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Natural Products

Aza-Piancatelli Cyclization as a Platform for the Preparation of Scaffolds of Natural Compounds: Application to the Total Synthesis of Bruceolline D

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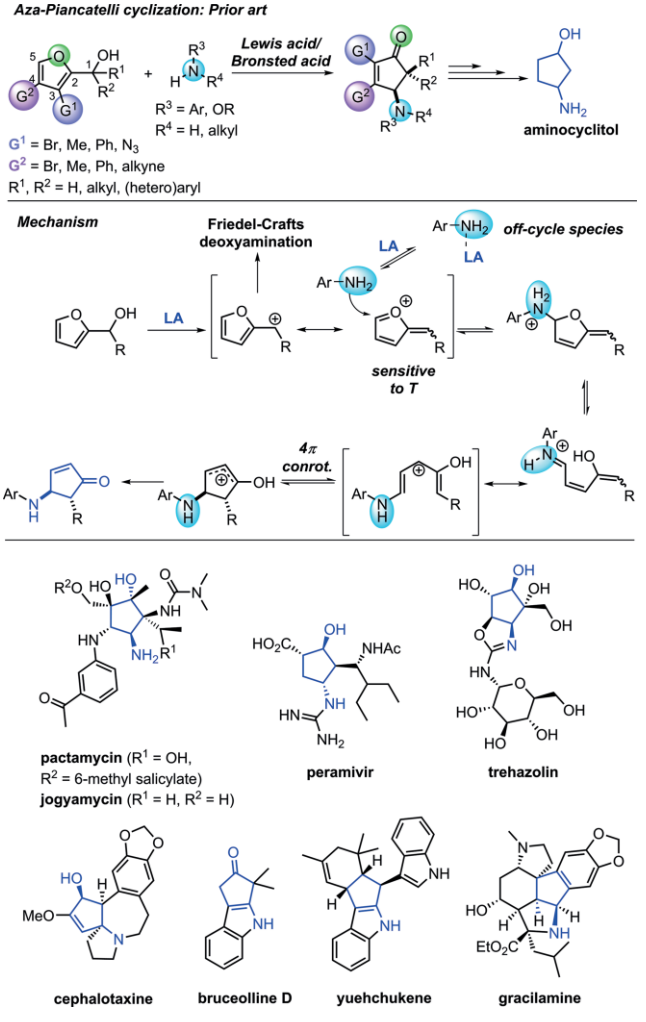
Abstract: The aza-Piancatelli cyclization provides an expedient synthesis of 4-aminocyclopentenone building blocks that may be converted into aminocyclopentitols, which are heavily represented motifs among natural products. However, its use as a key step in total synthesis was still unprecedented. Here, we disclose our in-depth investigations regarding this reaction in order to access highly complex structures representing the core of some natural molecules. The applicability of the cyclization was highlighted by the 3-step total synthesis of bruceolline D. Thus, we anticipate that this work will lay the ground for further applications in total synthesis.

In the last decade, the aza-Piancatelli cyclization has garnered a growing interest because it enables a rapid and efficient pathway to 4-aminocyclopententenone derivatives from biomass-derived furan feedstocks.[1] In general, this reaction represents a direct entry to aminocyclitol scaffolds that can be found in numerous bioactive and natural products (Scheme 1).[2] They include pactamycin (antibiotic, antiprotozoal and antiproliferative properties),[3] jogyamycin (antiprotozoal),[4] peramivir (antiviral),[5] and trehazolin (glycosidase inhibitor).[6] Furthermore, this reaction may also provide a straightforward access to more complex polycyclic targets such as cephalotaxine,[7] bruceolline D,[8] and yuehchukene,[9] which embed a cyclopenta[*b*]indole unit, or gracilamine.[10] This cyclization relies on the formation of a key oxonium intermediate, which can then undergo a nucleophilic attack of an aniline or hydroxylamine derivative. A subsequent 4π-conrotatory electrocyclization affords the corresponding 4-aminocyclopentenone with complete control of the diastereoselectivity. However, this reaction remains challenging as side reactions can take place at the carbinol position, including Friedel-Crafts and deoxyamination reactions, while the oxonium species can degrade at high temperatures. In addition, anilines incorporating electron-donating groups proved to be less reactive as they can entrap



Scheme 1. Aza-Piancatelli cyclization as a platform for natural compounds.

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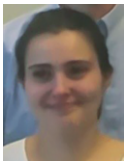
the Lewis or Brønsted acid catalyst to generate an off-cycle species.

Since the pioneering work of Denisov et al.[11] and Read de Alaniz group,[12] we and others have directed our efforts towards the preparation of even more densely functionalized targets using the aza-Piancatelli cyclization as a cornerstone[13] as well as the development of enantioselective versions.[13h,13k,14] In our case, we implemented new strategies for the synthesis of polycyclic structures such as cyclopenta[*b*]pyrroles,[13e–13f] cyclopenta[*b*]piperazinones[13g] and tetrahydrobenzo[*b*]azepines[13j] by pairing the aza-Piancatelli cyclization with a second key transformation, such as hydroamination, annulation or Michael addition. In turn, the studies related to the influence of the substitution pattern at the positions C3 and C4 of the furan ring on the reactivity have been limited.[13e–13g,15–16] This issue is particularly critical when considering the compounds mentioned above, which bear a multitude of additional functional groups, including heteroatoms on the cyclopentane ring. As a result, the question remains whether the aza-Piancatelli cyclization could be useful for the synthesis of natural products.[17] In this context, we disclose herein our recent findings to increase the synthetic utility of this reaction by developing (1) a general synthetic approach to install several key functionalities of pactamycin, jogyamycin, and peramivir, (2) a simple method to build the cyclopenta[*b*]indole moiety, which was highlighted by the total synthesis of bruceolline D, and finally (3) an aza-Piancatelli/Diels-Alder/fragmentation reaction sequence to access frameworks of interest. Besides, we provide an overview of the scope and limitations of this reaction, demonstrating that the presence of heteroatoms on the furan ring does not impede the reactivity.

In our initial investigations, we focused on a general route to access the core of pactamycin, jogyamycin, and peramivir (Scheme 2). We noticed that all their structures have in common the presence of an oxygen functionality (hydroxymethyl or carboxylic acid) in the same position. In order to perform the aza-Piancatelli cyclization, our first task was to prepare the 2-furylcarbinol precursors, which involved the installation of the desired functional groups at the position C3 of the furan ring. We hypothesized that the simplest way to achieve this goal would be to start from the inexpensive 3-furoic acid **1** (≈ 2 €/g). This strategy brings two advantages: (1) the key functional group or its direct precursor would be already present, and (2) it is well-documented that the carboxylic acid can serve as a directing group for the regioselective alkylation of furans with aldehydes to rapidly introduce the carbinol moiety.[18] Following this approach, we obtained the 2-furylcarbinol intermediates **3**, which were engaged in the next step without further purification. Then, we conducted the selective methylation of the carboxylic acid upon treatment with trimethylsilyldiazomethane to afford the corresponding esters **4** in good to excellent yields over two steps (up to 97 %). Finally, the reduction of the ester with $LiAlH_4$ and the subsequent protection of



Lucile Marin *received her Master degree in 2015 at the Paris-Sud University, and she obtained her Ph.D. under the supervision of Dr. Emmanuelle Schulz and Dr. David Lebœuf in 2018 at the Paris-Saclay University. Her Ph.D. focused on the development of the aza-Piancatelli cyclization and its use in total synthesis.*

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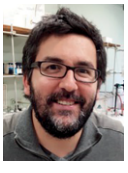
Emmanuelle Schulz *graduated from ESCIL in Lyon and received her Ph.D. degree in 1992 for studies concerning the total synthesis of Strigol (Pr. P. Welzel, Ruhr-Universität Bochum/Université de Lyon). After an industrial postdoc (RP Agro), she joined the group of Pr. M. Lemaire in Lyon and obtained a permanent position at the CNRS. Since 2000, she has been working at the Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO, Paris-Saclay University). Her research interests are mainly directed towards asymmetric catalysis. She particularly explores the enantioselective hydroamination reaction promoted by chiral rare-earth-based catalysts. New procedures for the easy recovery and reuse of chiral organometallic catalysts, specifically with enantiopure salen complexes, are also developed in her group.*



David Lebœuf *received his engineering degree from ESPCI (Ecole Supérieure de Physique et de Chimie Industrielles de la ville de Paris) in 2005, before pursuing a Ph.D. with Pr. Max Malacria at the University Pierre and Marie Curie-Paris 6 until 2009, where he explored new cobalt-, rhodium-, and gold-catalyzed cyclizations. After two and half years of postdoctoral research at the University of Rochester with Pr. Alison J. Frontier working on copper-mediated Nazarov electrocyclizations and one year at the Institute of Chemical Research of Catalonia (ICIQ) with Pr. Antonio M. Echavarren developing new gold catalysts, he was appointed by the CNRS as Chargé de Recherche in 2013 at the Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO, Paris-Saclay University). In 2019, he joined the Institut de Science et d'Ingénierie Supramoléculaires (ISIS, University of Strasbourg), where he is currently developing new synthetic methods featuring supramolecular chemistry. David has been the recipient of the ANR Young Researcher Grant, JSP Fellowship and Thieme Chemistry Journal Award (2020).*

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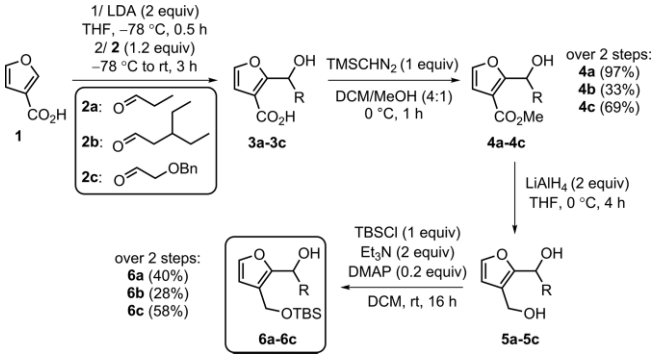
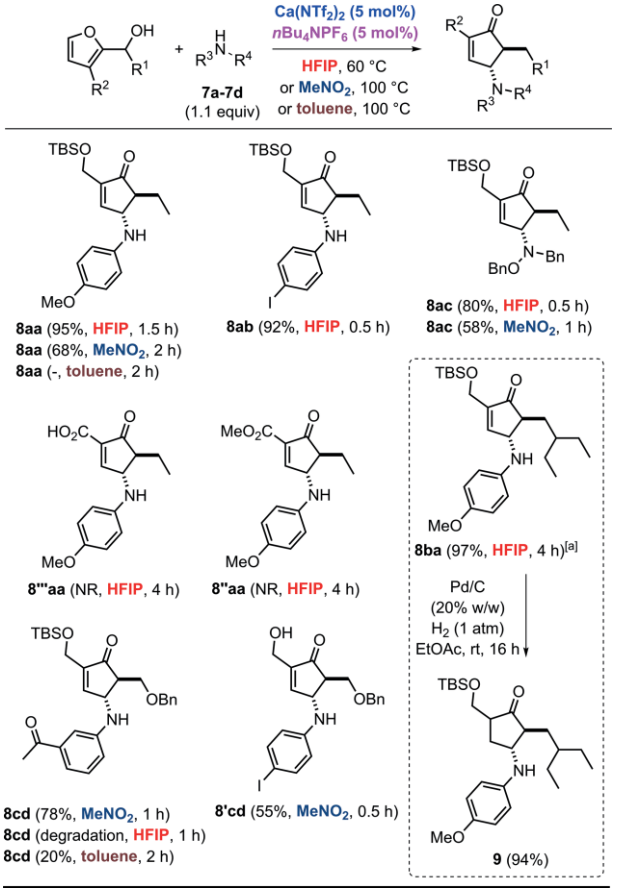
the primary alcohol formed **5** with *tert*-butyldimethylsilyl chloride (TBSCl) furnished the targeted precursors **6**.



Scheme 2. Preparation of 2-furylcarbinol precursors.

With these precursors in hand, we evaluated their reactivity in the aza-Piancatelli cyclization (Scheme 3). During our previous studies, we developed an efficient promoter system, combining three key components: $Ca(NTf_2)_2$ as a catalyst with nBu_4NPF_6 as an additive in hexafluoro2-propanol (HFIP) as a solvent.[19] This association allows operating under milder reaction conditions than in other classic solvents (nitromethane, toluene, acetonitrile, etc.), while circumventing the abovementioned limitations, including the reactivity of anilines bearing strong electron-donating groups, due to the remarkable ability of HFIP to stabilize carbocation species, to strongly donate hydrogen bonds, in addition to its low nucleophilicity.[20] At the outset, we examined the reaction between **6a** and a series of amines (**7a**–**7c**). In each case, the 4-aminocyclopentenone was obtained in high yield (up to 95 %), with most of the functionalities of jogyamycin being installed. Nitromethane and toluene were also screened as solvent with **7a** but either the product **8aa** was obtained in a lower yield ($MeNO_2$) or the precursor mainly decomposed (toluene). Of note, in the presence of an electron-withdrawing group at the C3-position of the furan (**3a** and **4a**), no reaction occurred, which might be explained by a significant decrease of the electrophilicity of the alcohol. In the same vein, we explored the reactivity of the precursor **6b** of peramivir, which yielded the target product **8ba** in 97 % yield. With peramivir in mind, we also conducted the hydrogenation of the cyclopentenone to deliver **9** in 94 % yield. However, its relative stereochemistry remained unclear due to the overlap of the signals by 2D NOESY NMR experiments (see the Supporting Information for details). Lastly, precursor **6c** was subjected to the same reaction conditions in the presence of aniline **7d**, which led only to the decomposition of the substrate. It might be caused by the presence of the benzyl ether that could be deprotected under the reaction conditions.[21] In turn, switching solvent from HFIP to nitromethane produced compound **8cd** in 78 % yield, thereby offering an entry point to pactamycin and potential analogues.[22] This transformation could also be conducted in the absence of the silyl group (**5c**), albeit in lower yield (55 %).

Another issue that we addressed was the possibility to directly introduce heteroatoms such as oxygen for the synthesis of trehazolin and cephalotaxine or nitrogen for the synthesis of



Scheme 3. Aza-Piancatelli cyclization of 2-furylcarbinols with amines **7a**–**7d**. [a] **6b** (1.2 equiv.) and **7a** (1 equiv.). NR = no reaction.

pactamycin and jogyamycin on the furan ring (Scheme 4). To assess such reactivity, we prepared model substrates bearing methoxy or azide functionalities that were easily introduced by direct nucleophilic substitution on 3-bromofuraldehyde. Importantly, in contrast with the case mentioned above with a strong electron-withdrawing group at the position C3, the presence of a strong electron-donating group renders the 2-furylcarbinol highly reactive and, therefore, not compatible with the standard conditions in HFIP. However, replacing HFIP by nitromethane provided **8db** in 70 % yield. Regarding the azide **6e**, the target product was obtained in high yield (95 %), offering the possibility to build cyclopentane rings with two nitrogen functionalities directly introduced.[23]

While our initial studies focused on the reactivity of 2-furylcarbinols bearing substituents at the C3-position, we then turned our attention to 2-furylcarbinols incorporating substituents at the C4-position with the aim of using the aza-Piancatelli cyclization to generate cyclopenta[*b*]indole scaffolds. As proof of concept, we explored the total synthesis of bruceolline D (Scheme 5). This molecule was isolated in 1994 by the group of Ohmoto from the root wood *Brucea mollis Wall. var. tonkinensis Lecomte* and is mostly employed in China for the treatment of malaria.[8a] To date, only three total syntheses were described for this molecule.[8c–8d] Here, we envisioned an intramolecular aza-Piancatelli cyclization from precursor **11** to deliver bruceol-

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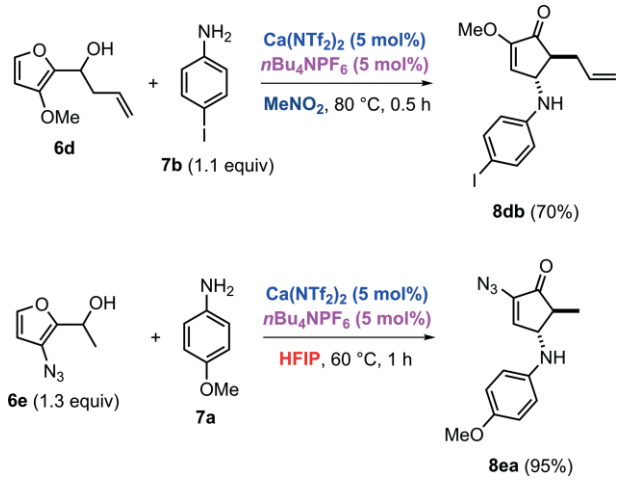
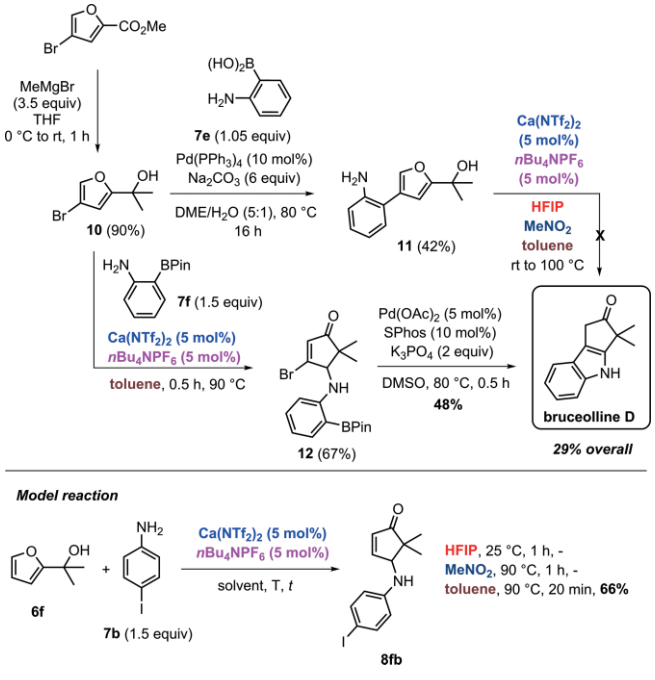


Scheme 4. Influence of the presence of heteroatoms on the aza-Piancatelli cyclization.

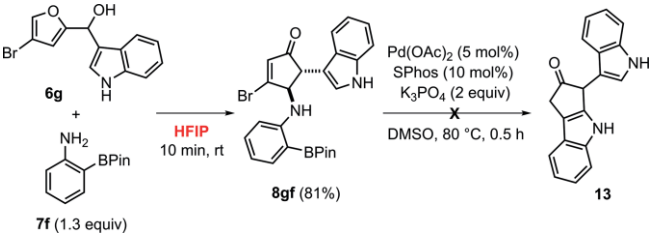
line D. This substrate was rapidly synthesized from commercially available methyl 4-bromofuran-2-carboxylate (≈ 30 €/g) by addition of methyl Grignard reagent (90 % yield) to the ester group and subsequent a Suzuki–Miyaura cross-coupling reaction with 2-aminophenylboronic acid **7e** (42 % yield). However, independent of the solvent employed, the cyclization step did not occur. We only observed the decomposition of **11**, which might suggest that the structure is too strained to allow the cyclization. Thus, we changed our approach by performing the aza-Piancatelli cyclization first, which was followed by a Suzuki–Miyaura cross-coupling. First, we studied the cyclization with a model substrate **6f** and aniline **7b** as a nucleophile. We noticed that the solvent was critical for this transformation because the dehydration of the alcohol occurred easily in HFIP or nitromethane to generate 2-isoprenylfuran, which is prone to oligomerize



Scheme 5. Total synthesis of bruceolline D.

under the reaction conditions. On the other hand, conducting the reaction in a solventless prone to H-bonding such as toluene provided the targeted 4-aminocyclopentenone **8fb** in 66 % yield.[24] Next, we examined the reactivity of 2-furylcarbinol **10** with both 2-aminophenylboronic acid **7e** and 2-aminophenylboronic acid pinacol ester **7f** in toluene. The reaction with the latter formed the cyclization product in higher yield (67 % vs. 40 %). Finally, a Suzuki–Miyaura cross-coupling reaction[25] led to bruceolline D in 48 % yield (3 steps, overall yield 29 %), demonstrating the synthetic utility of the aza-Piancatelli cyclization.

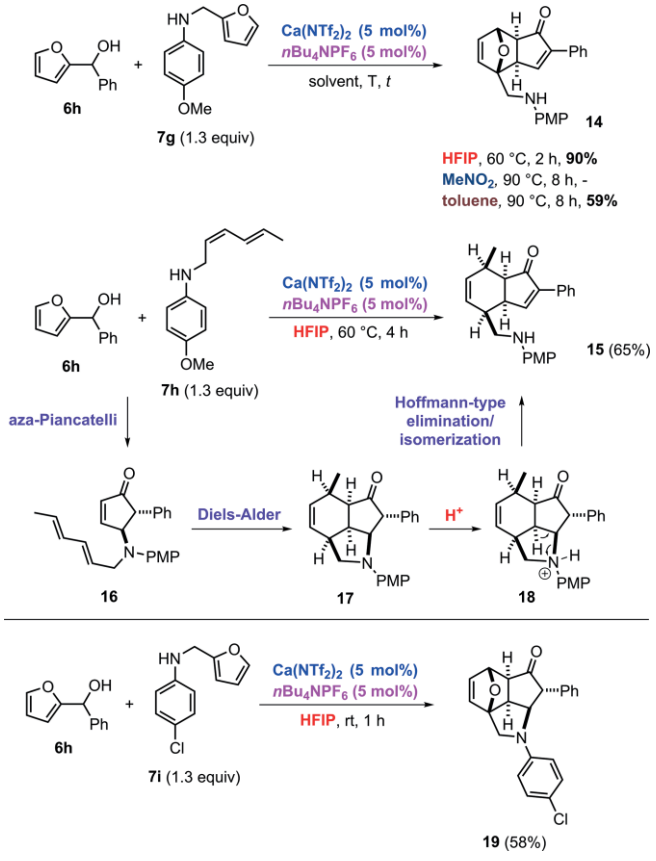
Similarly, we sought to exploit the same strategy to access the framework of yuehchukene (Scheme 6). While the cyclization reaction worked smoothly, without even requiring the utilization of $Ca(NTf_2)_2$ due to the intrinsic acidity of HFIP, our attempt to achieve the Suzuki–Miyaura cross-coupling reaction using the above reaction conditions failed. At this stage, we do not have a specific explanation for this result. Although further optimization studies would be necessary to accomplish this sequence, the approach enabled the construction of the cyclopentane ring of yuehchukene.



Scheme 6. Attempt towards yuehchukene.

Finally, we evaluated the possibility of taking advantage of the alkene moiety of the 4-aminocyclopentenone to implement a Diels-Alder reaction and, thus, build the 5–6–5 aza-tricyclic core of gracilamine in a single step. To fulfil this goal, we prepared an aniline derivative incorporating a furan moiety (**7g**), which is a well-established diene system for Diels-Alder processes. To our surprise, in contrast with precedent reports,[13i,13k] we did not obtain the classic Diels-Alder adduct, forming instead tetrahydro-1*H*-indene **14** in 90 % yield in HFIP (Scheme 7). This reactivity was also extended to 1,3-dienes to furnish the corresponding skeleton **15** in good yield (65 %) under identical reaction conditions. To account for the formation of such products, we hypothesized that, following the aza-Piancatelli cyclization and the Diels-Alder reaction, the amine might be protonated under the highly acidic reaction conditions and a subsequent Hofmann-type elimination would take place. Following an isomerization, compound **15** would be obtained. This type of reactivity is dependent on the aniline used as the presence of a moderate electron-withdrawing group (Cl) in *para*-position led only to the formation of the Diels-Alder product **19** in 58 % yield.[26]

In conclusion, we have demonstrated that the aza-Piancatelli cyclization could be used successfully to access densely decorated molecules that closely resemble natural molecules. It was notably showcased by the concise total synthesis of bruceolline D, which was achieved in 3 steps with 29 % overall yield. More importantly, we gained a better insight into the group



Scheme 7. Aza-Piancatelli/Diels-Alder/fragmentation reaction sequence. PMP = *para*-methoxyphenyl.

functional tolerance of this transformation and the influence of solvent on it, which should pave the way for its increasing utilization in total synthesis.

Acknowledgments

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Keywords: Aza-Piancatelli reaction · Electrocyclization · Lewis acids · Natural products · Synthetic methods

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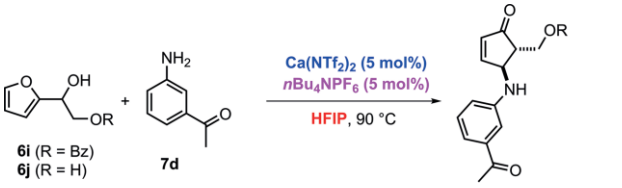
[22] Of note, regarding the synthesis of analogues of pactamycin, functionalities other than benzyl were also tested in model substrates but did not lead to the corresponding 4-aminocyclopentenones:



6i (R = Bz)
6j (R = H)
7d
8id (no reaction)
8jd (mixture of products)

[23] In reference 13g, we already demonstrated the compatibility of azide functional group in the aza-Piancatelli, but only in the case of highly reactive *para*-iodoaniline. Herein, we wanted to test its compatibility with less reactive *para*-anisidine.

[24] We also envisaged another strategy involving a Heck cross-coupling reaction; however, we did not pursue this idea as the cyclization between precursor **6f** and 2-iodoaniline did not give satisfactory yields (< 30 %).

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