprotonation event. Stepwise hydrolysis of dienamine **57** via an intermediate such as **58** could result in enamine **59**, a species that could subsequently cyclize to aminal **54**. Importantly, the regioisomer of **54** was not observed, ruling out any pathways that would involve the formation of free 2-methylpyrrolidine. Formation of quinoline **55** is readily explained by Friedländer condensation of **8c** with acetaldehyde, a byproduct from the hydrolysis of **58**.

Synthesis of Quinazolinone Alkaloids

There are a sizable number of natural products that contain aminal substructures.[22] Moreover, the ring-fused aminals obtained from aminobenzaldehydes and secondary amines represent direct precursors of certain quinazolinone alkaloids and are thus ideally suited to generate analogues of these biologically active species.[23,24] Oxidation of aminals to quinazolinones is readily accomplished under reflux in acetone with potassium permanganate as the oxidant (Scheme 16). Deoxyvasicinone, rutaecarpine, mackinazolinone, and the unnatural analogue **60** could thus be obtained in good yields via oxidation of the corresponding aminals. Selective oxidation of aminals to amidines without affecting the benzylic position was achieved via iodine-promoted oxidation of deprotonated precursors. This allowed for the synthesis of deoxyvasicine and vasicine. A limitation of the two-step vasicine synthesis is the poor yield obtained for the starting material **37**. As a potential solution to this shortcoming, we



Scheme 15 Attempts to capture azaquinonemethide intermediates



Scheme 16 Synthesis of quinazolinone alkaloids and analogues

found that the decarboxylative aminal formation of hydroxyprolines proceeds much more efficiently with aminobenzaldehyde **8c** than **8k**. This finding was applied to the synthesis of **62**, a novel regioisomer of vasicinone. Reaction of *trans*-4-hydroxyproline with **8c** provided regioselective access to aminal **61** in 50% yield. Subsequent oxidation with potassium permanganate, followed by removal of the bromine substituents via hydrogenolysis provided **62** in 32% overall yield in just three steps from commercially available materials.

Conclusion

Ring-fused aminals are readily available via condensation of secondary amines with *o*-aminobenzaldehydes. These reactions feature simultaneous reductive N-alkylation and oxidative α-amination, effectively rendering the process redox-neutral. While many of the aminal-forming reactions can be performed with conventional heating methods, microwave heating proved to be beneficial in all cases and for some substrates it is required. The aminal products are valuable precursors to various quinazolinone alkaloids and their analogues. The reaction exhibits interesting mechanistic features and *o*-azaquinonemethides and azomethine ylides have been identified as reactive intermediates. The overall process adds to the growing number of reactions that involve nonpericyclic reaction pathways of azomethine ylides, an area that is expected to experience further growth.

Reagents and solvents were purchased from commercial sources and were used as received unless otherwise stated. Toluene, THF, Et_2O, and Et_3N were distilled prior to use. All secondary amines were purified by distillation prior to use. Microwave reactions were carried out in a CEM Discover reactor. Silicon carbide (SiC) passive heating elements were purchased from Anton Paar. Purification of reaction products was carried out by flash column chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230–400 mesh). Analytical TLC was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light or $KMnO_4$, and Dragendorff–Munier stains followed by heating. Eluents for column chromatography and TLC were the same as those used for determining the R_f values. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on an ATI Mattson Genesis Series FT-IR spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian VNMRS-500 MHz and are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Standard abbreviations (besides app: apparent and com: complex) were used to denote signal multiplicities. Coupling constant(s) are given in Hz. Proton-decoupled ^{13}C NMR were recorded on a Varian VNMRS-500 MHz and are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-2000 polarimeter at 589 nm and at 25 °C. Products **9a–o**,[12a] **10a**,[12a] **10b**,[12c] **10c–h**,[12a] **10i**,[25a] **22–24**,[12c] **38**,[12c] **39**,**40**,[13g] **44**,**45**,[12c] **47–49**,[12c] **54**,[12a] **55**,[25b] **60**,[25c] deoxyvasicinone,[12b] rutaecarpine,[12a] mackinazolinone,[25d] deoxyvasicine,[25e] and vasicine[25f] were previously reported and their published characterization data matched our own in all regards.

General Microwave Procedure

A 10 mL microwave reaction tube was charged with a 10 × 8 mm SiC passive heating element, aminobenzaldehyde (1 mmol), *n*-BuOH (0.25 M), and amine (3 equiv). The reaction tube was sealed with a Teflon-lined snap cap, and heated in a microwave reactor (**Note**: *SiC passive heating elements must not be used in conjunction with stir bars because they may score glass and cause vessel failure*). After cooling with compressed air flow, the reaction mixture was transferred to a round-bottom flask and the vessel was rinsed with EtOAc (4 × 2 mL). The solvent was then removed in

vacuo and the residue was loaded onto a short column and purified by silica gel chromatography.

General Reflux Procedure
A 10 mL round-bottom flask was charged with a magnetic stir bar, aminobenzaldehyde (1 mmol), *n*-BuOH (4 mL), and amine (3 equiv). The resulting mixture was heated at reflux until the starting material was consumed as determined by TLC. The solvent was then removed in vacuo and the residue was loaded onto a short column and purified by silica gel chromatography.

General Oxidation Procedure
A 10 mL round bottom flask was charged with a magnetic stir bar, aminal (0.25 mmol), acetone (2.5 mL), and $KMnO_4$ (5 equiv). The resulting mixture was heated at reflux for 2 h. The solution was filtered through a pad of Celite and the filtrate was washed with acetone (20 mL). The solvent was removed in vacuo and the residue was loaded onto a short column and purified by silica gel chromatography.

Compound 10j
Following the general microwave procedure, **10j** was obtained from 2-amino-3,5-dibromobenzaldehyde (**8c**; 1 mmol) and *N*-phenylpiperazine (3 equiv) after 1 h at 250 °C; yield: 307.5 mg (73%); tan solid; mp 164–168 °C; R_f = 0.31 (hexanes–EtOAc, 85:15 v/v).

IR (KBr): 3317, 2952, 2925, 2830, 2785, 1599, 1491, 1458, 1325, 1267, 1250, 1214, 1145, 930, 844, 771, 757, 691, 608 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.43 (app dd, *J* = 2.3, 0.8 Hz, 1 H), 7.33–7.28 (comp, 2 H), 7.04 (d, *J* = 1.4 Hz, 1 H), 7.00–6.96 (comp, 2 H), 6.98 (app tt, *J* = 7.3, 1.1 Hz, 1 H), 4.31 (br s, 1 H), 4.19–4.08 (m, 1 H), 3.92 (d, *J* = 15.5 Hz, 1 H), 3.74 (d, *J* = 15.5 Hz, 1 H), 3.52 (dd, *J* = 11.7, 3.0 Hz, 1 H), 3.37–3.26 (comp, 2 H), 3.21 (dd, *J* = 11.8, 6.2 Hz, 1 H), 3.04 (ddd, *J* = 11.5, 6.3, 3.6 Hz, 1 H), 2.56 (ddd, *J* = 11.0, 7.0, 3.6 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.8, 138.6, 132.6, 129.3, 128.8, 121.9, 120.5, 116.7, 109.6, 109.1, 68.0, 54.8, 53.6, 49.2, 49.1.

MS-ESI: *m*/*z* = 423.9 $[M + H]^+$.

Compound 10k
Following the general microwave procedure, **10k** was obtained from **8c** (1 mmol) and *N*-methylpiperazine (3 equiv) after 1 h at 250 °C; yield: 212.6 mg (59%); off-white solid; mp 116–119 °C; R_f = 0.18 (EtOAc–MeOH, 90:10 v/v).

IR (KBr): 3389, 2933, 2842, 2897, 2516, 1594, 1475, 1346, 1323, 1285, 1143, 1079, 900, 856, 706 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 1.8 Hz, 1 H), 7.00 (s, 1 H), 4.27 (br s, 1 H), 4.12–3.75 (comp, 2 H), 3.68 (d, *J* = 15.1 Hz, 1 H), 2.91 (br s, 1 H), 2.78 (br s, 1 H), 2.67–2.36 (comp, 4 H), 2.34 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.7, 132.5, 128.7, 122.1, 109.4, 108.9, 67.9, 59.1, 54.7, 54.7, 50.0, 45.8.

MS-ESI: *m*/*z* = 362.0 $[M + H]^+$.

Compound 18
Following the general microwave procedure, **18** was obtained from **8c** (0.25 mmol) and 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (**17a**;[25g] 2 equiv) after 30 min at 200 °C in *n*-butanol (1 mL); yield: 92.5 mg (91%); tan solid; mp 124–127 °C; R_f = 0.40 (hexanes–EtOAc, 70:30 v/v).

IR (KBr): 3372, 2925, 2849, 1590, 1477, 1451, 1364, 1357, 1292, 1259, 1173, 1061, 946, 880, 749, 635 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 2.2 Hz, 1 H), 7.33–7.06 (comp, 4 H), 6.97 (d, *J* = 2.2 Hz, 1 H), 5.50 (d, *J* = 2.5 Hz, 1 H), 4.78 (br s, 1 H), 4.04 (d, *J* = 15.5 Hz, 1 H), 3.63 (d, *J* = 15.5 Hz, 1 H), 3.34 (ddd, *J* = 13.5, 7.3, 3.1 Hz, 1 H), 3.27–3.02 (comp, 2 H), 2.88 (ddd, *J* = 14.7, 9.3, 2.2 Hz, 1 H), 1.96–1.82 (m, 1 H), 1.82–1.68 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.7, 139.5, 137.8, 132.2, 130.0, 129.1, 128.9, 128.4, 126.1, 123.3, 109.1, 108.9, 74.4, 54.3, 53.1, 35.2, 26.0.

MS-ESI: *m*/*z* = 409.0 $[M + H]^+$.

Compound 19
Following the general microwave procedure, **19** was obtained from **8c** (0.25 mmol) and 1-methyl-1,2,3,4-tetrahydroisoquinoline (**17b**;[25h] 2 equiv) after 30 min at 200 °C in *n*-butanol (1 mL); yield: 90 mg (88%); tan solid; mp 121–123 °C; R_f = 0.14 (hexanes–EtOAc, 93:7 v/v).

IR (KBr): 3409, 2993, 2920, 2838, 1589, 1478, 1391, 1374, 1294, 1131, 1095, 1038, 933, 884, 753, 725, 700 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.57 (dd, *J* = 7.7, 1.6 Hz, 1 H), 7.46 (d, *J* = 2.2 Hz, 1 H), 7.38–7.25 (comp, 2 H), 7.17 (dd, *J* = 7.3, 1.8 Hz, 1 H), 7.12 (d, *J* = 1.5 Hz, 1 H), 4.63 (br s, 1 H), 4.55 (d, *J* = 17.0 Hz, 1 H), 3.72 (d, *J* = 17.0 Hz, 1 H), 3.17–3.06 (m, 1 H), 2.92 (app td, *J* = 10.9, 3.5 Hz, 1 H), 2.85–2.69 (comp, 2 H), 1.73 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.5, 137.6, 134.1, 132.2, 129.2, 128.6, 127.4, 126.7, 124.7, 120.5, 109.1, 107.9, 69.8, 51.2, 46.3, 29.6, 26.4.

MS-ESI: *m*/*z* = 409.0 $[M + H]^+$.

Compound 20
Following the general microwave procedure, **20** was obtained from **8c** (0.25 mmol) and 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**17c**;[25i] 2 equiv) after 1.5 h at 200 °C in *n*-butanol (1 mL); yield: 123 mg (93%); white solid; mp 73–76 °C; R_f = 0.29 (hexanes–EtOAc, 70:30 v/v).

IR (KBr): 3412, 2931, 2831, 1609, 1589, 1515, 1472, 1290, 1251, 1233, 1168, 1140, 1021, 793, 754, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.46 (dd, *J* = 2.3, 0.7 Hz, 1 H), 7.44–7.36 (comp, 2 H), 7.31–7.21 (comp, 3 H), 6.94 (d, *J* = 2.0 Hz, 1 H), 6.63 (s, 1 H), 6.20 (s, 1 H), 4.77 (br s, 1 H), 3.91–3.79 (comp, 4 H), 3.60 (s, 3 H), 3.45 (d, *J* = 16.9 Hz, 1 H), 3.30 (ddd, *J* = 16.0, 12.4, 6.1 Hz, 1 H), 3.01 (app td, *J* = 11.7, 3.6 Hz, 1 H), 2.82 (ddd, *J* = 11.7, 6.1, 1.6 Hz, 1 H), 2.72 (ddd, *J* = 16.0, 3.7, 1.6 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.4, 147.7, 145.9, 137.6, 132.3, 132.2, 128.8, 128.3, 127.5, 127.4, 126.4, 121.4, 111.0, 110.7, 108.2, 108.1, 75.9, 56.0, 55.8, 51.7, 45.9, 29.3.

MS-ESI: *m*/*z* = 530.9 $[M + H]^+$.

Compound 21
Following the general microwave procedure, **21** was obtained from **8c** (0.25 mmol) and 1-phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**17d**;[25j] 2 equiv) after 1 h at 200 °C in *n*-butanol (1 mL); yield: 111 mg (87%); oil; R_f = 0.35 (hexanes–EtOAc 70:30, v/v).

IR (KBr): 3398, 3056, 2903, 2841, 1589, 1463, 1298, 1171, 1106, 1028, 1016, 979, 932, 858, 743, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.58 (app d, *J* = 7.7 Hz, 1 H), 7.55–7.46 (comp, 3 H), 7.38–7.28 (comp, 4 H), 7.27–7.22 (comp, 2 H), 7.17 (app dtd, *J* = 20.1, 7.1, 1.2 Hz, 2 H), 6.99 (br s, 1 H), 4.93 (br s, 1 H), 3.93 (d, *J* = 16.8 Hz, 1 H), 3.56 (d, *J* = 16.8 Hz, 1 H), 3.26–3.05 (comp, 2 H), 3.03–2.92 (m, 1 H), 2.92–2.79 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.9, 137.1, 136.5, 135.6, 132.5, 129.0, 128.8, 128.7, 128.4, 127.4, 126.7, 122.6, 121.9, 120.0, 119.1, 111.4, 109.3, 108.8, 73.3, 50.7, 46.8, 21.8.

MS-ESI: *m*/*z* = 510.0 $[M + H]^+$.

Compound 25
Following the general microwave procedure, **10e** was obtained from **8c** (1 mmol) and 1,2,3,4-tetrahydroisoquinoline (2.0 mmol) after 1 h at 220 °C in 69% yield as yellow solid and matches reported spectroscopic data in all regards.[12c] In addition, the title com-

pound **25** was isolated as a pale yellow solid; yield: 54.2 mg (14%); mp 135–138 °C; R_f = 0.20 (hexanes–EtOAc, 80:20 v/v).

IR (KBr): 3384, 3067, 2926, 1701, 1685, 1676, 1589, 1560, 1478, 1342, 1290, 1265, 1128, 1030, 855, 738 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 2.0 Hz, 1 H), 7.21–7.13 (comp, 3 H), 7.07–7.00 (comp, 2 H), 4.73–4.69 (m, 1 H), 4.29 (d, *J* = 16.2 Hz, 1 H), 4.24 (s, 1 H), 3.92 (d, *J* = 15.0 Hz, 1 H), 3.80 (d, *J* = 16.2 Hz, 1 H), 3.69 (d, *J* = 15.0 Hz, 1 H), 3.36 (dd, *J* = 17.0, 4.8 Hz, 1 H), 2.89 (dd, *J* = 17.0, 3.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.3, 133.4, 132.4, 129.9, 129.1, 128.8, 126.5, 126.4, 126.2, 121.6, 108.9, 108.8, 66.1, 54.7, 49.7, 34.5.

MS-ESI: *m*/*z* = 395.0 $[M + H]^+$.

Compound 26

Following the general microwave procedure, **26** was obtained from **8c** (0.25 mmol) and 2-methylpiperidine (2 equiv) after 30 min at 250 °C; yield: 58 mg (64%); tan semi-solid; R_f = 0.17 (hexanes–EtOAc, 70:30 v/v).

IR (KBr): 3405, 2917, 2849, 1643, 1480, 1451, 1371, 1296, 1162, 1122, 858 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 2.1 Hz, 1 H), 7.03 (s, 1 H), 4.35 (d, *J* = 17.0 Hz, 1 H), 4.24 (br s, 1 H), 3.45 (d, *J* = 17.0 Hz, 1 H), 2.49–2.44 (comp, 2 H), 1.77–1.51 (comp, 6 H), 1.31 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.2, 132.1, 128.9, 120.5, 109.1, 107.7, 77.2, 67.6, 51.0, 49.3, 38.0, 25.8, 20.3.

MS-ESI: *m*/*z* = 361.1 $[M + H]^+$.

In addition, **27** was obtained as a white solid in 15% yield (1:1 mixture of diastereomers).

Compound 28a

Following the general microwave procedure, **28a** was obtained from **8c** (0.25 mmol) and 2-(4-methoxyphenyl)pyrrolidine[25k] (3 equiv) after 30 min at 200 °C in *n*-butanol (1 mL); yield: 90.6 mg (83%); clear oil; R_f = 0.23 (hexanes–EtOAc, 90:10 v/v).

IR (KBr): 2856, 2360, 2342, 1734, 1700, 1507, 1473, 1457, 1247, 1172, 830, 668 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 1.8 Hz, 1 H), 7.40–7.31 (m, 2 H), 6.91 (s, 1 H), 6.88–6.81 (m, 2 H), 4.75 (br s, 1 H), 3.78 (s, 3 H), 3.68 (d, *J* = 17.0 Hz, 1 H), 3.56 (d, *J* = 17.0 Hz, 1 H), 3.16 (app td, *J* = 8.7, 3.1 Hz, 1 H), 2.77–2.68 (m, 1 H), 2.29–2.14 (m, 1 H), 2.13–1.95 (comp, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 138.5, 136.1, 132.3, 129.3, 127.8, 121.3, 114.1, 108.4, 107.9, 79.3, 55.5, 50.2, 45.7, 43.4, 21.1.

MS-ESI: *m*/*z* = 438.9 $[M + H]^+$.

In addition, **29a** was obtained as a white semi-solid in 14% yield (1:1 mixture of diastereomers).

Compound 28b

Following the general microwave procedure, **28b** was obtained from **8c** (0.25 mmol) and 2-phenylpyrrolidine[25k] (3 equiv) after 30 min at 200 °C in *n*-butanol (1 mL); yield: 64.9 mg (64%); clear oil; R_f = 0.32 (hexanes–EtOAc, 90:10 v/v).

IR (KBr): 3410, 2954, 1593, 1475, 1445, 1285, 1178, 1149, 1121, 993, 756, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.54–7.38 (comp, 3 H), 7.38–7.29 (comp, 2 H), 7.29–7.21 (m, 1 H), 6.91 (s, 1 H), 4.79 (br s, 1 H), 3.68 (d, *J* = 17.0 Hz, 1 H), 3.58 (d, *J* = 17.0 Hz, 1 H), 3.19 (app td, *J* = 8.7, 3.5 Hz, 1 H), 2.84–2.67 (m, 1 H), 2.31–2.20 (m, 1 H), 2.14–1.96 (comp, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.0, 138.2, 132.08, 129.1, 128.5, 127.5, 126.3, 121.0, 108.2, 107.7, 79.3, 50.2, 45.5, 43.4, 21.1.

MS-ESI: *m*/*z* = 409.0 $[M + H]^+$.

In addition, **29b** was obtained as a white semi-solid in 33% yield (1:1 mixture of diastereomers).

Compound 28c

Following the general microwave procedure, **28c** was obtained from **8c** (0.25 mmol) and 2-(4-trifluoromethylphenyl)pyrrolidine[25k] (3 equiv) after 30 min at 200 °C in *n*-butanol (1 mL); yield: 69.3 mg (58%); clear oil; R_f = 0.34 (hexanes–EtOAc, 90:10 v/v).

IR (KBr): 3414, 2955, 1593, 1475, 1406, 1325, 1164, 1126, 1071, 1017, 840 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.61–7.57 (comp, 4 H), 7.45 (d, *J* = 2.0 Hz, 1 H), 6.93 (s, 1 H), 4.77 (br s, 1 H), 3.73–3.53 (comp, 2 H), 3.20 (app td, *J* = 8.7, 3.3 Hz, 1 H), 2.86–2.67 (m, 1 H), 2.31–2.15 (m, 1 H), 2.15–1.95 (comp, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.4, 137.8, 132.3, 129.9, 129.7, 129.2, 127.0, 125.6 (q, $J_{C,F}$ = 3.6 Hz), 120.8, 108.4, 108.3, 79.1, 50.2, 45.4, 43.6, 21.2.

MS-ESI: *m*/*z* = 477.0 $[M + H]^+$.

In addition, **29c** was obtained as a white semi-solid in 37% yield (1:1 mixture of diastereomers).

Compound 30a

Following the general microwave procedure, **30a** was obtained from **8c** (1 mmol) and *N*-methyl-*p*-methoxybenzylamine[25l] (3 equiv) after 30 min at 250 °C; yield: 171.3 mg (41%); clear oil; R_f = 0.36 (hexanes–EtOAc–Et_3N, 69:30:1 v/v/v).

IR (KBr): 3409, 2950, 2835, 1611, 1595, 1510, 1484, 1346, 1301, 1247, 1170, 1126, 1035, 957, 805 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 2.2 Hz, 1 H), 7.38–7.33 (comp, 2 H), 6.99 (d, *J* = 2.3 Hz, 1 H), 6.94–6.88 (comp, 2 H), 4.90 (d, *J* = 2.2 Hz, 1 H), 4.75 (br s, 1 H), 3.81 (s, 3 H), 3.77 (d, *J* = 15.9 Hz, 1 H), 3.64 (d, *J* = 15.9 Hz, 1 H), 2.27 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.0, 139.0, 132.8, 132.6, 129.1, 128.8, 122.2, 114.2, 108.5, 108.4, 75.3, 55.6, 53.2, 40.2.

MS-ESI: *m*/*z* = 412.9 $[M + H]^+$.

Compound 30b

Following the general microwave procedure, **30b** was obtained from **8c** (1 mmol) and *N*-methylbenzylamine (3 equiv) after 30 min at 250 °C; yield: 109.5 mg (29%); light yellow solid; mp 108–112 °C; R_f = 0.38 (hexanes–EtOAc–Et_3N, 69:30:1 v/v/v).

IR (KBr): 3058, 2937, 1684, 1594, 1485, 1447, 1339, 1275, 1158, 1103, 1040, 1013, 983, 864, 742, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.48–7.41 (comp, 3 H), 7.41–7.31 (comp, 3 H), 7.00 (d, *J* = 1.0 Hz, 1 H), 5.01 (d, *J* = 2.3 Hz, 1 H), 4.79 (br s, 1 H), 3.77 (d, *J* = 15.9 Hz, 1 H), 3.65 (d, *J* = 15.9 Hz, 1 H), 2.32 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.5, 138.6, 132.4, 129.0, 128.7, 128.5, 127.2, 121.8, 108.3, 108.2, 75.2, 52.5, 40.3.

MS-ESI: *m*/*z* = 383.0 $[M + H]^+$.

Compound 30c

Following the general microwave procedure, **30c** was obtained from **8c** (1 mmol) and *N*-methyl-*p*-trifluoromethylbenzylamine[25m] (3 equiv) after 30 min at 250 °C; yield: 89.9 mg (20%); clear oil; R_f = 0.37 (hexanes–EtOAc–Et_3N, 69:30:1 v/v/v).

IR (KBr): 3399, 2945, 1618, 1595, 1486, 1411, 1325, 1273, 1161, 1125, 1125, 1067, 1014, 856, 823, 739 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.2 Hz, 2 H), 7.56 (d, *J* = 8.2 Hz, 2 H), 7.47 (d, *J* = 2.3 Hz, 1 H), 7.00 (d, *J* = 2.3 Hz, 1 H), 5.09 (d, *J* = 2.1 Hz, 1 H), 4.84 (br s, 1 H), 3.71 (d, *J* = 16.3 Hz, 1 H), 3.58 (d, *J* = 16.3 Hz, 1 H), 2.37 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.8, 137.9, 132.5, 130.6 (q, $J_{C,F}$ = 31.4 Hz), 129.1, 127.6, 125.6 (q, $J_{C,F}$ = 3.8 Hz), 123.9 (q, $J_{C,F}$ = 272.3 Hz), 121.6, 108.7, 108.5, 74.3, 51.4, 40.6.

MS-ESI: *m*/*z* = 451.1 $[M + H]^+$.

Compound 31

Following the general microwave procedure, **31** was obtained from 2-aminobenzophenone (0.5 mmol) and pyrrolidine (3 equiv) after 1 h at 250 °C; yield: 65.9 mg (53%) (1:1.5 mixture of diastereomers); yellow semi-solid; R_f = 0.36 (hexanes–EtOAc, 70:30 v/v).

IR (KBr): 3219, 2956, 2871, 2368, 2602, 1473, 1364, 1300, 1248, 1152, 1089, 1029, 1007, 940, 923, 756, 703 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.27 (comp, 7 H), 7.24–7.19 (comp, 3 H), 7.08 (app td, *J* = 8.4, 1.6 Hz, 1 H), 7.02 (app td, *J* = 7.5, 1.5 Hz, 1 H), 6.91 (dd, *J* = 7.5, 1.6 Hz, 1 H), 6.73–6.60 (comp, 3 H), 6.58–6.53 (comp, 2 H), 4.92 (s, 1 H), 4.58 (s, 1 H), 4.37 (d, *J* = 4.3 Hz, 1 H), 4.11 (br s, 1 H), 3.89–3.84 (m, 1 H), 3.75 (br s, 1 H), 3.05 (app td, *J* = 8.5, 3.7 Hz, 1 H), 2.90 (app td, *J* = 8.9, 2.2 Hz, 1 H), 2.86–2.77 (m, 1 H), 2.24–2.12 (comp, 2 H), 2.10–1.85 (comp, 4 H), 1.85–1.72 (comp, 2 H), 1.66–1.58 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.2, 143.6, 143.0, 129.6, 129.4, 128.8, 128.6, 128.3, 128.1, 127.6, 127.5, 127.1, 126.8, 126.6, 119.2, 118.6, 117.1, 116.6, 113.9, 104.7, 73.7, 69.9, 65.0, 61.0, 50.8, 50.0, 32.7, 30.4, 21.3, 20.0.

MS-ESI: *m*/*z* = 251.1 $[M + H]^+$.

Compound 32

Following the general microwave procedure, **32** was obtained from 2-aminoacetophenone (0.5 mmol) and pyrrolidine (3 equiv) after 1 h at 250 °C; yield: 25.9 mg (28%) (1:1.4 mixture of diastereomers); tan oil; R_f = 0.25 (EtOAc–MeOH, 95:5 v/v).

IR (KBr): 3330, 2965, 2874, 1633, 1609, 1496, 1445, 1372, 1342, 1266, 1188, 1101, 1035, 938, 753 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.12–7.06 (m, 1 H), 7.06–6.93 (comp, 3 H), 6.79–6.71 (m, 1 H), 6.69–6.61 (m, 1 H), 6.58–6.54 (m, 1 H), 6.48–6.42 (m, 1 H), 4.70 (app t, *J* = 4.5 Hz, 1 H), 4.07–4.02 (m, 1 H), 3.96–3.90 (m, 1 H), 3.90–3.83 (m, 1 H), 3.64 (br s, 1 H), 3.13 (app td, *J* = 9.0, 4.3 Hz, 1 H), 2.97 (app td, *J* = 8.3, 4.3 Hz, 1 H), 2.72–2.61 (m, 1 H), 2.52–2.42 (m, 1 H), 2.20–1.80 (comp, 7 H), 1.75–1.63 (comp, 2 H), 1.52–147 (comp, 3 H), 1.46–1.42 (comp, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.1, 141.6, 128.0, 127.0 (6), 127.0 (5), 126.1, 125.3, 122.6, 118.5, 117.0, 115.5, 113.8, 72.6, 64.2, 56.2, 52.4, 49.6, 47.9, 32.9, 31.2, 24.9, 21.0, 20.4, 19.1.

MS-ESI: *m*/*z* = 189.1 $[M + H]^+$.

Compound 33

Following the general microwave procedure, **33** was obtained from 2-aminobenzaldehyde (**8k**; 0.5 mmol) and morpholine (3 equiv) after 2 h at 250 °C; yield: 11.8 mg (12%); light yellow solid; mp 78–81 °C; R_f = 0.36 (EtOAc–MeOH, 90:10 v/v).

IR (KBr): 3357, 2979, 2852, 1608, 1493, 1456, 1362, 1342, 1290, 1274, 1126, 1045, 1030, 930, 857, 743, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.04 (app td, *J* = 7.8, 1.6 Hz, 1 H), 6.93 (app d, *J* = 7.5 Hz, 1 H), 6.72 (app td, *J* = 7.5, 1.2 Hz, 1 H), 6.58 (dd, *J* = 7.8, 1.1 Hz, 1 H), 4.11–3.73 (comp, 6 H), 3.70 (d, *J* = 15.3 Hz, 1 H), 3.58 (dd, *J* = 11.3, 5.5 Hz, 1 H), 3.06–2.87 (m, 1 H), 2.52–2.32 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.7, 127.4, 127.0, 119.0, 118.6, 115.3, 69.8, 67.2, 67.1, 55.1, 49.2.

MS-ESI: *m*/*z* = 189.3 $[M + H]^+$.

In addition, **34a** was also isolated.

34a

Yield: 24.8 mg (38%); white solid; mp 251–253 °C; R_f = 0.19 (hexanes–EtOAc 70:30, v/v).

IR (KBr): 3318, 2024, 2955, 2855, 2807, 1612, 1498, 1479, 1450, 1368, 1308, 1216, 1115, 1094, 1072, 1020, 963, 892, 871, 749 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30–7.21 (comp, 4 H), 7.15–7.02 (comp, 3 H), 7.02–6.97 (m, 1 H), 6.94–6.81 (comp, 3 H), 6.71 (app d, *J* = 8.0 Hz, 1 H), 5.82 (s, 1 H), 5.31 (d, *J* = 3.2 Hz, 1 H), 4.84 (br s, 1 H), 4.54 (s, 1 H), 3.87–3.82 (comp, 4 H), 3.45–3.31 (m, 2 H), 2.84 (app dt, *J* = 11.6, 4.6 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.3, 144.4, 140.7, 130.7, 129.1, 129.0, 128.8, 128.7, 128.5, 127.9, 125.3, 124.4, 124.2, 123.7, 123.3, 123.3, 120.00, 117.4, 84.8, 70.4, 67.7, 64.5, 50.5.

MS-ESI: *m*/*z* = 397.0 $[M + H]^+$.

Compound 34b

A 10 mL round-bottom flask was charged with 2-aminobenzaldehyde (**8k**; 0.363 g, 3 mmol), absolute ethanol (4 mL), and pyrrolidine (0.083 mL, 1 mmol) and was stirred at r.t. for 2 days. After this time, the solvent was removed in vacuo and the residue was purified by silica gel chromatography; yield: 232.5 mg (61%); light yellow solid; mp 184–187 °C; R_f = 0.26 (hexanes–EtOAc, 70:30 v/v).

IR (KBr): 3375, 3050, 2967, 2800, 1734, 1610, 1572, 1494, 1480, 1447, 1369, 1334, 1305, 1243, 1218, 1128, 1070, 1007, 963, 952, 873, 792, 742 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.18 (comp, 3 H), 7.14 (app d, *J* = 7.7 Hz, 1 H), 7.11–7.00 (comp, 3 H), 7.00–6.93 (comp, 2 H), 6.92–6.80 (comp, 2 H), 6.71 (app d, *J* = 7.6 Hz, 1 H), 5.95 (s, 1 H), 5.29 (d, *J* = 1.8 Hz, 1 H), 4.85 (br s, 1 H), 4.50 (s, 1 H), 3.37–3.22 (m, 2 H), 2.95–2.78 (m, 2 H), 2.03–1.82 (comp, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.9, 144.2, 140.8, 130.2, 129.4, 128.9, 128.5, 128.4, 128.3, 127.8, 127.8, 124.6, 124.2, 123.6, 123.5, 123.1 119.9, 117.4, 83.8, 70.8, 63.8, 51.2, 23.8.

MS-ESI: *m*/*z* = 381.0 $[M + H]^+$.

Compound 36

Following the general microwave procedure, **36** was obtained from 2-aminobenzaldehyde (**8k**; 0.25 mmol) and *trans*-4-hydroxy-L-proline (2.1 equiv) after 15 min at 150 °C in *n*-butanol (1 mL); yield: 8.4 mg (18%) (1:1.2 mixture of diastereomers); white solid; mp 126–129 °C; R_f = 0.17 (EtOAc–MeOH, 90:10 v/v).

IR (KBr): 3284, 2922, 2806, 2361, 1610, 1491, 1379, 1267, 1152, 1091, 1018, 822, 746 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.07–6.92 (comp, 4 H), 6.77 (app t, *J* = 7.6 Hz, 1 H), 6.70 (app t, *J* = 7.3 Hz, 1 H), 6.60 (app d, *J* = 7.8 Hz, 1 H), 6.51 (app d, *J* = 8.0 Hz, 1 H), 4.56 (br s, 1 H), 4.52–4.47 (m, 1 H), 4.47–4.40 (m, 1 H), 4.23–4.15 (comp, 2 H), 4.07 (d, *J* = 15.8 Hz, 1 H), 3.88 (d, *J* = 15.8 Hz, 1 H), 3.83 (d, *J* = 16.0 Hz, 1 H), 3.30 (dd, *J* = 9.7, 5.9 Hz, 1 H), 3.17 (dd, *J* = 10.4, 6.2 Hz, 1 H), 2.96 (app d, *J* = 10.4 Hz, 1 H), 2.73 (app d, *J* = 9.7 Hz, 1 H), 2.50–2.39 (comp, 2 H), 2.20–2.00 (comp, 3 H), 1.76 (app d, *J* = 13.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.7, 142.6, 127.4, 127.3, 119.7, 119.3, 118.6, 118.4, 116.0, 114.7, 104.8, 103.0, 70.9, 70.8, 70.4, 69.9, 60.8, 59.6, 50.1, 49.3, 44.1, 43.3.

MS-ESI: *m*/*z* = 191.2 $[M + H]^+$.

Compound 37

Following the general microwave procedure, **37** was obtained from 2-aminobenzaldehyde (**8k**; 0.25 mmol) and *trans*-3-hydroxy-L-proline (2.1 equiv) after 15 min at 150 °C in *n*-butanol (1 mL); yield:

5.2 mg (11%); (1:1.1 mixture of diastereomers); white solid; mp 128–130 °C; R_f = 0.21 (EtOAc–MeOH, 90:10 v/v).

IR (KBr): 3271, 2924, 2841, 2784, 1609, 1493, 1451, 1378, 1303, 1263, 1151, 1132, 1087, 1037, 992, 843, 752 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.06 (app t, *J* = 7.7 Hz, 1 H), 7.04–6.98 (m, 1 H), 6.99–6.91 (comp, 2 H), 6.75 (app t, *J* = 7.4 Hz, 1 H), 6.72–6.66 (comp, 2 H), 6.50 (app d, *J* = 8.0 Hz, 1 H), 4.35 (app dt, *J* = 7.6, 3.8 Hz, 1 H), 4.27 (br s, 1 H), 4.21 (d, *J* = 16.2 Hz, 1 H), 4.09–4.05 (m, 1 H), 3.90 (d, *J* = 15.0 Hz, 1 H), 3.87–3.79 (comp, 3 H), 3.21 (app td, *J* = 9.3, 4.0 Hz, 1 H), 2.99 (app td, *J* = 9.0, 4.6 Hz, 1 H), 2.91 (app td, *J* = 9.2, 6.0 Hz, 1 H), 2.53–2.41 (comp, 2 H), 2.42–2.27 (comp, 2 H), 1.93–1.73 (comp, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.5, 142.4, 127.4 (2), 127.4 (0), 127.3, 127.2, 120.4, 118.8, 118.3, 114.6, 104.8, 104.3, 77.2, 76.9, 73.8, 71.6, 52.0, 49.3, 49.0, 48.5, 33.0, 32.0.

MS-ESI: *m*/*z* = 191.1 $[M + H]^+$.

Compound 41

A 50 mL round-bottom flask was charged with NaH (0.077 g, 1.934 mmol), DMF (10 mL), and 18-crown-6 (0.025 mL, 0.117 mmol) and cooled to 0 °C under N_2 atmosphere. 2,2,2-Trifluoro-*N*-(2-formylphenyl)acetamide[25n] (0.4 g, 1.842 mmol) dissolved in DMF (5 mL) was added to the solution dropwise. The solution was stirred for 20 min at r.t., then ethyl (*E*)-4-bromobut-2-enoate (0.381 mL, 2.211 mmol) dissolved in DMF (5 mL) was added dropwise. The mixture was heated at 60 °C for 4 h. After this time, the solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 (20 mL). The organic layer was washed with distilled H_2O (1 × 15 mL) and brine (1 × 15 mL) and dried (Na_2SO_4). The solid was filtered off, the solvent removed in vacuo and purified by silica gel chromatography to give ethyl (*E*)-4-[2,2,2-trifluoro-*N*-(2-formylphenyl)acetamido]but-2-enoate; yield: 255.4 g (42%); R_f = 0.29 (hexanes–EtOAc, 80:20 v/v). A 10 mL round-bottom flask fitted with a magnetic stir bar was charged with the above intermediate product (0.050 g, 0.152 mmol) and absolute EtOH (1.5 mL). To this stirred mixture, aq 5% (w/v) $NaHCO_3$ (1 mL) was added dropwise, resulting in the formation of a precipitate. The resulting mixture was heated at reflux until a homogenous solution resulted. This solution was then removed from its heat source and allowed to stir for 2 h. After this time, brine (10 mL) was added to the solution and the product was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and the solvent was subsequently removed in vacuo. The crude mixture was purified by silica gel chromatography; yield: 31.8 mg (90%); yellow oil; R_f = 0.23 (hexanes–EtOAc 90:10 v/v).

IR (KBr): 3334, 2981, 2747, 1717, 1659, 1580, 1520, 1432, 1276, 1180, 1041, 753 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.84 (s, 1 H), 8.55 (br s, 1 H), 7.50 (dd, *J* = 7.7, 1.6 Hz, 1 H), 7.42–7.34 (m, 1 H), 7.00 (app dt, *J* = 15.7, 4.4 Hz, 1 H), 6.78–6.70 (m, 1 H), 6.58 (d, *J* = 8.5 Hz, 1 H), 5.99 (dt, *J* = 15.7, 2.8 Hz, 1 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 4.09–4.05 (m, 2 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.2, 166.0, 150.0, 143.9, 136.7, 135.9, 121.9, 118.7, 115.7, 110.9, 60.4, 43.2, 14.2.

MS-ESI: *m*/*z* = 234.0 $[M + H]^+$.

Compound 42

A 10 mL round-bottom flask fitted with a magnetic stir bar was charged with aminobenzaldehyde **41** (0.117 g, 0.5 mmol), absolute EtOH (2 mL), and pyrrolidine (0.123 mL, 1.5 mmol). The resulting mixture was heated at reflux for 14 h and the solvent was subsequently removed in vacuo. The crude mixture was purified by silica gel chromatography; yield: 65.4 mg (61%); yellow oil; R_f = 0.19 (hexanes–EtOAc, 75:25 v/v).

IR (KBr): 3420, 3065, 2982, 2938, 1733, 1571, 1497, 1465, 1368, 1340, 1255, 1158, 1030, 908, 788, 753, 638, 616 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.84 (d, *J* = 2.2 Hz, 1 H), 8.08 (app d, *J* = 8.3 Hz, 1 H), 8.07–8.05 (m, 1 H), 7.77 (app d, *J* = 8.3 Hz, 1 H), 7.68 (ddd, *J* = 8.3, 7.2, 1.1 Hz, 1 H), 7.52 (app t, *J* = 7.2 Hz, 1 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 3.79 (s, 2 H), 1.25 (app td, *J* = 7.1, 0.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 151.6, 147.2, 132.7, 129.2, 129.1, 127.8, 127.5, 127.0, 126.8, 61.2, 38.7, 14.2.

MS-ESI: *m*/*z* = 216.2 $[M + H]^+$.

Compound 51

Following the general reflux procedure, **51** was obtained from **8c** (0.5 mmol) and 2-allylpyrrolidine (**50**)[25o] after heating for 24 h at reflux in absolute EtOH (2 mL). Products **51** and **52** were obtained together as an off-white solid in 15% and 3% yield, respectively. In addition, **54** and **55** were obtained in 29% and 27% yield, respectively.

Data for 51

Yield: 27.9 mg (15%); mp 75–77 °C; R_f = 0.13 (hexanes–EtOAc, 90:10 v/v).

IR (KBr): 3414, 2889, 1593, 1490, 1341, 1109, 914, 863 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 2.1 Hz, 1 H), 6.99 (s, 1 H), 5.88–5.69 (m, 1 H), 5.22–4.97 (comp, 2 H), 4.78 (d, *J* = 4.1 Hz, 1 H), 4.33–4.11 (comp, 2 H), 3.78 (d, *J* = 17.1 Hz, 1 H), 2.89–2.78 (m, 1 H), 2.56–2.43 (m, 1 H), 2.43–2.34 (m, 1 H), 2.28–1.95 (comp, 2 H), 1.83–1.54 (comp, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.5, 135.3, 132.2, 128.8, 120.4, 116.8, 108.0, 107.5, 71.7, 57.6, 46.2, 38.8, 31.2, 27.8.

MS-ESI: *m*/*z* = 373.2 $[M + H]^+$.

Deoxyvasicine

To a 25 mL round-bottom flask was added compound **9k** (0.174 g, 1.0 mmol) and THF (5 mL). The mixture was cooled to –78 °C under N_2 atmosphere in a dry ice/acetone bath and stirred for 5 min. *n*-BuLi (2.5 M in hexanes, 0.42 mL, 1.05 equiv) was added to the mixture and allowed to stir for 1 h. I_2 (0.329 g, 1.3 mmol) dissolved in THF (5 mL) was added to the solution dropwise and stirred for 30 min. Et_3N (0.418 mL, 3 mmol) was added to the solution, which was then allowed to warm to r.t. and stirred for 30 min. The mixture was then quenched with distilled H_2O (15 mL), extracted with EtOAc (3 × 15 mL), and the solvent was removed in vacuo. The resulting residue was purified by silica gel chromatography with Et_3N–MeOH–EtOAc (1:10:89) as the eluent. Deoxyvasicine was obtained as a tan solid (146 mg, 85%) and matched reported spectroscopic data in all regards.[25e]

Vasicine

To a 10 mL round-bottom flask was added compound **37** (0.014 g, 0.074 mmol) and Et_2O (1 mL). The mixture was cooled to –78 °C under N_2 atmosphere in a dry ice/acetone bath and stirred for 5 min. BuLi (2.5 M in hexanes, 0.031 mL, 1.05 equiv) was added to the mixture and was allowed to stir for 1 h. I_2 (0.021 g, 0.081 mmol) dissolved in Et_2O (1 mL) was added dropwise and the mixture stirred for 30 min. Et_3N (0.031 mL, 0.221 mmol) was then added to the solution, which was then allowed to warm to r.t. and stir for 30 min. The mixture was then quenched with distilled H_2O (5 mL), extracted with EtOAc (3 × 5 mL), and the solvent was removed in vacuo. The resulting residue was purified by silica gel chromatography with Et_3N–MeOH–EtOAc (1:10:89) as the eluent. Vasicine was obtained as a tan solid (10.9 mg, 79%) (R_f = 0.16 in *i*-$PrNH_2$–MeOH–EtOAc, 2:10:88 v/v/v) and matches reported spectroscopic data in all regards.[25f]

Compound 61

Following the general microwave procedure, **61** was obtained from **8c** (0.25 mmol) and *trans*-4-hydroxy-L-proline (2.1 equiv) after 30 min at 150 °C in *n*-butanol (1 mL); yield: 44.3 mg (50%) (1:1.2

mixture of diastereomers); tan solid; mp 122–125 °C; R_f = 0.19 (EtOAc–MeOH, 95:5 v/v).

IR (KBr): 3302, 2940, 2819, 2360, 2342, 1596, 1483, 1375, 1285, 1258, 1152, 1023, 862, 683 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 2.1 Hz, 1 H), 7.39 (d, *J* = 2.1 Hz, 1 H), 7.04 (s, 1 H), 7.01 (s, 1 H), 4.63 (dd, *J* = 5.4, 2.2 Hz, 1 H), 4.58–4.52 (m, 1 H), 4.52–4.45 (m, 1 H), 4.38 (br s, 1 H), 4.34–4.29 (m, 1 H), 4.22 (d, *J* = 16.6 Hz, 1 H), 4.17 (br s, 1 H), 4.07 (d, *J* = 15.7 Hz, 1 H), 3.84–3.72 (comp, 2 H), 3.22 (dd, *J* = 10.2, 6.4 Hz, 1 H), 3.07 (dd, *J* = 10.0, 5.6 Hz, 1 H), 2.83–2.73 (comp, 2 H), 2.48 (ddd, *J* = 13.7, 7.6, 5.1 Hz, 1 H), 2.23 (ddd, *J* = 14.0, 7.3, 2.3 Hz, 1 H), 2.15 (ddd, *J* = 14.0, 5.3, 2.8 Hz, 1 H), 1.88–1.79 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.1 (3), 139.1 (0), 132.5, 132.3, 129.1, 129.0, 122.0, 121.0, 109.9, 109.4, 108.6, 108.4, 70.9, 70.7, 70.5, 69.9, 60.0, 59.0, 49.4, 48.4, 44.5, 43.3.

MS-ESI: *m*/*z* = 349.2 $[M + H]^+$.

Compound 62

To a 10 mL round-bottom flask was added **61** (0.05 g, 0.144 mmol), acetone (4 mL), $KMnO_4$ (0.068 g, 0.431 mmol). The solution was heated at reflux for 2 h, after which time the solution was cooled to r.t. and filtered through a pad of Celite. The filtrate was washed with acetone (10 mL) and MeOH (10 mL), and the solvent was removed in vacuo. The residue was purified by column chromatography, resulting in the isolation of (*R*)-5,7-dibromo-2-hydroxy-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one as a tan solid; yield: 33.4 mg (64%); R_f = 0.28 (EtOAc). To a 10 mL round-bottom flask was added the above intermediate product (0.0073 g, 0.02 mmol), MeOH (1 mL), 10% Pd/C (2.158 mg, 0.1 equiv), and Et_3N (8.48 μL, 3 equiv). The atmosphere was evacuated and replaced with H_2 gas using a three-way glass adaptor. The mixture was stirred for 2 h and was then filtered. The filtrate was washed with MeOH (15 mL) and the solvent was removed in vacuo; yield: 4.01 mg (98%); white solid; mp 168–171 °C; R_f = 0.16 (EtOAc–MeOH v/v); $[\alpha]_D^{25}$ –35.0 (*c* 0.167, $CHCl_3$).

IR (KBr): 3395, 2917, 2849, 2357, 1682, 1633, 1607, 1454, 1392, 1277, 773 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.21 (app d, *J* = 8.0 Hz, 1 H), 7.75–7.67 (m, 1 H), 7.61 (app d, *J* = 8.2 Hz, 1 H), 7.43 (app t, *J* = 7.5 Hz, 1 H), 4.87–4.77 (m, 1 H), 4.32 (app d, *J* = 13.2 Hz, 1 H), 4.21 (dd, *J* = 13.2, 4.8 Hz, 1 H), 3.40 (dd, *J* = 17.5, 5.7 Hz, 1 H), 3.18 (app d, *J* = 17.5 Hz, 1 H), 2.92 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.9, 157.5, 148.8, 134.3, 126.7, 126.5, 126.4, 120.5, 65.8, 55.2, 42.3.

MS-ESI: *m*/*z* = 203.0 $[M + H]^+$.

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