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A Modular Synthesis of Functionalized Pyridines through Lewis-Acid-Mediated and Microwave-Assisted Cycloadditions between Azapyrylium Intermediates and Alkynes

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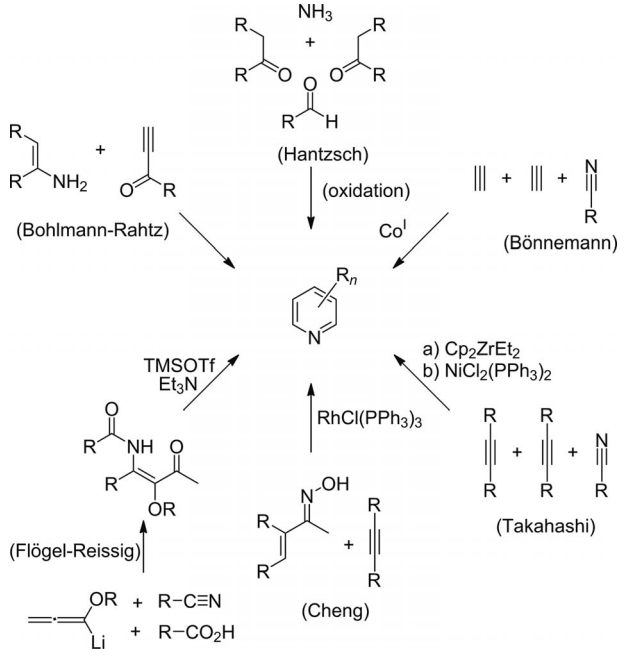
In this report we describe the synthesis of differentially functionalized pyridine derivatives **3** and the related 3-bromo-substituted pyridines **11**. Dissociation of 6*H*-1,2-oxazine precursors (**1a**, **1b**, **5**, **6**, or **12**) in situ, mediated by boron trifluoride–diethyl ether, generates the azapyrylium intermediates **A**, which undergo hetero-Diels–Alder reactions with various mono- and disubstituted alkynes **2**. In general, these pyridine syntheses proceeded with high efficiencies and were very flexible with respect to all positions in the pyridine cores. For the 3-phenyl-substituted pyridine derivatives **3a**–**3j** and **11a**–**11f** the best results were obtained by a new microwave-assisted protocol, which is clearly superior to the previously used conventional procedure at low temperature in dichloromethane. Furthermore, 3-(trifluoromethyl)- and 3-acryloyl-substituted 6*H*-1,2-oxazines reacted cleanly under microwave irradiation conditions to furnish the expected pyridine derivatives **3k** and **3l** in respectable yields. The 3-bromo-substituted pyridines **11** were further functionalized through palladium-catalyzed couplings such as Suzuki or Sonogashira reactions, which led smoothly to tri- or tetrasubstituted pyridine derivatives such as **19**–**21** and **23**. Reductive debromination of **11e** afforded the pyridine **17** in excellent yield, whereas oxidation of the pyridinyl thioether **3g** with oxone led to the corresponding sulfoxide **24**. Our method thus establishes a new and versatile approach to highly substituted pyridine derivatives.

Introduction

Pyridines constitute a very important class of monocyclic nitrogen-containing heterocycles, and thanks to their wide spectrum of applications they unquestionably represent one of the most studied heterocyclic systems.[1] As a consequence of this importance, a large number of strategies for the synthesis of polyfunctionalized specifically substituted pyridine derivatives have been developed. The spectrum of efficient and flexible pyridine syntheses includes simple condensation reactions, such as the classical Hantzsch reaction, various cycloadditions, and numerous transition-metal-promoted processes, as well as novel and powerful multicomponent reactions, as illustrated in Scheme 1.[2] Because of the important role of this heterocyclic skeleton as a component in biologically active compounds,[3] natural products,[4] or functional materials (e.g., as building blocks in supramolecular chemistry[5] or as ligands in transition-metal catalysis[6]) the design of new strategies for the efficient synthesis of pyridine derivatives continues to be of great interest in organic chemistry. New methods allowing the preparation of diversely functionalized pyridine derivatives are still highly desirable.



Scheme 1. Selected strategies for the synthesis of highly substituted pyridine derivatives.

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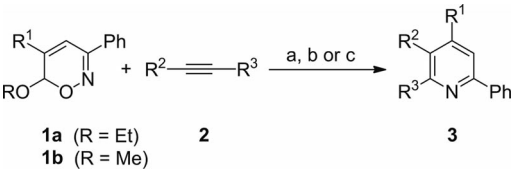
In this account we describe in full detail our efforts relating to the synthesis of pyridine derivatives through cycloadditions between 1,2-azapyrylium intermediates (generated in situ) and mono- or disubstituted alkynes. We have previously reported some preliminary examples[7] and now wish to disclose more results to demonstrate the scope and limitations of this approach to pyridine synthesis.

Results and Discussion

In a previous communication we reported on the formation of pyridine derivatives from easily available 6*H*-1,2-oxazines[8] of type **1** (Scheme 2). Treatment of compounds **1** with boron trifluoride–diethyl ether at –78 °C in the presence of the alkynes **2** in excess furnished the products **3** in low to moderate yields.[7] We therefore became interested in finding improved reaction conditions that would enhance the applicability of this flexible and new approach to pyridine synthesis. In particular, we wanted to test alternative synthetic techniques such as microwave-assisted reactions. When the reaction between the 6*H*-1,2-oxazine **1a** and phenylacetylene (**2a**) was performed in the presence of boron trifluoride–diethyl ether in 1,2-dichloroethane at 70 °C under microwave irradiation conditions (Method B) the expected 2-phenyl-substituted pyridine derivative **3a**[9] was formed in excellent yield (Table 1, Entry 2), a result that compares very well with the previously employed conditions (Method A), which provided **3a** in only 67% yield (Entry 1). In order to examine the scope of the new microwave-assisted conditions[10] we then studied a range of mono- and disubstituted alkynes **2** together with the 6*H*-1,2-oxazines **1a** and **1b**. As shown in Table 1, the reactions proceeded smoothly to give the corresponding 2-phenyl-substituted pyridine derivatives **3b** and **3c** in yields better than those obtained by Method A as applied earlier (Entries 4–7). Substituents and functional groups such as cyclopropyl, imidazolyl, or phenylthio groups are tolerated well under the conditions of Method B (Entries 8–11, 13). Not surprisingly, the use of 1-(*p*-methoxybenzyl)-3-phenylprop-2-yne (**2e**) led to the deprotected 3-hydroxymethyl-substituted pyridine **3h** in 63% yield as product (Entry 12). Most remarkably, a cyclic alkyne was also successfully converted into the corresponding bicyclic pyridine derivative **3j** (Entry 14).



Scheme 2. Synthesis of the 2-phenyl-substituted pyridine derivatives **3**. (a) Method A: BF_3·OEt_2, CH_2Cl_2, –78 °C to room temp., 18 h; b) Method B: BF_3·OEt_2, DCE, 70 °C, microwave irradiation, 1 h; c) Method C: BF_3·OEt_2, DCE, 70 °C, overnight. DCE = 1,2-dichloroethane.

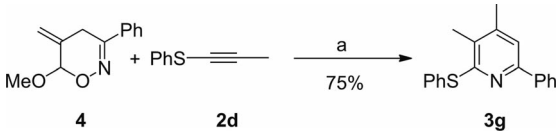
Table 1. Synthesis of the 2-phenyl-substituted pyridine derivatives **3**.[a]

Entry	**1**	R^1	**2**	R^2	R^3	Method	**3**	Yield
1	**1a**	H	**2a**	H	Ph	A	**3a**	67%[b]
2	**1a**	H	**2a**	H	Ph	B	**3a**	96%
3	**1a**	H	**2a**	H	Ph	C	**3a**	64%
4	**1b**	Me	**2a**	H	Ph	A	**3b**	39%[b]
5	**1b**	Me	**2a**	H	Ph	B	**3b**	68%
6	**1a**	H	**2b**	Ph	Ph	A	**3c**	48%[b]
7	**1a**	H	**2b**	Ph	Ph	B	**3c**	62%
8	**1b**	Me	**2b**	Ph	Ph	B	**3d**	53%
9	**1b**	Me	**2c**	H	cyclopropyl	B	**3e**	51%
10	**1a**	H	**2d**	Me	PhS	B	**3f**	48%
11	**1b**	Me	**2d**	Me	PhS	B	**3g**	84%
12	**1a**	H	**2e**	$PMBOCH_2$[c]	Ph	B	**3h**	63%[d]
13	**1a**	H	**2f**	H	imidazolyl[e]	B	**3i**	54%
14	**1a**	H	**2g**	$(CH_2)_{11}$		B	**3j**	49%

[a] Reaction and conditions are shown in Scheme 2. [b] Taken from ref.[7] [c] PMB = *p*-methoxybenzyl. [d] R^2 = CH_2OH. [e] 2-Methyl-1,5-diphenylimidazol-4-yl.[12]

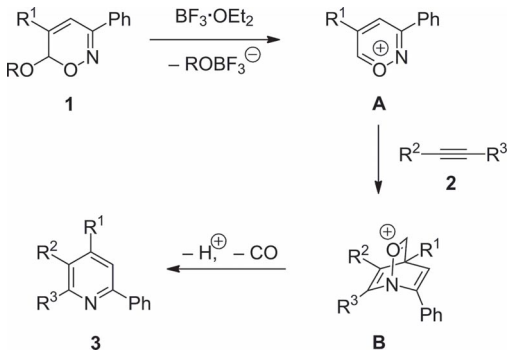
We were surprised that the 1,2-azapyrylium intermediates **A**[11] are sufficiently stable to survive the fairly high temperatures and to act as heterodiene components under the harsh microwave conditions employed (see mechanistic interpretation in Scheme 4). We even have to assume that the formation and reaction of **A** essentially start at room temperature and were possibly not complete under our previously applied conventional conditions (Method A). The microwave conditions apparently help to enhance the conversion of the 1,2-oxazines **1** and strongly improve the overall efficacy of the pyridine synthesis. A control experiment carried out with **1a** and **2a** gave a significantly lower yield (64%) of the expected pyridine derivative **3a**, indicating that conventional heating in 1,2-dichloroethane at 70 °C overnight (Method C) is less efficient (cf. Entries 2 and 3).

In general, 6*H*-1,2-oxazines such as **1b** are accessible by base- or acid-promoted isomerization of the precursor 5-methylene-4*H*-1,2-oxazine **4** (Scheme 3),[8] which is obtained as the primary cycloadduct from the hetero-Diels–Alder reaction between methoxyallene and α-nitrosostyrene (produced in situ).[13] We also investigated the preparation of a pyridine derivative directly with compound **4** as precursor. This transformation was examined with **4** and 1-(phenylthio)prop-1-yne (**2d**) under the microwave-assisted reaction conditions (Method B). Gratifyingly, the expected pyridine derivative **3g** was formed in a yield comparable with that of the procedure mentioned above in Table 1 (Scheme 3), making the overall route to **3g** more straightforward.



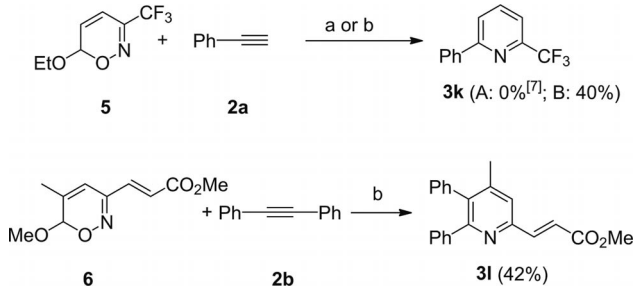
Scheme 3. Preparation of the pyridine derivative **3g** from the 5-methylene-substituted 4*H*-1,2-oxazine **4**. (a) Method B: BF_3·OEt_2, DCE, 70 °C, microwave irradiation, 1 h.

A plausible mechanism for the formation of the pyridine derivatives **3** from **1** is illustrated in Scheme 4. Firstly, the 6-alkoxy-6*H*-1,2-oxazines **1** could undergo dissociation with assistance from Lewis acids such as $BF_3{\cdot}OEt_2$ or $TiCl_4$,[14] leading to the corresponding 1,2-azapyrylium ions **A**. These intermediates would be able to act as heterodiene components in ionic [4+2] cycloadditions, and subsequent reactions with the alkynes **2** could provide the bridged bicyclic intermediates **B**. These could furnish the pyridines **3** through retro-Diels–Alder reactions, together with the formyl cation, which would dissociate into carbon monoxide and a proton. The gain in aromaticity is certainly the major driving force for this process. Despite the multistep characters of the transformations and the assumed sensitivities of the intermediates **A** and **B** the overall efficacies of pyridine formation are remarkable, with yields in the 48–96% range (Table 1).



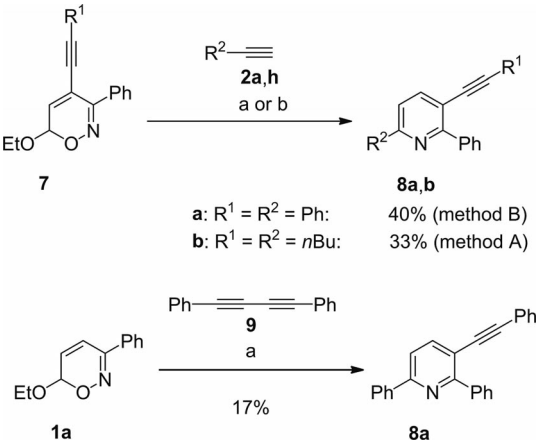
Scheme 4. Proposed mechanism for the formation of pyridine derivatives.

We next examined various 6*H*-1,2-oxazines bearing 3-substituents other than phenyl (e.g., electron-withdrawing groups such as trifluoromethyl[15] or $MeO_2CCH{=}CH$[16]). It had previously been observed that the synthesis of pyridines from the 3-(trifluoromethyl)-substituted 6*H*-1,2-oxazine **5** failed with Method A.[7] Gratifyingly, reactions between **5** and **2a** or between **6** and **2b** under microwave conditions (Method B) afforded the corresponding pyridine derivatives **3k** and **3l** in at least moderate yields (Scheme 5).



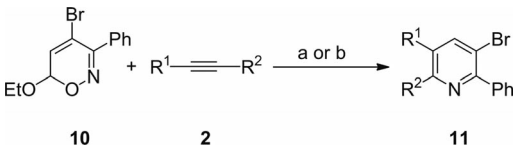
Scheme 5. Preparation of the 2-substituted pyridine derivatives **3k**,**l**. (a) Method A: $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C to room temp., 18 h; (b) Method B: $BF_3{\cdot}OEt_2$, DCE, 70 °C, microwave irradiation, 1 h.

For the preparation of 3-alkynyl-substituted pyridine derivatives we applied Methods A and B to reactions between the 4-alkynyl-substituted 6*H*-1,2-oxazines **7a** or **7b**[17] and phenylacetylene (**2a**) or hex-1-yne (**2h**). The desired 3-alkynyl-substituted pyridine derivatives **8a** and **8b** were isolated in moderate yields (Scheme 6). These results should be compared with the reaction between **1a** and 1,4-diphenylbuta-1,3-diyne (**9**) as dienophile component, which afforded a complex mixture of products from which the pyridine **8a** could be isolated only in disappointingly poor yield.



Scheme 6. Preparation of the 3-alkynyl-substituted pyridine derivatives **8a**,**b**. (a) Method B: $BF_3{\cdot}OEt_2$, DCE, 70 °C, microwave irradiation, 1 h; (b) Method A: $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C to room temp., 18 h.

The results described above show that alkyne units either in the 1,2-oxazine or in the dienophile are not well tolerated under standard conditions. We hence became interested in developing an alternative approach with incorporation of the Lewis-acid-sensitive functionalities at a later stage. The easily accessible 4-bromo-substituted 6*H*-1,2-oxazine **10**[17] (Scheme 7) was subjected to both methods described above. As shown in Table 2, the resulting 3-bromo-substituted pyridines **11** were obtained in good yields. Again it was observed that Method B is superior to Method A (cf. Entries 1/2 and 3/4). Nevertheless, the yields of the 3-bromopyridine derivatives **11** are generally lower than those for the corresponding products **3** without bromo substituents (cf. **3a** in Table 1, Entry 2 and **11a** in Table 2, Entry 2). With the 4,5-dibromo-6*H*-1,2-oxazine **12**[17] (Scheme 8) and phenylacetylene (**2a**) the expected 3,4-dibromopyridine derivative **13** was isolated only in very poor yield (12%), with recovery of 63% of the starting material **12**. These results indicate that the electron-withdrawing bromo substituents



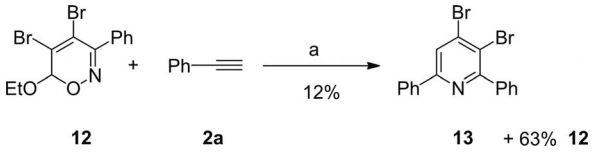
Scheme 7. Preparation of the 3-bromo-2-phenylpyridine derivatives **11**. (a) Method A: $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C to room temp., 18 h; (b) Method B: $BF_3{\cdot}OEt_2$, DCE, 70 °C, microwave irradiation, 1 h.

strongly hamper the formation of the azapyrylium species **A**, hence making the Diels–Alder step less likely and leading to low levels of conversion.

Table 2. Synthesis of the 3-bromo-2-phenylpyridine derivatives **11**.[a]

Entry	2	R^1	R^2	Method	11	Yield
1	**2a**	H	Ph	A	**11a**	22%
2	**2a**	H	Ph	B	**11a**	76%
3	**2h**	H	*n*Bu	A	**11b**	19%
4	**2h**	H	*n*Bu	B	**11b**	51%
5	**2d**	Me	PhS	B	**11c**	68%
6	**2i**	Ph	$MeOCH_2$	B	**11d**	50%
7	**2j**	Ph	$BnOCH_2$	B	**11e**	37%
8	**2k**	4-$MeOC_6H_4$	$MeOCH_2$	B	**11f**	63%

[a] Reaction and conditions are shown in Scheme 7.

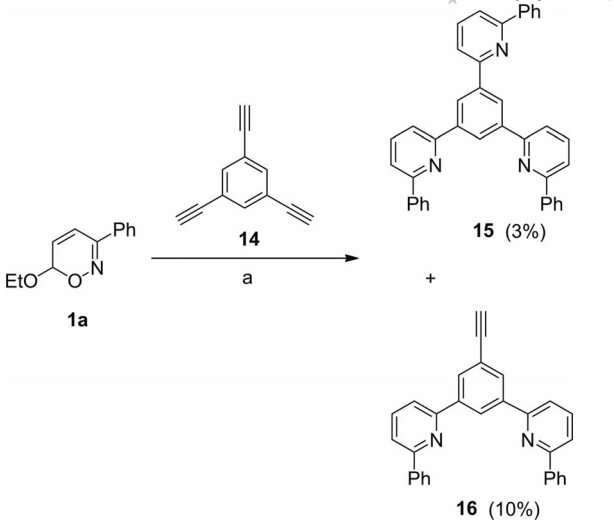


Scheme 8. Preparation of the 3,4-dibromo-2-phenylpyridine derivative **13**. (a) Method B: $BF_3{\cdot}OEt_2$, DCE, 70 °C, microwave irradiation, 1 h.

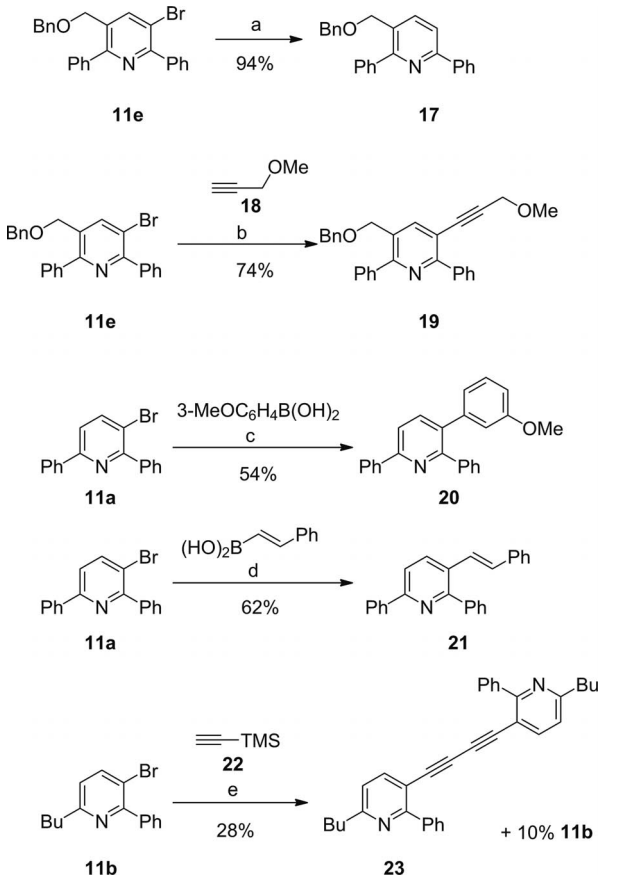
The successful preparation of pyridines as shown in Schemes 2, 3, 5, 6, 7, and 8 caused us to extend the series of functionalized heterocycles by employment of compounds bearing more than one alkyne unit. We therefore chose 1,3,5-triethynylbenzene (**14**, Scheme 9) as a suitable alkyne component. Application of Method B to treatment of **14** with the 1,2-oxazine **1a** (excess, 5 equiv.) afforded a very low yield of the expected symmetrical star-shaped product **15** together with the disubstituted product **16** as the major component. No attempts to optimize this reaction have been undertaken so far. Nevertheless, the obtained alkynyl-substituted compound **16** could be an interesting building block in an ongoing research project directed towards the formation of self-assembled monolayers.[18] The alkyne **16** was used as component in a Sonogashira coupling with 4′-nonaflyl-substituted terpyridine and provided the expected unsymmetrical molecule, for study by scanning tunneling microscopy (STM).[19]

The synthetic usefulness of the obtained 3-bromo-substituted pyridine derivatives **11** depends on their ability to undergo subsequent reactions. These compounds did indeed serve as suitable components for palladium-catalyzed reactions (Scheme 10).

Firstly, the pyridine derivative **11e** was treated with hydrogen in the presence of catalytic amounts of palladium on charcoal in methanol to provide an excellent yield of the debrominated product **17** in a chemoselective fashion, still bearing the untouched benzyl ether moiety. More interesting are palladium-catalyzed cross-couplings of these bromo-substituted pyridines. The Sonogashira reaction between the 3-bromopyridine **11e** and methyl propargyl ether (**18**) by a standard protocol afforded the alkynyl-substituted pyridine derivative **19** in good yield. The Suzuki couplings



Scheme 9. Synthesis of compounds **15** and **16**. (a) Method B: $BF_3{\cdot}OEt_2$, DCE, 70 °C, microwave irradiation, 1 h.

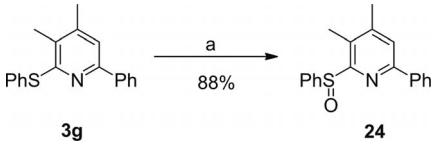


Scheme 10. Palladium-catalyzed reactions of the 3-bromopyridines **11a**, **11b** and **11e**. (a) H_2, Pd/C, MeOH, room temp., 90 min. (b) $PdCl_2(PPh_3)_2$, CuI, Et_3N, 70 °C, 2 h. (c) $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 80 °C, 48 h. (d) $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 80 °C, 4 d. (e) $PdCl_2(PPh_3)_2$, CuI, iPr_2NH, 70 °C, 48 h.

of the heterocycle **11a** with (3-methoxyphenyl)boronic acid and with styrylboronic acid furnished the expected trisubstituted pyridine derivatives **20** and **21**, respectively, in ca.

60% yield. In contrast, when the 3-bromo-6-butylpyridine **11b** was treated with (trimethylsilyl)acetylene (**22**) by the standard Sonogashira protocol the product **23** was obtained in 28% yield. It appears that the initially formed coupling product underwent desilylation and oxidative Glaser-type coupling under the employed reaction conditions to form the dialkyne **23**.

An alternative option for functional group transformation is offered by the phenylthio groups in pyridine derivatives such as **3g**. This compound was smoothly oxidized under standard conditions in the presence of oxone as reagent to afford the corresponding sulfoxide **24** in excellent yield (Scheme 11).



Scheme 11. Oxidation of the pyridine derivative **3g** into the sulfoxide **24**. (a) Oxone (2 equiv.), acetone, H_2O, room temp., 2 h.

Conclusions

We have been able to demonstrate that Lewis-acid-mediated and microwave-assisted reactions between 6*H*-1,2-oxazines and appropriate mono- or disubstituted alkynes via azapyrylium intermediates allow synthetically useful and practical access to pyridine derivatives in a highly flexible manner. Of particular value is the fact that the easily accessible 3-bromo-substituted pyridines **11** can be further functionalized through palladium-catalyzed reactions. Even acid-sensitive groups such as alkynyl substituents can be successfully installed on the pyridine core, as demonstrated by the synthesis of product **19**. With the access to the (trifluoromethyl)- and acryloyl-substituted pyridines **3k** and **3l** we have successfully extended the collection of highly functionalized pyridines. It is known that pyridine derivatives of this type are potentially useful compounds as pharmaceuticals.[2s,3i,20]

Experimental Section

General Methods: Reactions were generally performed under argon in flame-dried flasks. Solvents and reagents were added by syringe. Solvents were dried by standard procedures. Reagents were purchased and used as received without further purification unless otherwise stated. Microwave-assisted reactions were carried out in a microwave oven ("micro Chemist", MLS GmbH). Unless stated otherwise, products were purified by flash chromatography on silica gel (230–400 mesh, Merck or Fluka) or by HPLC (Nucleosil 50–5). Yields refer to analytically pure samples. NMR spectra were recorded with Bruker (AC 250, AC 500) and JOEL (Eclipse 500 and ECX 400) instruments. Chemical shifts are reported relative to TMS (^{1}H: δ = 0.00 ppm) or $CDCl_3$ (^{1}H: δ = 7.26 ppm; ^{13}C: δ = 77.0 ppm). Integrals are in accordance with assignments; coupling constants are given in Hz. All ^{13}C NMR spectra are proton-decoupled. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), m_c (centered multiplet), dd (doublet of doublet), br. s (broad singlet). Due to overlapping signals not all signals of carbon atoms in the aromatic region could be assigned. For detailed peak assignments 2D spectra were measured (COSY, HMBC, and HMQC). IR spectra were measured with a Nicolet 5 SXC FT-IRD spectrometer or with a Nexus FT-IR spectrometer fitted with a Nicolet Smart DuraSample IR ATR. MS and HRMS analyses were performed with Finnigan MAT 711 (EI, 80 eV, 8 kV), MAT CH7A (EI, 80 eV, 3 kV), or CH5DF (FAB, 3 kV), Varian Ionspec QFT-7 (ESI-FT ICRMS), and Agilent 6210 (ESI-TOF) instruments. Elemental analyses were carried out with a Perkin–Elmer CHN Analyzer 2400 and a Vario EL Elemental Analyzer. Melting points were measured with a Reichert apparatus (Thermovar) and are uncorrected. The 1,2-oxazines **1a**,[8c] **1b**,[8b] **4**,[8b] **5**,[8c] **7a** and **7b**,[17] and **12**[17] and the alkynes **2i**, **2j**,[21] **2k**,[22] **2f**,[12] **2g**,[23] and **18**[24] were prepared according to literature procedures.

Typical Procedure for Pyridine Synthesis at Low Temperature (Method A): The 6*H*-1,2-oxazine **1** (1 equiv.) was dissolved in dry CH_2Cl_2 (20 mL mmol^{-1}) under argon, and the alkyne **2** (2–10 equiv.) was added at –78 °C. The mixture was then treated with $BF_3{\cdot}OEt_2$ (2 equiv.) and allowed to warm to room temperature overnight. After addition of H_2O (20 mL mmol^{-1}), the organic layer was extracted with CH_2Cl_2 (3 × 20 mL mmol^{-1}), and the combined extracts were dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by column chromatography.

Typical Procedure for Pyridine Synthesis under Microwave Conditions (Method B): The 6*H*-1,2-oxazine **1** (1 equiv.) was placed in a microwave tube under argon and dissolved in 1,2-dichloroethane. The alkyne **2** (1.5–8 equiv.) and $BF_3{\cdot}OEt_2$ (2 equiv.) were then added. The reaction mixture was irradiated in the microwave oven at 350 W and 70 °C for 1 h. After cooling to room temperature, the mixture was quenched with H_2O (7–10 mL mmol^{-1}) and extracted with CH_2Cl_2 (3 × 8–20 mL mmol^{-1}). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography.

2,6-Diphenylpyridine (3a): The 6*H*-1,2-oxazine **1a** (113 mg, 0.556 mmol), phenylacetylene (**2a**, 454 mg, 4.45 mmol), and $BF_3{\cdot}OEt_2$ (140 μL, 1.11 mmol) in 1,2-dichloroethane (5 mL) were used in the typical procedure (Method B). The crude product was purified by column chromatography (silica gel; toluene/hexane, 4:1) to give **3a** (121 mg, 96%) as colorless crystals, m.p. 80–81 °C (ref.[9] m.p. 81.5–82 °C). The NMR spectroscopic data are consistent with those reported.

Preparation of the Pyridine 3a by Heating without Microwave Conditions (Method C): The 6*H*-1,2-oxazine **1a** (203 mg, 1.00 mmol) was dissolved in 1,2-dichloroethane (8 mL) under argon. After addition of phenylacetylene (**2a**, 408 mg, 4.00 mmol) and $BF_3{\cdot}OEt_2$ (280 μL, 2.00 mmol), the reaction mixture was stirred at 70 °C overnight. After cooling to room temperature, the mixture was quenched with H_2O (8 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (toluene/hexane, 4:1) to give **3a** (148 mg, 64%).

3,4-Dimethyl-6-phenyl-2-(phenylthio)pyridine (3g): The 5-methylene-4*H*-1,2-oxazine **4** (113 mg, 0.556 mmol), 1-(phenythio)prop-1-yne (**2d**, 659 mg, 4.45 mmol), and $BF_3{\cdot}OEt_2$ (140 μL, 1.11 mmol) in 1,2-dichloroethane (5 mL) were used in the typical procedure (Method B). The crude product was purified by column chromatography (silica gel; toluene/hexane, 4:1) to give **3g** (121 mg, 75%) as a colorless solid, m.p. 104–106 °C. ^{1}H NMR ($CDCl_3$,

400 MHz): δ = 2.28, 2.31 (2 s, 3 H each, Me), 7.22–7.31, 7.33–7.42, 7.55–7.60, 7.67–7.73 (4 m, 4 H, 3 H, 2 H, 2 H, Py, Ph) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 14.6, 20.1 (2 q, Me), 118.3, 126.2, 127.9, 128.3, 128.4, 128.6, 131.9, 134.5, 138.6, 146.1, 153.1, 157.0 (6 d, s, d, 4 s, Py, Ph) ppm. IR (ATR): $\tilde{\nu}$ = 3080–3030 (=C–H), 2950–2870 (C–H) cm^{-1}. $C_{19}H_{17}NS$ (291.4): calcd. C 78.31, H 5.88, N 4.81, S 11.00; found C 78.47, H 6.00, N 4.80, S 11.28.

2-(2-Methyl-1,5-diphenyl-1*H*-imidazol-4-yl)-6-phenylpyridine (3i): The 6*H*-1,2-oxazine **1a** (104 mg, 0.500 mmol), $BF_3{\cdot}OEt_2$ (0.13 mL, 1.00 mmol), and the alkyne **2f** (129 mg, 0.515 mmol) in 1,2-dichloroethane (3 mL) were used in the typical procedure (Method B). The crude product was purified by chromatography on silica gel (hexane/EtOAc, 4:1 to 1:1) to give **3i** (104 mg, 54%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.38 (s, 3 H, Me), 7.09–7.40, 7.46–7.50 (2 m, 13 H, 2 H, Py, Ph), 7.54 (d, J = 8.1 Hz, 1 H, Py), 7.70 (dd, J = 7.4, 8.1 Hz, 1 H, Py), 7.84 (d, J = 7.4 Hz, 1 H, Py) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 14.1 (q, Me), 117.1, 119.3, 126.7, 127.2, 128.0, 128.1, 128.4, 129.2, 131.0, 131.6, 132.3, 136.5, 136.8, 136.9, 139.1 (9 d, 4 s, d, s, Py, Im, Ph), 145. 1 (s, Im), 153.4, 155.5 (2 s, C-2, C-6) ppm. IR (ATR): $\tilde{\nu}$ = 3060–2840 (=C–H, C–H), 1600 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{27}H_{21}N_3$ [M + H]$^+$ 388.1808, found 388.1849; calcd. for [M + Na]$^+$ 410.1628, found 410.1667.

3-Bromo-2,6-diphenylpyridine (11a): The 4-bromo-6*H*-1,2-oxazine **10** (614 mg, 2.18 mmol), phenylacetylene (**2a**, 2.23 g, 21.8 mmol), and $BF_3{\cdot}OEt_2$ (622 mg, 4.38 mmol) in CH_2Cl_2 (20 mL) were used in the typical procedure (Method A). The crude product was purified by column chromatography (alumina; hexane/EtOAc, 10:1 then 8:1) to give **11a** (151 mg, 22%) as a yellow oil.

The 4-bromo-6*H*-1,2-oxazine **10** (113 mg, 0.556 mmol), phenylacetylene (**2a**, 454 mg, 4.45 mmol), and $BF_3{\cdot}OEt_2$ (140 μL, 1.11 mmol) in 1,2-dichloroethane (5 mL) were also used in the typical procedure (Method B). The crude product was purified by column chromatography (silica gel; toluene/hexane, 4:1) to give **11a** as a yellow oil (131 mg, 76%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.39–7.49 (m, 6 H, Ph), 7.52 (d, J = 8.3 Hz, 1 H, 5-H), 7.76–7.81 (m, 2 H, Ph), 7.97 (d, J = 8.3 Hz, 1 H, 4-H), 8.00–8.05 (m, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 119.2 (s, Ar), 119.8 (d, C-5), 126.9, 127.9, 128.7, 129.6 (4 d, Ar, Ph), 138.2, 139.8 (2 s, Ph), 141.9 (d, C-4), 155.7, 157.4 (2 s, Ar) ppm. IR (neat): $\tilde{\nu}$ = 3105–2980 (=CH, C–H) cm^{-1}. MS (EI, 80 eV, 80 °C): m/z (%) = 311 (31) [M]$^+$, 230 (100) [M – Br]$^+$, 288 (17), 77 (35) [C_6H_5]$^+$. HRMS (EI, 80 eV): calcd. for $C_{17}H_{12}BrN$ 309.01532, found 309.01475.

3-Bromo-5-(methoxymethyl)-2,6-diphenylpyridine (11d): A mixture of the 6*H*-1,2-oxazine **10** (150 mg, 0.532 mmol), $BF_3{\cdot}OEt_2$ (156 mg, 1.06 mmol), and methyl 3-phenylpropargyl ether (**2i**, 117 mg, 0.800 mmol) in DCE (4 mL) was treated as described in the typical procedure (Method B). The mixture was allowed to cool to room temperature, diluted with water (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (hexane/EtOAc, 4:1) to give **11d** (93 mg, 50%) as a pale yellow solid, m.p. 83–86 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.41 (s, 3 H, OMe), 4.51 (s, 2 H, CH_2), 7.36–7.47, 7.56–7.61, 7.71–7.76 (3 m, 6 H, 2 H, 2 H, Ph), 8.16 (s, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 58.6 (q, OMe), 70.8 (t, CH_2), 118.2 (s, C-3), 127.8, 128.2, 128.6, 129.0, 129.5 (5 d, Ph), 131.4 (s, C-5), 139.3, 139.7 (2 s, Ph), 141.9 (d, C-4), 156.4, 156.5 (2 s, C-2, C-6) ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{16}BrNO$ [M – H]$^+$ 354.0488, found 354.0506. $C_{19}H_{16}BrNO$ (354.2): calcd. C 64.42, H 4.55, N 3.95; found C 64.00, H 4.38, N 4.03.

3-Bromo-5-(methoxymethyl)-6-(4-methoxyphenyl)-2-phenylpyridine (11f): A mixture of the 6*H*-1,2-oxazine **10** (150 mg, 0.532 mmol), $BF_3{\cdot}OEt_2$ (130 μL, 1.06 mmol), and 3-(4-methoxyphenyl)propargyl methyl ether (**2k**, 375 mg, 2.13 mmol) in DCE (4 mL) was treated as described in the typical procedure (Method B). The mixture was allowed to cool to room temperature, diluted with water (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (hexane/EtOAc, 6:1) to give **11f** (129 mg, 63%) as a yellow solid, m.p. 95–97 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.44, 3.85 (2 s, 3 H each, OMe), 4.45 (s, 2 H, CH_2), 6.95–6.98, 7.39–7.45, 7.54–7.61, 7.72–7.76 (4 m, 2 H, 3 H, 2 H, 2 H, Ph), 8.14 (s, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 55.3, 58.5 (2 q, OMe), 71.0 (t, CH_2), 117.5 (s, C-3), 127.8, 128.6, 129.5, 130.4, 131.0, 131.1, 131.2 (5 d, 2 s, Ph), 139.5 (s, C-5), 142.0 (d, C-4), 156.2 (s, C-6), 156.3 (s, C-2) ppm. HRMS (ESI-TOF): calcd. for $C_{20}H_{18}BrNO_2$ [M – H]$^+$ 384.0599, found 384.0591. $C_{20}H_{18}BrNO_2$ (384.3): calcd. C 62.51, H 4.72, N 3.65; found C 62.05, H 4.67, N 3.64.

Reaction between 1a and 1,3,5-Triethynylbenzene (14): A mixture of the 6*H*-1,2-oxazine **1a** (1.02 g, 5.00 mmol), $BF_3{\cdot}OEt_2$ (1.00 mL, 8.00 mmol), and 1,3,5-triethynylbenzene (**14**, 150 mg, 1.00 mmol) in DCE (5 mL) was treated as described in the typical procedure (Method B). The mixture was allowed to cool to room temperature, diluted with water (7 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (hexane/EtOAc, 6:1, 4:1 to 1:1) to give a mixture (16 mg) of **15** and **16** (3:1, calcd. 3% **15**, 0.5% **16**) as a pale yellow oil, as well as **16** (39 mg, 9.5%) as a pale yellow solid, m.p. 120–122 °C. **Compound 15:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.32–7.45, 7.50–7.59, 7.64–7.67, 7.78–7.95, 8.20–8.25 (5 m, 4 H, 6 H, 3 H, 5 H, 3 H, Ph, Py, Ar), 8.26 (d, J = 1.5 Hz, 3 H, Py), 9.03 (s, 3 H, Py) ppm. HRMS (ESI-TOF): calcd. for $C_{39}H_{27}N_3$ [M + H]$^+$ 538.2283, found 538.2286. **Compound 16:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.21 (s, 1 H, ≡CH), 7.43–7.48, 7.50–7.55 (2 m, 2 H, 4 H, Ph), 7.75 (d, J = 6.0 Hz, 2 H, Py), 7.79 (d, J = 6.3 Hz, 2 H, Py), 7.86 (dd, J = 6.0, 6.3 Hz, 2 H, Py), 8.18–8.23 (m, 4 H, Ph), 8.35 (d, J = 1.4 Hz, 2 H, Py), 8.95 (t, J = 1.4 Hz, 2 H, Py) ppm. ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 77.4 (d, ≡CH), 83.8 (s, ≡C), 118.8, 119.1, 122.9, 126.1, 127.0, 128.7, 129.1, 131.0, 137.6, 139.3, 140.1 (2 d, s, 6 d, 2 s, Ph, Ar, Py), 155.7, 156.9 (2 s, Py) ppm. IR (ATR): $\tilde{\nu}$ = 3065–2850 (=C–H, C–H) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{30}H_{20}N_2$ [M + H]$^+$ 409.1705, found 409.1709.

5-[(Benzyloxy)methyl]-3-(3-methoxyprop-1-yn-1-yl)-2,6-diphenylpyridine (19): The pyridine derivative **11e** (67 mg, 0.155 mmol), methyl propargyl ether (**18**, 109 mg, 1.55 mmol), $PdCl_2(PPh_3)_2$ (11.2 mg, 0.016 mmol), and CuI (1.5 mg, 0.008 mmol) were dissolved in Et_3N (5 mL) in a heat-gun-dried and argon-flushed flask, and the reaction mixture was stirred at 70 °C for 2 h. The solvent was then removed under reduced pressure, and the residue was dissolved in EtOAc (5 mL), washed with water (5 mL), and dried with Na_2SO_4. Purification of the crude product by column chromatography (SiO_2; hexane/EtOAc, 4:1) afforded the 3-alkynyl-substituted pyridine **19** (48 mg, 74%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.39 (s, 3 H, OMe), 4.28 (s, 2 H, CH_2), 4.53, 4.60 (AB system, J_{AB} = 15.7 Hz, 4 H, CH_2), 7.20–7.55, 7.60–7.65, 7.95–8.05 (3 m, 11 H, 2 H, 2 H, Ph), 8.10 (s, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 57.7 (q, OMe), 60.4, 69.0, 72.9 (3 t, OCH_2), 84.4, 90.5 (2 s, C≡C), 115.6, 127.9, 128.2, 128.4, 128.5, 128.7, 129.1, 129.3, 137.7, 139.15, 139.2 (s, 7 d, 2 s, Ph, Py), 142.9 (d, C-4), 157.2, 158.3 (2 s, C-2, C-6) ppm. IR (neat): $\tilde{\nu}$ = 3105–

2980 (=CH, C–H), 2200 (C≡C) cm^{-1}. $C_{29}H_{25}NO_2$ (419.5): calcd. C 83.03, H 6.01, N 3.34; found C 83.60, H 6.39, N 3.03.

3,4-Dimethyl-6-phenyl-2-(phenylsulfinyl)pyridine (24): A solution of oxone (1.24 g, 2.02 mmol) dissolved in water (6 mL) was added to a solution of the pyridine **3g** (280 mg, 0.962 mmol) in acetone (25 mL). The mixture was stirred at room temperature for 2 h and was then diluted with water (40 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were washed with water (2 × 20 mL) and brine (1 × 20 mL), dried with $MgSO_4$, and concentrated to dryness. The residue was purified by chromatography on silica gel (hexane/EtOAc, 4:1) to give **24** (261 mg, 88%) as colorless crystals, m.p. 170–171 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.32, 2.47 (2 s, 3 H each, Me), 7.36–7.50 (m, 6 H, Ph), 7.56 (s, 1 H, 5-H), 7.73–7.79, 7.95–8.01 (2 m, 2 H each, Ph) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 12.3, 19.8 (2 q, Me), 122.9, 125.1, 126.6, 128.5, 128.8, 129.2, 130.5, 130.9, 137.7, 143.6, 149.6, 154.4, 160.2 (7 d, 6 s, Py, Ph) ppm. IR (ATR): $\tilde{\nu}$ = 3055–3030 (=C–H), 2910–2855 (C–H), 1085 (S=O) cm^{-1}. $C_{19}H_{17}NOS$ (307.4): calcd. C 74.24, H 5.57, N 4.56, S 10.44; found C 73.94, H 5.60, N 4.55, S 10.66.

Supporting Information (see footnote on the first page of this article): Procedures for the synthesis of **2e**, **3b**–**d**, **3f**–**h**, **3j**–**l**, **8a**, **8b**, **11b**, **11c**, **11e**, **13**, **17**, **20**, **21**, **23**, and **24a**.

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