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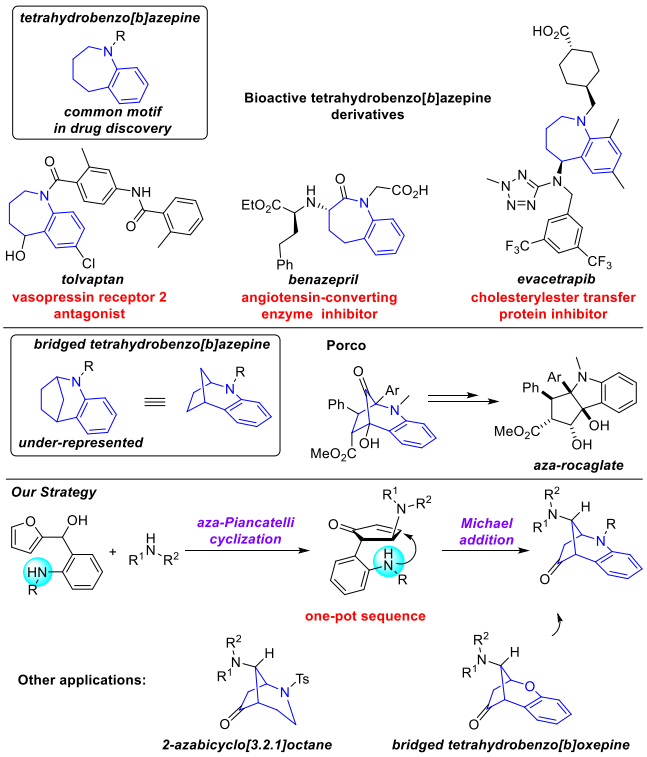
Synthesis of Bridged Tetrahydrobenzo[*b*]azepines and Derivatives through an Aza-Piancatelli Cyclization/Michael Addition Sequence

Shengdong Wang,[a] Régis Guillot,[a] Jean-François Carpentier,[b] Yann Sarazin,[b] Christophe Bour,[a] Vincent Gandon,*,[a] and David Lebœuf*,[a]

Abstract: Herein, we report the preparation of bridged tetrahydrobenzo[*b*]azepines, which was accomplished via an aza-Piancatelli cyclization/Michael addition sequence in a one-pot fashion from readily available precursors. It is noteworthy that a general method to access these scaffolds was hitherto unprecedented. Additionally, the multifaceted aspects of this process have been exemplified through its application to the synthesis of 2-azabicyclo[3.2.1]octanes and bridged tetrahydrobenzo[*b*]oxepines, along with post-derivatizations.

Tetrahydrobenzo[*b*]azepines represent an important class of medium-size nitrogen heterocycles, whose scaffolds can be found in a large variety of bioactive molecules, including tolvaptan,[1] benazepril[2] and evacetrapib[3] (Scheme 1). Consequently, tremendous efforts have been recently dedicated to devise creative, efficient, and flexible strategies to prepare these compounds,[4] while providing molecular complexity and diversity for applications in drug discovery. In this context, bridged tetrahydrobenzo[*b*]azepines remain an elusive subclass of this family, the development of which has been clearly underexplored.[5] Currently, one of the few applications of these compounds is to serve as intermediates for the synthesis of aza-rocaglate derivatives, which was reported by the group of Porco.[6] The limited output for these challenging molecules might find its origins in the difficulty to prepare these frameworks, which has hampered any real study on their potential bioactive properties. Therefore, we believed that designing a general approach to access these synthons could make a difference, not only by boosting the interest in them from the pharmaceutical industry but also, more generally, by filling a void in the synthesis of *N*-heterocycles. To accomplish this objective, we wondered whether the aza-Piancatelli cyclization could be exploited to close this gap.[7] Over the past few years, this Nazarov-type electrocyclization[8] has been at the heart of our research program, granting rapid access to privileged building blocks such as 4-aminocyclopentenones, cyclopenta[*b*]pyrroles and cyclopenta[*b*]piperazinones from readily available 2-furylcarbinols.[9] In that respect, by taking a close look at the compounds generated during the cyclization, we reasoned that the introduction of a nitrogen functionality on the carbinol moiety might be the answer to this issue. In practice, once the aza-Piancatelli cyclization is complete (first step), adding a base to the reaction mixture would be sufficient to trigger a Michael addition (second step) and assemble tetrahydrobenzo[*b*]azepines in a one-pot sequence.[10,11] Another enticing feature of this strategy is that the cyclization ends up installing the substituents in *trans*-relationship, which should prevent any steric hindrance during the second step. Conceptually, this route would not only offer the advantage of being short and simple, while relying on flexible precursors, but would yield also the desired targets with two additional anchors, a ketone and an amine functionalities, which could be easily employed for diversity-oriented synthesis. Furthermore, we considered that this protocol could be implemented to synthesize 2-azabicyclo[3.2.1]octanes, which are also challenging scaffolds in synthesis,[12] and bridged tetrahydrobenzo[*b*]oxepines, both motifs can be encountered in other natural products such as enokipodin A[13] and hosieine A.[14]



Scheme 1. Biologically relevant tetrahydrobenzo[*b*]azepines and our strategy to prepare bridged tetrahydrobenzo[*b*]azepines and related compounds.

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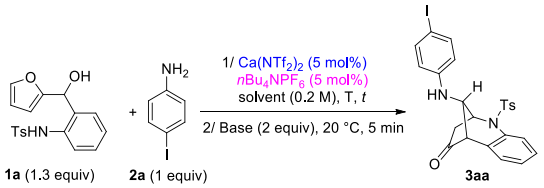
In our preliminary investigations (Table 1), we explored the reactivity of 2-furylcarbinol **1a** incorporating a sulfonamide group with 4-iodoaniline **2a** using our standard catalytic system for the aza-Piancatelli cyclization ($Ca(NTf_2)_2$ (5 mol%) and nBu$_4$NPF$_6$ (5 mol%)) in hexafluoroisopropanol (HFIP)[15] under air (Entry 1). Indeed, we recently reported that the use of this solvent allows the cyclization to take place under mild reaction conditions, typically at room temperature, which proved to be particularly beneficial with sensitive substrates.[9b] Then, after the complete formation of the 4-aminocyclopentenone intermediate, triethylamine was added to the reaction mixture, delivering the targeted bridged tetrahydrobenzo[*b*]azepine **3aa** in 66% yield within 5 min. The structure of compound **3aa** was confirmed by X-Ray crystallography (Figure 1). The solvent plays a key role in this transformation as other usual solvents were also screened but led only to the decomposition of **1a** (Entries 2-4). However, employing HFIP as a solvent might raise significant concerns regarding the utility of this method because of its cost and high corrosivity and, thus, we focused on the use of mixtures of solvents to mitigate these disadvantages (Entries 5-11). To our delight, we found that not only the amount of HFIP could be decreased, but also that the reactivity could be drastically improved to afford **3aa** in 91% yield with a toluene/HFIP 3:1 (*v*/*v*) mixture (Entry 6). In addition, the catalyst loading could be lowered to 1 mol% with still satisfactory yields (79%) along with a slower reaction rate (Entry 7). In the next set of experiments, several bases were evaluated; however, it did not result in better yields (Entries 11-14). As a final point, it is important to stress out that the reaction is scalable, furnishing **3aa** in 86% yield (2.34 g) without any setback while starting from 5 mmol of **2a** (Entry 8).

Table 1. Reaction optimization for the formation of bridged tetrahydrobenzo[*b*]azepine **3aa**.[a]



Entry	Solvent	Base	T [°C]	*t* [h]	Yield **3aa** [%]
1	HFIP	Et_3N	20	8	66
2	toluene	Et_3N	80	17	-
3	$MeNO_2$	Et_3N	80	17	-
4	1,2-DCE	Et_3N	80	17	-
5	toluene/HFIP (4:1)	Et_3N	20	9	59
6	toluene/HFIP (3:1)	Et_3N	20	9	91
7[b]	toluene/HFIP (3:1)	Et_3N	20	20	79
8[c]	toluene/HFIP (3:1)	Et_3N	20	20	86
9	toluene/HFIP (2:1)	Et_3N	20	9	80
10	$MeNO_2$/HFIP (3:1)	Et_3N	20	9	85
11	1,2-DCE/HFIP (3:1)	Et_3N	20	9	15
12	toluene/HFIP (3:1)	DBU	20	9	82
13	toluene/HFIP (3:1)	NaH	20	9	16
14	toluene/HFIP (3:1)	K_2CO_3	20	9	36
15	toluene/HFIP (3:1)	*t*BuOK	20	9	54

[a] Reactions conditions: (1) 2-furylcarbinol **1a** (0.26 mmol, 1.3 equiv) and aniline **2a** (0.2 mmol, 1 equiv) in the indicated solvent (0.2 M) in the presence of $Ca(NTf_2)_2$ (5 mol%) and nBu$_4$NPF$_6$ (5 mol%) at the indicated temperature, (2) base (0.52 mmol, 2 equiv), 20 °C, 5 min. [b] $Ca(NTf_2)_2$ (1 mol%) and nBu$_4$NPF$_6$ (1 mol%). [c] aniline **2a** (5 mmol).

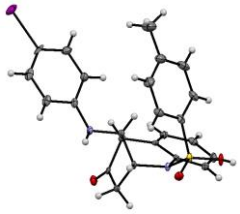


Figure 1. ORTEP drawing of compound **3aa**. Thermal ellipsoids are shown at 30% probability level.

With these optimized conditions in hand, we assessed the scope of the reaction and the results are summarized in Scheme 2. A series of anilines bearing either electron-donating or electron-withdrawing groups at the *para*, *meta* or *ortho* position were all converted into the corresponding tetrahydrobenzo[*b*]azepines in good to excellent yields, ranging from 63 to 90%. Of note, aniline **2q** containing a boronic ester substituent demonstrated a remarkable reactivity to give **3fq** in 89% yield. In addition, the reaction was not limited to primary anilines but could be also applied to *N*-alkyl anilines and hydroxylamines such as **2q** and **2r** to deliver **3aq** (66%) and **3ar** (81%).[16] Then, we examined the influence of the substitution pattern of the benzenesulfonamide. The introduction of an electron-donating or -withdrawing substituent at the *para*-position of the sulfonamide did not preclude the transformation, producing the desired compounds in good yields (**3ba**-**3da**). We were also pleased to find that the reaction was compatible with a naphthyl moiety to furnish **3ea** in 88% yield. The presence of a relatively non-basic nucleophile at the carbinol moiety proved to be crucial since, in the presence of an acetamide group (**1g**), a [1,2]-migration of the *p*-anisidine group was observed during the second step (see the Supporting Information for details) and the decomposition of 2-furylcarbinol **1h** was observed during the first step in the absence of a sulfonyl group.[17] Moreover, tertiary 2-furylcarbinols could be engaged in this route to prepare the highly functionalized compounds **3ia** and **3ja** in 63% and 56% yields, respectively. Another interesting feature is that phenol could be also employed in this type of reaction sequence to provide the corresponding bridged tetrahydrobenzo[*b*]oxepines (**3ka**-**3kc**, **3ki**, **3lb** and **3mb**) (yields up to 93%). Encouraged by these results, we turned our attention to the reactivity of 2-furylcarbinol **1n**, which incorporates a *N*-alkyl sulfonamide moiety instead of a benzenesulfonamide one. This type of 2-furylcarbinols proved was less reactive as the aza-Piancatelli cyclization had to be carried out at 40 °C for 48 h, while the Michael addition reached its full conversion after 36 h. It might be explained by the formation of a less constrained intermediate, which in turn may slow down the second step. The yields remained overall satisfactory (33-65%) when one considers the complexity of the structures obtained (**3na**, **3ni** and **3nk**). Herein, the major hurdle is the lack of control of the diastereoselectivity during the first step (substituents in *trans*- and *syn*-relationship), which is usually one of the strengths of the aza-Piancatelli cyclization, suggesting that another mechanism might come into play. Indeed, in the case of an aliphatic chain, which is the case here, an aldol-type mechanism has sometimes been mentioned to account for this behaviour.[7,18]

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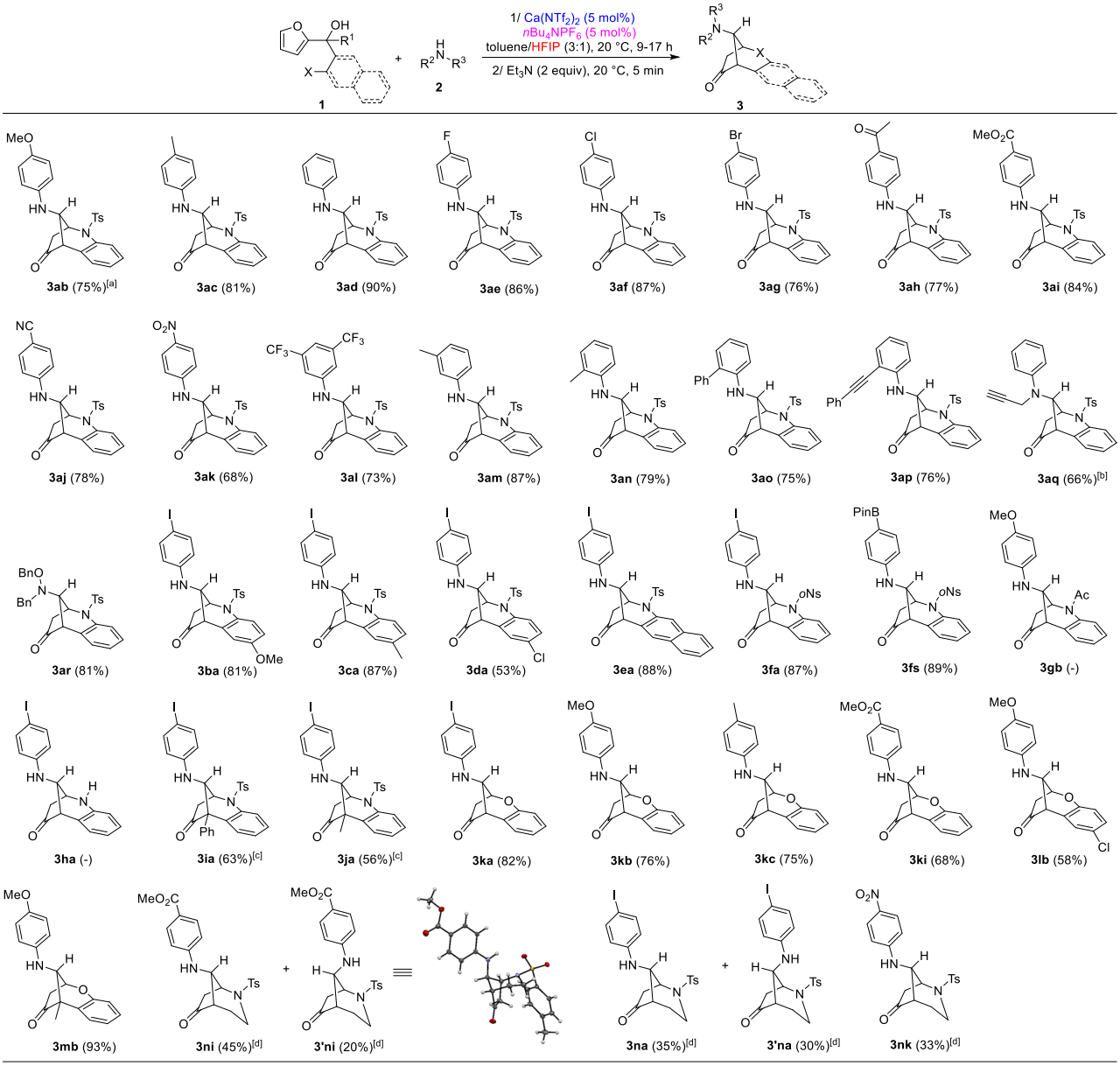

Scheme 2. Substrate scope of the aza-Piancatelli cyclization/Michael addition sequence. [a] (1): 17 h at 40 °C, (2): 5 min at 20 °C. [b] (1): 1 h at 60 °C; (2): 5 min at 20 °C. [c] (1): 17 h at 70 °C; (2): 17 h at 20 °C. [d] 48 h at 40 °C, (2): 36 h at 20 °C. ORTEP drawing of compound **3'ni**. Thermal ellipsoids are shown at 30% probability level.

On the positive side, it means that the steric hindrance exhibited by the aniline moiety is not a barrier for the Michael addition.

Then, to showcase the synthetic utility of this transformation, we performed post-modifications on these compounds. First, we turned our attention to the reactivity of the ketone functionality (Scheme 3). We demonstrated that compound **3aa** could undergo a diastereoselective reduction of the ketone as well as a 1,2-addition of allyl Grignard to afford the corresponding alcohols in 95% (**4**) and 85% (**5**) yields, respectively. Moreover, in the presence of *m*CPBA, azoxabicyclo[3.3.1]nonanone **7** could be isolated in 83% yield via a Baeyer-Villiger oxidation.[19] These reaction conditions were also tested on substrate **3aa** but led to a mixture of products resulting likely from the formation of hypervalent iodine derivatives.[20] Importantly, compound **3aa** could be engaged in a cross-coupling such as a Sonogashira reaction to produce compound **6** in 76% yield. Regarding this methodology, an important factor was to be able to remove the various protecting groups on the nitrogen functionalities for potential derivatizations. For instance, the cleavage of the *o*-nosyl group (**3fa**) occurred smoothly to return the unprotected amine **3ha** in 89% yield upon treatment with thiophenol and potassium carbonate. We also attempted to obtain the free amine **9** starting from **3ab**. However, in the presence of cerium ammonium nitrate (CAN), the reaction failed and gave instead the stable *p*-benzoquinone imine **8** in a excellent yield of 93%. A subsequent acidic treatment had to be carried out to lead to the desired product **9** (44% over two steps). On the other hand, amine **9** could be directly obtained from **3ar** by a simple hydrogenation (71%). In the case of compound **3ak**, the nitroarene group could be reduced to the corresponding aniline **10** by hydrogenation as well (96%). Finally, we took advantage of the alkyne moiety of

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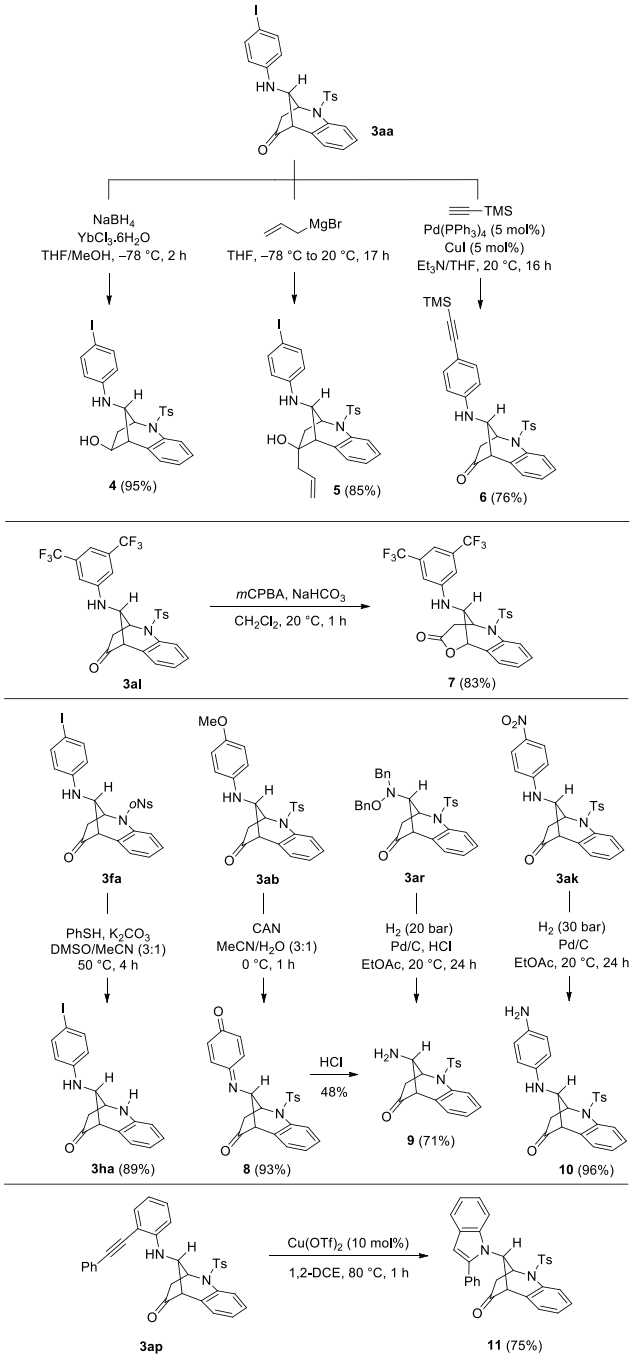
compound **3ap** to engineer a copper-catalyzed hydroamination process[21] with the aim of generating the corresponding indole **11** in 75% yield. The reaction mimics an aza-Piancatelli cyclization between 2-furylcarbinol **1a** and an indole. Yet, it is well-established that the NH functionality is not nucleophilic enough to exhibit such reactivity, leading instead to Friedel-Crafts products.[22]



Scheme 3. Post-derivatizations of bridged tetrahydrobenzo[*b*]azepines.

In summary, the combination of an aza-Piancatelli cyclization and a Michael addition enabled the first general synthesis of densely functionalized bridged tetrahydrobenzo[*b*]azepines from common 2-furylcarbinols, which has the means of having a significant impact in medicinal chemistry. This reaction sequence displays a tolerance to a large range of functional groups, delivering the desired products in good to excellent yields. This method was also extended to the preparation of 2-azabicyclo[3.2.1]octanes and bridged tetrahydrobenzo[*b*]oxepines to enhance its synthetic utility. Our current goal is to develop an asymmetric version of this transformation.

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Keywords: tetrahydrobenzo[*b*]azepines • medium-size *N*-heterocycles • electrocyclization • Lewis acid • hexafluoroisopropanol

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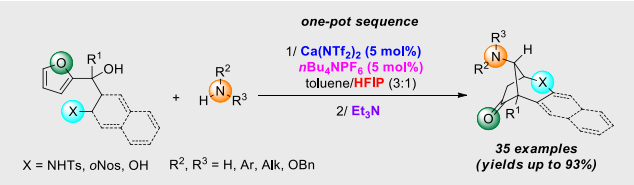

Building bridges: For the first time, we disclose a unified approach to convert 2-furylcarbinols into bridged tetrahydrobenzo[*b*]azepines and related bridged compounds using amines as nucleophiles under mild conditions. The transformation demonstrates both a broad functional group tolerance and an excellent efficacy toward the preparation of densely functionalized molecules.

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Synthesis of Bridged Tetrahydrobenzo[*b*]azepines and Derivatives through an Aza-Piancatelli Cyclization/Michael Addition Sequence

Accepted Manuscript