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Modular Synthesis of 9,10-Dihydroacridines through an *ortho*-C Alkenylation/Hydroarylation Sequence between Anilines and Aryl Alkynes in Hexafluoroisopropanol

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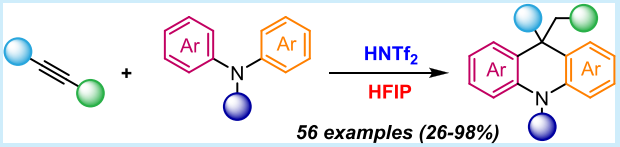
ABSTRACT: 9,10-Dihydroacridines are frequently encountered as key scaffolds in OLEDs. However, accessing those compounds from feedstock precursors typically requires multiple steps. Herein, a modular one-pot synthesis of 9,10-dihydroacridine frameworks is achieved through a reaction sequence featuring a selective *ortho*-C alkenylation of diarylamines with aryl alkynes followed by an intramolecular hydroarylation of the olefin formed as an intermediate. This transformation was accomplished by virtue of the combination of hexafluoroisopropanol and triflimide as a catalyst that triggers the whole process.



In the past decade, 9,10-dihydroacridines have emerged as privileged structural motifs in chemistry owing to their remarkable electronic properties. They are now extensively used in the field of materials science as electron-donor units, notably for organic light-emitting diode (OLED) devices. Hence, they have been employed as an integral part of fluorescent emitters, thermally activated delayed fluorescence (TADF) materials, or hole-transport materials.[1] Moreover, they have recently proven particularly effective in other areas such as photocatalysis,[2] detection of explosives,[3] and medicinal chemistry.[4] However, despite the wealth of reports regarding their utilization, the development of efficient and versatile synthetic methods to access those building blocks from readily available precursors remain strikingly sparse,[5] representing a serious impediment to broadening their range of applications. Currently, their preparation usually requires multistep synthesis from anilines, which are furthermore not always commercially available (Scheme 1a).[1j] On this basis, most of the applications reported tend to be limited to simple 9,10-dimethyl and -diphenylacridines. As an alternative, the group of Stephan described, in 2017, an elegant approach to access 9,10-dihydroacridines following a one-pot sequence featuring an *ortho*-C alkenylation of an aniline with an aryl alkyne and a subsequent hydroarylation of the styrene intermediate in the presence of a phosphonium dication catalyst (Scheme 1b).[5c] The selective *ortho*-C alkenylation of the aniline with the alkyne is the key part of the process;[6,7] however, the applicability of this type of reactivity is still underdeveloped when compared to the *ortho*-C alkylation of anilines with olefins.[8] It might be explained by the formation of an sp hybridized carbenium center, which is a sluggish electrophile compared to its sp^2 carbenium counterpart generated from alkenes.[9] As a result, the scope exhibited by this reaction sequence proved to be limited. In this context, we questioned whether we could address the limitations of this transformation by employing hexafluoroisopropanol (HFIP) as a solvent.[10] In the past years, HFIP has become a prominent solvent in organic synthesis due to its combination of atypical properties, including strong H-bond donating ability, low nucleophilicity, redox stability, and mild acidity.[11] It allowed us to achieve reactions that were unlikely to take place in traditional organic solvents,[8k,10d,12] emphasizing that, when HFIP was associated with a Lewis acid or a Brønsted acid, the acidity of the corresponding combination could be considerably boosted to even activate unreactive substrates such as highly deactivated styrenes. Recently, we applied this principle to the *ortho*-C alkylation of anilines with alkenes,[8k] which relies on a concerted-like mechanism that is fostered by the presence of HFIP and prevents common regioselectivity issues associated with this type of process (Scheme 1c). While rather efficient and general, this transformation is still fraught with a few limitations in terms of reactivity. For instance, electron-rich styrenes or triarylamines preferentially led to *para*-adducts due to a facile protonation of the olefin moiety under the reaction conditions. Following this work, we assumed that this strategy could be transposed to aryl alkynes to afford the target 9,10-dihydroacridines. We hypothesized that, since the protonated alkynes (vinyl carbocations) are less reactive than protonated

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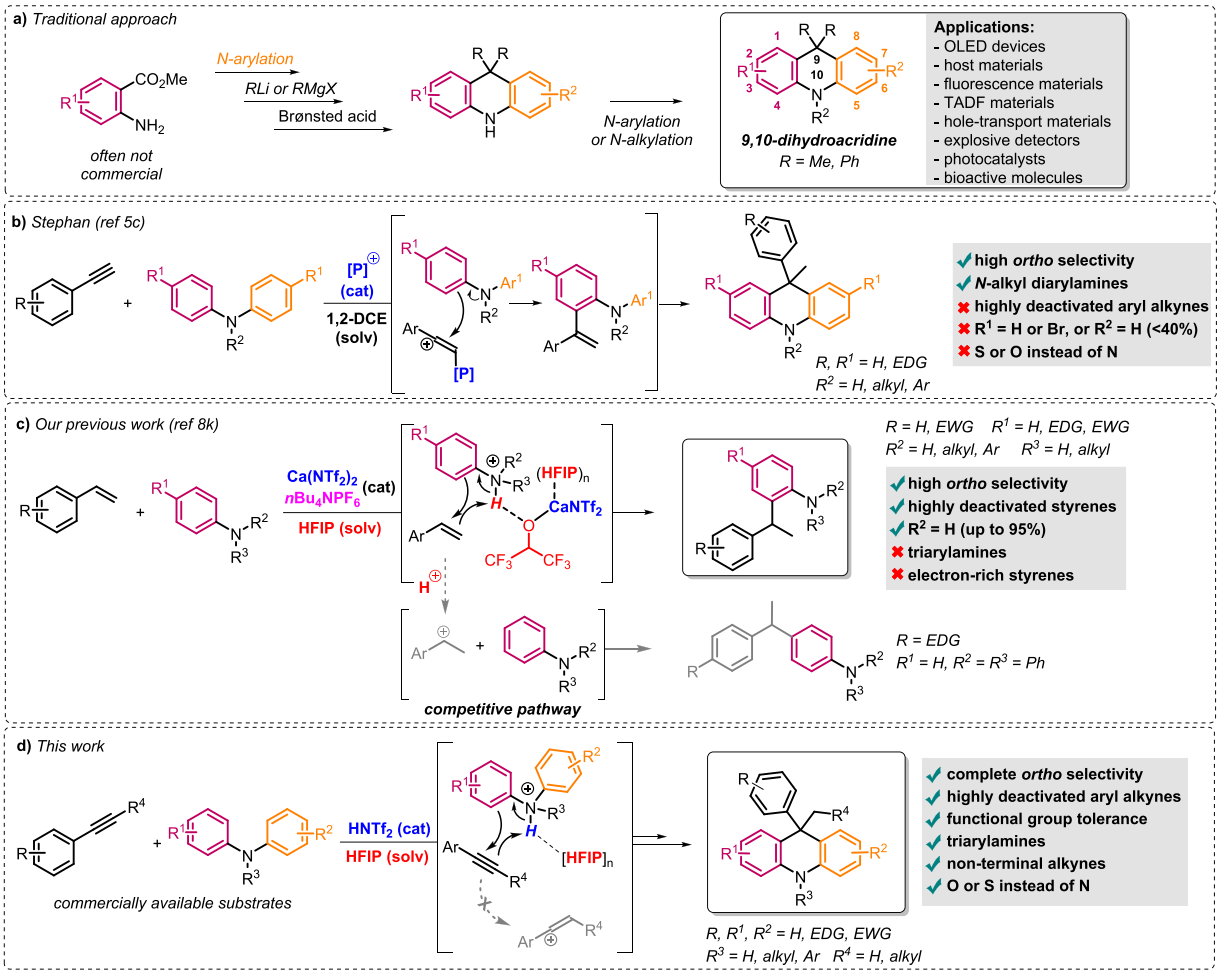
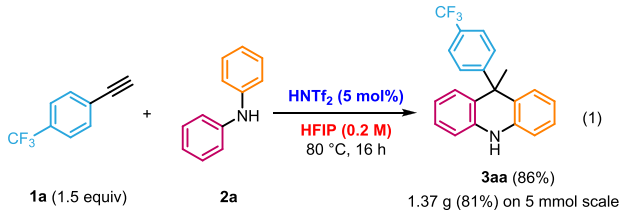
Scheme 1. Strategies to Access 9,10-Dihydroacridines[a]



[a][P]$^+$ = [(PhO)P(2(*N*-Mepy))Ph$_2$]$^{2+}$.

alkenes, a concerted mechanism pathway would be predominant, bypassing the above-mentioned limitations. This strategy would thus enable a straightforward and modular synthesis of 9,10-dihydroacridines so that the properties of the corresponding organic materials could be easily tuned, enabling new applications for this class of compounds. Herein, we disclose our findings regarding this reaction sequence to produce an array of structurally varied 9,10-dihydroacridines in good to high yields and with an excellent functional group compatibility. Moreover, we show that the developed conditions also allow the preparation of xanthenes and thioxanthenes.

We started our investigations by examining the reaction between 1-ethynyl-4-(trifluoromethyl)benzene **1a** (highly deactivated aryl alkyne) and diphenylamine **2a** in HFIP (see the Supporting Information for more details). We established that using Brønsted acid HNTf$_2$[13] as catalyst proved to be optimal to deliver the target 9,10-dihydroacridine **3aa** in 86% yield after 16 h at 80 °C (eq 1).[14] A survey of the reaction optimization revealed that HFIP is crucial for the reaction outcome, as another fluorinated solvent such as trifluoroethanol (TFE) yielded the product **3aa** in a low yield (5%); only traces of **3aa** were observed in common solvents such as 1,2-DCE, toluene, and nitromethane. Gratifyingly, the reaction worked smoothly on a larger scale (5 mmol), furnishing **3aa** in 81% yield (1.37 g). An issue regularly mentioned with the utilization of HFIP is its cost, but it is important to stress that,



because of its low boiling point, it can be easily recovered by distillation,[15] counterbalancing this issue.

We next examined the scope of this transformation (Scheme 2), first evaluating a variety of terminal aryl alkynes (**1aa**−**1ua**) in reactions with diphenylamine **2a**. In this respect, the tested aryl alkynes bearing moderate and strong electron-donating and -withdrawing groups at the *para*-position were all tolerated and provided the corresponding 9,10-dihydroacridines **3aa**−**3ka** in high yields, ranging from 73 to 98%. Of note, in the case of strong electron-withdrawing groups such as nitrile and nitro (**1c** and **1d**), the reaction had to be conducted at 120 °C to reach complete conversion of the alkyne starting materials. In the case of strong electron-donating groups such as methoxy and amine (**1j** and **1k**), the reaction proceeded faster than the previous examples (6 vs 16 h), providing the target products **3ja** and **3ka** in 86 and 79% yield, respectively. The use of highly electron-poor alkynes such as the 3,5-*bis*(trifluoro-

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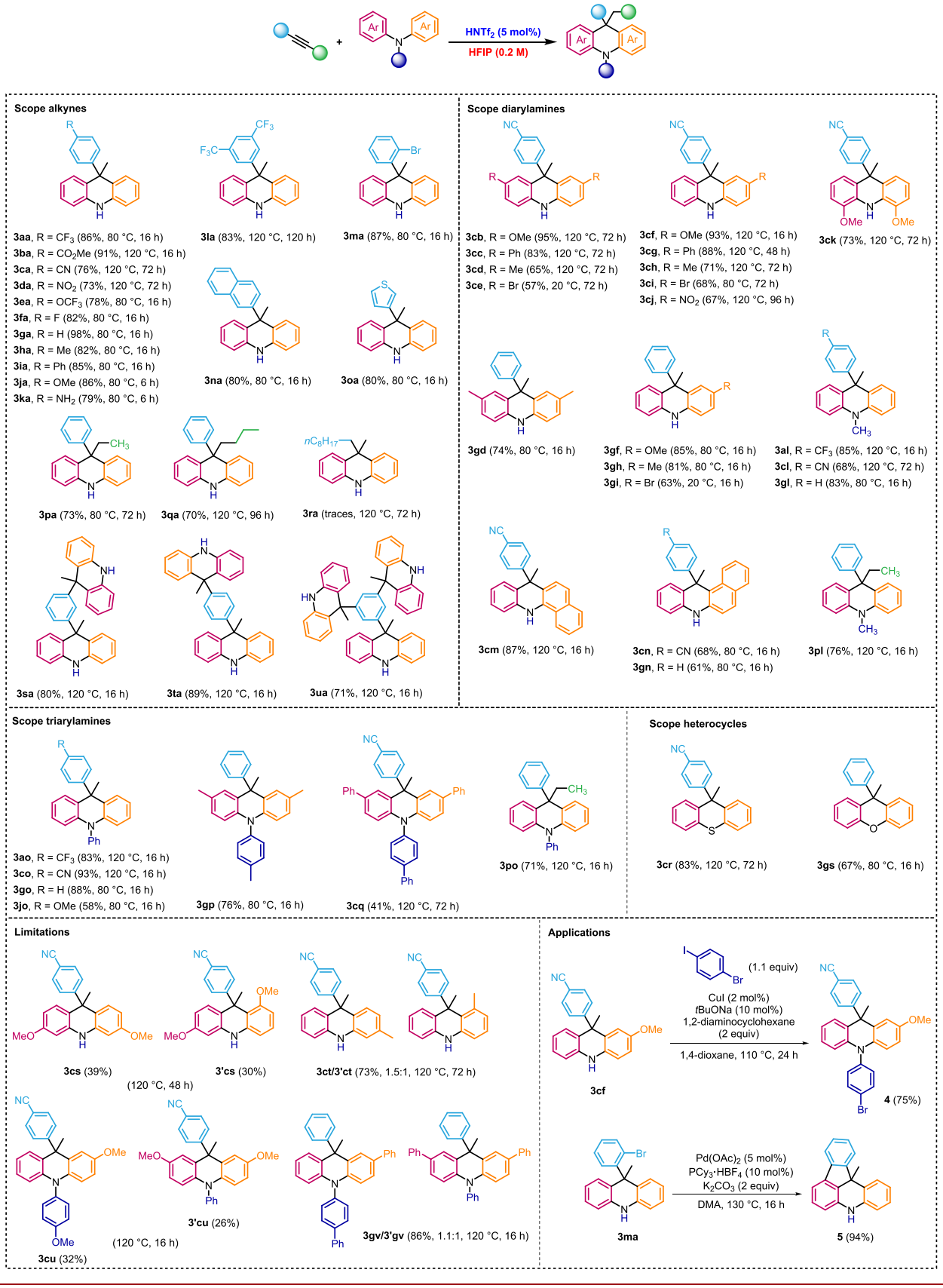
Scheme 2. Scope of 9,10-Dihydroacridines and Other Heterocycles



methyl)phenyl derivative required an increase in the catalyst loading to 10 mol % to afford 9,10-dihydroacridine **3la** in 83% yield. The presence of an *ortho*-substituent was also well tolerated (**3ma**, 87%). The reaction sequence was not limited to a phenyl group but could also be extended to a naphthyl or thienyl group, delivering both **3na** and **3oa** in 80% yield. More

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importantly, the transformation occurred also for internal alkynes incorporating alkyl substituents (e.g., adducts **3pa** and **3qa** were generated in 73 and 70% yield), albeit at a slower rate than the reactions involving terminal alkynes. Gratifyingly, dialkynes **1s**−**1t** and trialkyne **1u** were readily accommodated in the reactions to provide multiple-9,10-dihydroacridine-bearing compounds in high yields (71−89%). On the other hand, bis-alkyl alkynes proved to not be competent precursors for the reaction, essentially leading to decomposition of the substrate with only traces of the target product **3ra** detected.

We then explored the scope with respect to the diarylamine component (**2b**−**2n**), using representative aryl alkynes **1c** (R = CN) and **1g** (R = H) as benchmark precursors. In the case of 2,7-substituted 9,10-dihydroacridines (**3cb**−**3cj**, **3gd**, **3gf**, and **3gi**), the reaction demonstrated a broad functional group compatibility from both symmetrical and dissymmetrical diarylamines to provide the products in medium to high yields (57−95%). Both electron-donating and -withdrawing substituents were amenable to the reaction; notably, bromide substituents were easily introduced to generate products **3ce**, **3ci**, and **3gi** (57−68%), which constitute useful platforms for further derivatizations. In addition, 4,5-substituted 9,10-dihydroacridines such as **3ck** could be generated in 73% yield. *N*-Alkyl diarylamines such as **1l** also underwent the reaction process in high yields (up to 85%), employing both terminal and internal alkynes (**3al**, **3cl**, **3gl**, and **3pl**). By incorporating a naphthyl moiety, we could prepare complex polycyclic structures (**3 cm**, **3cn**, and **3gn**) in yields ranging from 61 to 87%.

Triarylamines, notably triphenylamine **2o**, displayed a satisfying reactivity with respect to this process to form the products in medium to high yields (41−93%), regardless of the electronic demand of the aryl alkyne and its nature (terminal or internal). Another key feature of this method is that the reaction of diphenyl sulfide **2r** in place of **2a** yielded the corresponding thioxanthene **3cr** in 83% yield. In the same vein, the reaction with diphenyl ether **2s** underwent the diarylation to give xanthene **3gs** in 67% yield. However, it should be stressed that diphenyl ether is less reactive than diarylamines and diphenyl sulfide, as it was ineffective with highly deactivated aryl alkyne such as **1c** (10% yield after 1 week at 120 °C). Regarding the limitations of this approach, we noticed that the use of *meta*-substituted diarylamines (**2s** and **2t**) and triarylamines with nonidentical aryl groups led to the formation of a mixture of 2 regioisomers that could not be separated in some cases by flash column chromatography.

To further illustrate the synthetic utility of this method, we carried out a few postfunctionalizations. As stated above, the reaction sequence with dissymmetrical diarylamines occurred with ease to return the corresponding products in high yields. Those results could be used to our advantage to generate densely functionalized 9,10-dihydroacridines such as **4** incorporating four different aryl units, following a Ullmann C−N cross-coupling.[16] It also represents a simple way to circumvent the reactivity issue mentioned with triarylamines. Additionally, we executed a Pd(II)-catalyzed C−H activation to convert **3ma** into pentacyclic compound **5** in 94% yield.[17,18]

In summary, we have developed an efficient protocol for the assembly of 9,10-dihydroacridines and related heterocycles from inexpensive precursors through the cooperation of HFIP and a Brønsted acid catalyst. The wide array of substrates tolerated validates the utility of this transformation as a means to provide a rapid access to molecules that could find applications in the field of materials science and photocatalysis. In addition, the viability at scale of this method was also demonstrated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00487.

Experimental procedures, characterization data, and NMR spectra of all new compounds (PDF)

FAIR data, including the primary NMR FID files, for compounds **3aa**−**3′gv**, **4**, and **5** (ZIP)

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Notes

The authors declare no competing financial interest.

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