SYNTHESIS AND REACTIVITY OF PYRIDIN-4-OLS BASED ON THE THREE-COMPONENT REACTION OF ALKOXYALLENES, NITRILES AND CARBOXYLIC ACIDS

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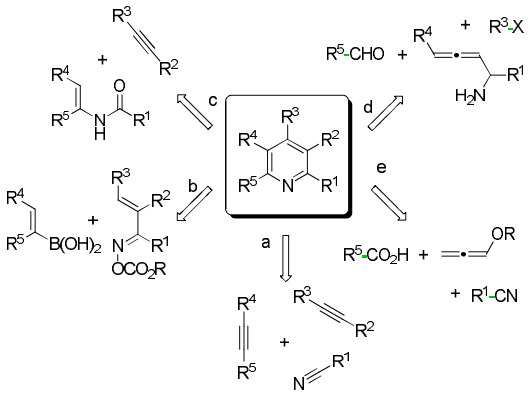
Abstract. *The reaction of lithiated alkoxyallenes with nitriles and carboxylic acids constitutes a new and flexible three-component approach to highly substituted pyridin-4-ol derivatives. A four-component protocol leads to the corresponding pyridin-4-yl nonaflates that are extremely versatile precursors for subsequent synthetic steps, in particular for palladium-catalyzed processes. Scope and limitations as well as applications of this new route to pyridine derivatives are discussed.*

Contents

1. Introduction

Pyridine derivatives belong to the most important heterocycles due to their role as biological active compounds and their suitability to serve as ligand for metal ions. This latter property led to countless applications of pyridine derivatives in catalysis, as component of innovative materials (e.g. in organic electronics) and as key building blocks in supramolecular chemistry.[1] The high importance and versatility of pyridine derivatives requires efficient and flexible synthetic approaches. It is not surprising that a constant flow of new strategies and methods to prepare pyridine, bipyridine and terpyridine rings can be observed. Scheme 1 presents a few recent approaches with clever combinations of easily available starting materials as examples.[2] Particularly important methods involve multi-component reactions such as routes a and d (Scheme 1). The current review describes the discovery and exploration of the three-component synthesis of pyridin-4-ols starting from alkoxyallenes, nitriles and carboxylic acids (route e).



Scheme 1. Selected routes to highly substituted pyridine derivatives.

The pyridine synthesis discussed in this review was serendipitously discovered by Oliver Flögel in our group in the year 2001 when he investigated new reactions of lithiated alkoxyallenes. For more than two decades our group explored the remarkable synthetic versatility of alkoxyallenes that is sketched in Figure 1.[3] Whereas electrophiles add to the central carbon atom due to the enol ether subunit, nucleophiles react with the terminal carbon of the allene system. Most importantly, by deprotonation at C-1, alkoxyallenes can easily be transferred into the lithiated species which is a strong nucleophile and able to react with electrophiles at this carbon. These addition reactions generally furnish intermediates with a new nucleophilic center that are able to add either spontaneously or by catalytic processes to the terminal allene carbon to provide heterocyclic compounds.

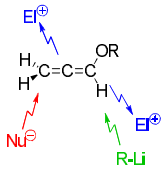
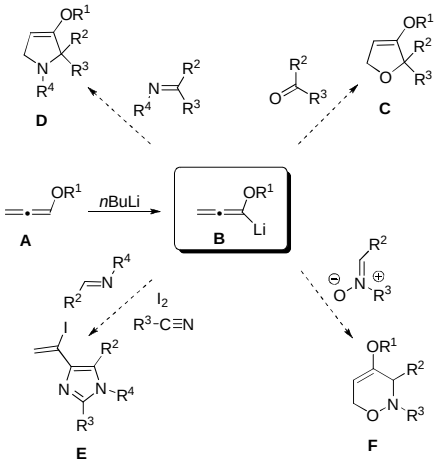


Figure 1. Reactivity pattern of alkoxyallenes.[3]

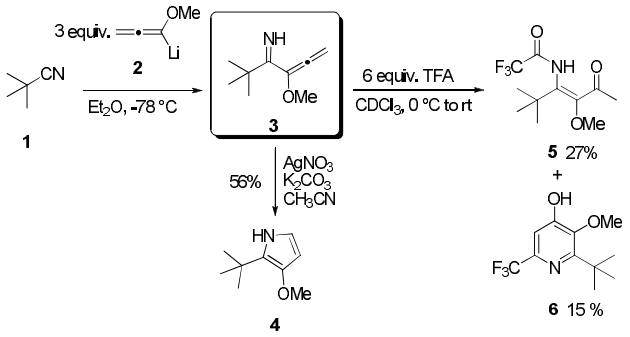
In Scheme 2 we briefly summarize the most important reactions. Alkoxyallenes **A** and *n*-butyllithium provide in ethereal solvents the lithiated species **B** that react with different electrophiles to give heterocyclic compounds. Its reactions with carbonyl compounds – already investigated in the seminal studies of Arens et al. – furnish dihydrofuran derivatives **C**,[4] whereas the analogous additions of imines give the expected dihydropyrroles **D** with a broad substrate scope.[5] Combination of the primary addition products of **B** and imines with iodine and nitriles allowed a new four-component synthesis of functionalized imidazole derivatives **E**.[6] The reaction of lithiated alkoxyallenes **B** with nitrones constitutes a productive method to generate directly 1,2-oxazine derivatives **F** that are extremely versatile intermediates for the synthesis of other heterocycles,[7] including natural products,[8] glycosidase inhibitors[9] or carbohydrate mimetics.[10] In heterocycles of type **C**, **D** and **F** the still present enol ether moieties allow subsequent reactions with electrophiles. This feature is key for the synthetic versatility of these heterocyclic building blocks.



Scheme 2. Alkoxyallene-based synthesis of heterocycles **C**-**F**.[3]

2. Discovery of a new three-component reaction to pyridine derivatives

Due to the broad scope of the reactions depicted in Scheme 2 and the synthetic utility of the products **C**-**F** the unknown addition of lithiated alkoxyallenes **B** with nitriles as electrophiles suggested itself. Oliver Flögel selected pivalonitrile **1** and tested its suitability to react with lithiated methoxyallene **2**. Methoxyallene is generally used as standard reagent to test new reactions since it is easily available from methyl propargyl ether.[4] It can be employed in excess because unconsumed reagent is easily removed by evaporation after a reaction. Nitrile **1** and lithiated methoxyallene **2** cleanly furnished the expected primary addition product **3** in essentially quantitative yield (Scheme 3).[11] However, the cyclization of this compound to the desired pyrrole derivative **4** turned out to be not trivial.

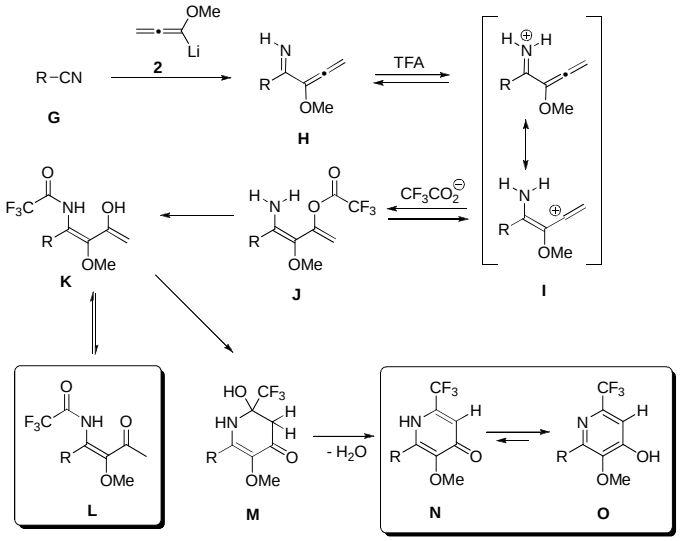


Scheme 3. Reaction of lithiated methoxyallene **2** with pivalonitrile **1** and subsequent reactions.

After many experiments, a mixture of silver nitrate in the presence of potassium carbonate delivered **4** in moderate yield. It should be mentioned here that electron-rich pyrrole derivatives such as **4** are fairly sensitive compounds due to their high tendency to undergo oxidative degradation. Other examples with smaller substituents than the *t*-butyl group of **4** gave considerably lower yields and unstable and impure

products. The key observation of Oliver Flögel was that solutions of primary product **3** in $CDCl_3$ showed unexpected signals in the NMR spectra when these were recorded only after a few hours. The obvious suspicion was therefore that traces of DCl present in $CDCl_3$ induce a transformation of **3** and therefore this compound was deliberately treated with an excess of trifluoroacetic acid (TFA). This NMR experiment was the discovery of a new extremely useful and versatile pyridine synthesis, since we could figure out that it generated the two entirely unexpected compounds **5** and **6**, both isolated in low yield.[11]

A plausible mechanism of the formation of these two compounds is illustrated in Scheme 4. Lithiated methoxyallene **2** and the nitrile **G** furnish the primary addition product as shown before. Protonation of this intermediate by TFA generates an iminium ion **I** whose mesomeric formulas reveal its electrophilicity at the central allene carbon. Reaction at this carbon with trifluoroacetate affords the 1,3-diene system **J** that undergoes an acyl shift to the amino group to give the new *N*-acylated 1,3-diene **K** followed by a proton shift to enamide **L** (corresponding to the isolated compound **5** of Scheme 3). Dienol **K** can also undergo an intramolecular aldol type addition of its nucleophilic terminal carbon to the amide carbonyl group forming the new C-C bond of intermediate **M**. This species suffers an acid-induced elimination of water to give the pyridin-4-one **N** and tautomerization provides pyridin-4-ol **O** (corresponding to isolated compound **6** of Scheme 3). The ratio of the two tautomers **N** and **O** strongly depends on the substituents of the heterocyclic system and the solvent. We depict only the major tautomer in this review which is the pyridine form in most cases.

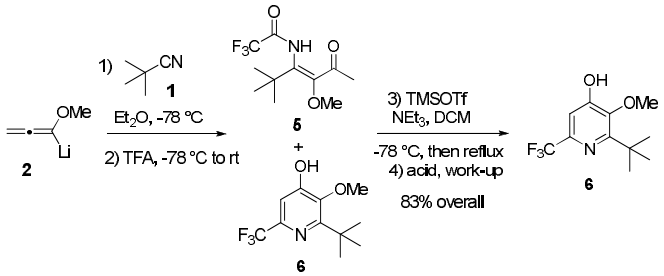


Scheme 4. Mechanism of the formation of pyridin-4-ol **O**.

The unique multi-step reaction of Scheme 4 is remarkable since the protonation of **H** to **I** implies an "umpolung of reactivity" of the alkoxyallene subunit of **I**. Its central carbon now reacts with a nucleophile (carboxylate). Moreover, the aldol type cyclization reaction involves an amide carbonyl group that is regarded as weak electrophile. With the trifluoroacetyl group the electrophilicity is apparently sufficiently

high to start the cyclization reaction in the presence of the excess of the strong carboxylic acid TFA. As shown below the reaction described in Schemes 3 and 4 also proceeds with simple carboxylic acids without fluorine substituents. However, in these examples the reaction stops at the enamide intermediate since the amide carbonyl group is less electrophilic in these cases. Nevertheless, suitable conditions were found to convert these intermediates into the desired pyridine derivatives.

The mechanism described in Scheme 4 is fascinating, but a reaction forming a mixture of two compounds in low yield as shown in Scheme 3 is certainly not a useful synthetic transformation. We therefore optimized the formation of pyridin-4-ol derivative **6** by treating lithiated methoxyallene **2** with pivalonitrile **1** at low temperature and then added an excess of TFA (Scheme 5). After warm-up to room temperature, the resulting mixture was evaporated and no attempts to purify and separate compounds **5** and **6** were made. Instead, we tried to complete the aldol type cyclization by treating the crude product mixture with suitable reagents under appropriate conditions. Therefore, the **5**/**6** mixture was dissolved in dichloromethane and treated with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and triethylamine. This mixture was subsequently heated to reflux for three days to complete the cyclization. Gratifyingly, after acid work-up of the mixture the desired pyridin-4-ol derivative **6** was isolated in 83% overall yield. With this successful optimization, a new three-component synthesis of highly functionalized pyridine derivatives was established.[11] It turned out that a very broad range of alkoxyallenes, nitriles and carboxylic acids can be used as starting materials and that the resulting pyridinol derivatives are excellent precursors for further functionalizations or substitutions due to the two oxygen substituents, this at C-4 being a free hydroxyl group, the other at C-3 being protected as alkoxy group. This pattern allows a variety of selective transformations as shown in this review.



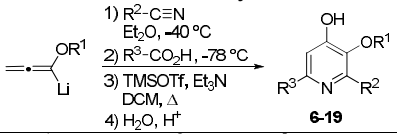
Scheme 5. Optimization of the synthesis of pyridin-4-ol **6**.

3. Synthesis of fluoroalkyl- and fluoroaryl-substituted pyridin-4-ols or their nonaflates

Scope and limitations of our new three-component pyridine synthesis were first checked using TFA as carboxylic acid. It was expected that the required cyclization to the pyridine moiety occurs most easily because of the higher electrophilicity of the amide group. Moreover, the resulting pyridine derivatives bear a trifluoromethyl group at C-2 and hence these products are of particular interest, e.g. as intermediates for the synthesis of crop protection products. In our method, the CF_3 group originates from cheap TFA and we therefore applied and received a patent.[12] The results summarized in Table 1 show that the scope is indeed very broad. Although the highest yields were achieved with the already described example **6** (Scheme 5, Table 1, entry 1) other alkyl nitriles also provided the expected pyridin-4-ols **7**-**11** (entries 2-6). The yields

range from 23% to 83%, with a tendency to lower yields if smaller substituents R^2 are involved. Possibly, side reactions occur when nitriles such as acetonitrile are employed. For this electrophile the formation of a side-product could be shown.[13] With aromatic nitriles such as benzonitrile or the related thiophene derivative decent yields of the pyridin-4-ols **12** and **13** could be achieved (entries 7 and 8). We also employed a perfluorinated carboxylic acid with a longer chain that provided the expected product **14** in moderate yield (entry 9). Entry 10 reveals that pentafluorobenzoic acid could also be employed giving the expected perfluorophenyl-substituted compound **15** in 43% yield. Entries 11-14 demonstrate that other alkoxyallenes may also be employed leading to pyridin-4-ol derivatives with alternative alkoxy groups at C-3.

Table 1. Synthesis of fluorinated pyridin-4-ols **6-19** from alkoxyallenes, nitriles and TFA or related fluorinated carboxylic acids.

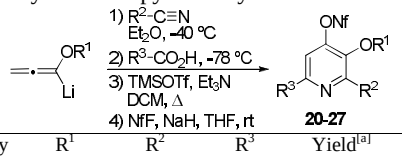


6-19

Entry	R^1	R^2	R^3	Yield	Ref.
1	Me	*t*Bu	CF_3	**6**, 83%	11
2	Me	Me	CF_3	**7**, 37%	13
3	Me	Et	CF_3	**8**, 63%	11
4	Me	Allyl	CF_3	**9**, 32%	13
5	Me	*i*Pr	CF_3	**10**, 54%	11
6	Me	CMe_2OH	CF_3	**11**, 23%	13
7	Me	Ph	CF_3	**12**, 60%	11
8	Me	2-Thienyl	CF_3	**13**, 67%	13
9	Me	*t*Bu	C_7F_{15}	**14**, 27%	13
10	Me	*t*Bu	C_6F_5	**15**, 43%	13
11	Bn	Me	CF_3	**16**, 43%	13
12	Bn	*t*Bu	CF_3	**17**, 50%	13
13	3-$MeOC_6H_4CH_2$	*t*Bu	CF_3	**18**, 37%	13
14	$Me_3SiCH_2CH_2$	*t*Bu	CF_3	**19**, 42%	13

The coexistence of the pyridin-4-ol and pyridin-4-one tautomers (**N** and **O** in Scheme 4) of the prepared pyridine derivatives complicates the identification of the products and it also causes problems during their isolation and purification. In both tautomeric forms they are relatively polar and hence purification by chromatography was often not efficient. We therefore modified our three-component reaction and added a fourth component to the system. The crude pyridin-4-ol/pyridin-4-one mixtures obtained after cyclization were dissolved in THF and by treatment with sodium hydride deprotonated to the corresponding pyridin-4-olate. This intermediate was then *O*-sulfonylated employing nonafluorobutanesulfonyl fluoride (NfF) to give compounds with lower polarity that were easy to purify by chromatography. In many cases this method has the advantage of higher efficacy, but the introduced ONf group at C-4 of the pyridine derivative is also an excellent functional group to be used for substitution reactions, in particular for transition metal-catalyzed processes.[14] Table 2 summarizes the results obtained with different nitriles and fluorinated carboxylic acids. The overall yields of pyridin-4-yl nonaflates **20-27** are moderate to good. The examples of Tables 1 and 2 reveal that the scope of the pyridine synthesis is very broad. It should be mentioned that trifluoroacetonitrile and trialkylsilyl cyanides as nitrile components failed to provide the expected compounds.

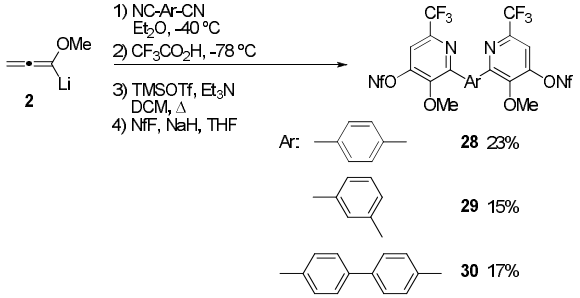
Table 2. Four-component synthesis to pyridin-4-yl nonaflates **20**-**27** by direct nonaflation.



Entry	R^1	R^2	R^3	Yield[a]	Ref.
1	Me	*t*Bu	CF_3	**20**, 62%	13
2	Bn	*t*Bu	CF_3	**21**, 37%	13
3	TMSE	*t*Bu	CF_3	**22**, 30%	13
4	Me	*n*Oct	CF_3	**23**, 51%	13
5	Me	*c*Pr	CF_3	**24**, 38%	13
6	Me	Ph	CF_3	**25**, 48%	13
7	Me	*t*Bu	CHF_2	**26**, 26%	13
8	Me	*t*Bu	C_6F_5	**27**, 41%	13

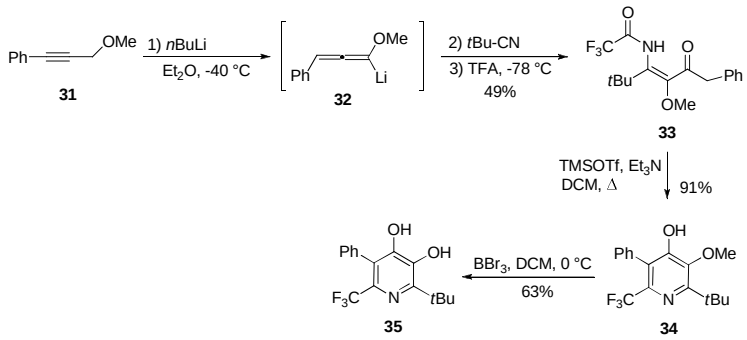
[a] Overall yields for three steps.

We also studied three aromatic dinitriles as electrophiles in the four-component reaction with lithiated methoxyallene **2** (Scheme 6).[15]



Scheme 6. Use of aromatic dinitriles in four-component syntheses of pyridin-4-yl nonaflates **28**-**30**.

Although the yields of the corresponding bisnonaflates **28**-**30** were only in the range of 20% it should be kept in mind that in the overall process ten new bonds per molecule are formed. The use of phenyl-substituted propargylic ether **31** allowed the preparation of pentasubstituted pyridin-4-ols (Scheme 7).[13]



Scheme 7. *In situ* generation of 3-phenyl-substituted lithiated methoxyallene **32** and its conversion into pentasubstituted pyridin-4-ol derivatives **34** and **35**.

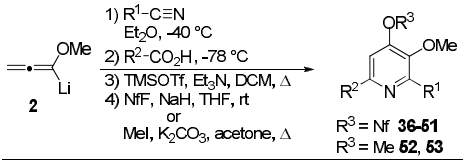
Compound **31** was deprotonated with *n*-butyllithium leading to lithiated methoxyallene **32** with a phenyl substituent at C-3 (this process requires an additional proton shift). Intermediate **32** was treated with pivalonitrile and TFA to give the enamide **33** in 49% yield whose cyclocondensation smoothly furnished the pentasubstituted pyridin-4-ol **34** in excellent yield. The methoxy group of this product could be dealkylated by employing boron tribromide affording pyridin-3,4-diol **35**.[16]

This paragraph demonstrates that the scope concerning the nitrile and the alkoxyallene components is very broad. Together with fluorinated carboxylic acids they provide an impressive library of new highly substituted pyridine derivatives bearing (per)fluoroalkyl or perfluoroaryl substituents.

4. Scope of the pyridin-4-ol synthesis employing other carboxylic acids

Next scope and limitations with respect to the carboxylic acid component should be discussed. As seen from Table 3 all types of carboxylic acids can be employed in the multi-component pyridine synthesis: aliphatic (entries 2, 3), aromatic (entries 1, 4), heteroaromatic (entries 5, 14-16), α,β-unsaturated (entries 6-12) and alkynyl-substituted (entry 13) carboxylic acids were successfully converted into the corresponding pyridine nonaflates **36-51**.

Table 3. Scope of carboxylic acids employed in the multi-component synthesis of pyridin-4-ols.



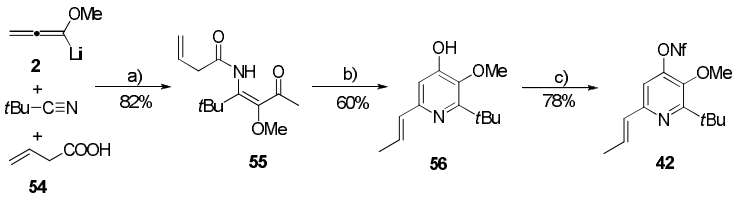
Entry	R^1	R^2	Yield[a]	Ref.
1	*i*Pr	Ph	**36**, 52%	17
2	*c*Pr	*c*Pr	**37**, 42%	17
3	*t*Bu	Me	**38**, 57%	17
4	*t*Bu	Ph	**39**, 38%	17
5	*t*Bu	2-Py	**40**, 91%	18
6	*t*Bu	Vinyl	**41**, 46%	19
7	*t*Bu		**42**, 48%	19
8	*t*Bu		**43**, 42%	19
9	*t*Bu		**44**, 32%	19
10	*t*Bu		**45**, 33%	19
11	Ph		**46**, 32%	19
12	2-Thienyl		**47**, 37%	19
13[a]	*t*Bu	C≡C-TMS	**48**, 22%	17
14	Ph	2-Py	**49**, 55%	17
15	Ph	2-Thienyl	**50**, 23%	17
16	2-Thienyl	2-Thienyl	**51**, 41%	20
17	Me	2-Py	**52**, 53%	17
18	2-Thienyl	Me	**53**, 58%	17

[a] Propiolic acid was used as starting material.

It should be mentioned again, that due to the lower electrophilicity of the amide group no partial cyclization occurs at the enamide stage (intermediates of type **L**, Scheme 4). In general, the crude enamide was directly treated with TMSOTf/NEt_3 and then with NaH/NfF to give the pyridin-4-yl nonaflates. A

limitation of the method concerns the use of formic acid as carboxylic acid component that did not lead to the formation of the corresponding pyridin-4-ol derivative unsubstituted at C-6. Possibly, the involved intermediate **L** (see Scheme 4) which now bears a formamide moiety undergoes alternative processes (e.g. isonitrile formation) and thus disfavors the desired cyclization. As a new modification we also attempted the *in situ O*-methylation (instead of the nonaflation) as fourth step, delivering the methoxy-substituted pyridine derivatives **52** and **53** in good overall yield (entries 17 and 18).

The reaction of lithiated methoxyallene **2** with pivalonitrile **1** and the β,γ-unsaturated carboxylic acid **54** furnished the enamide intermediate **55** in high yield. The double bond of the substituent is still at the terminal position, however, during the cyclization a shift of the double bond into conjugation was unavoidable; pyridin-4-ol **56** and the subsequently prepared nonaflate **42** contain a *trans*-propen-1-yl group at C-6 (Scheme 8).[19]



Scheme 8. Generation and conversion of allyl-substituted enamide **55** into pyridin-4-ol **56** and nonaflate **42**. Reagents and conditions: a) Et_2O, -70 °C to rt; b) TMSOTf, Et_3N, DCE, 90 °C; c) NaH, NfF, THF, rt.

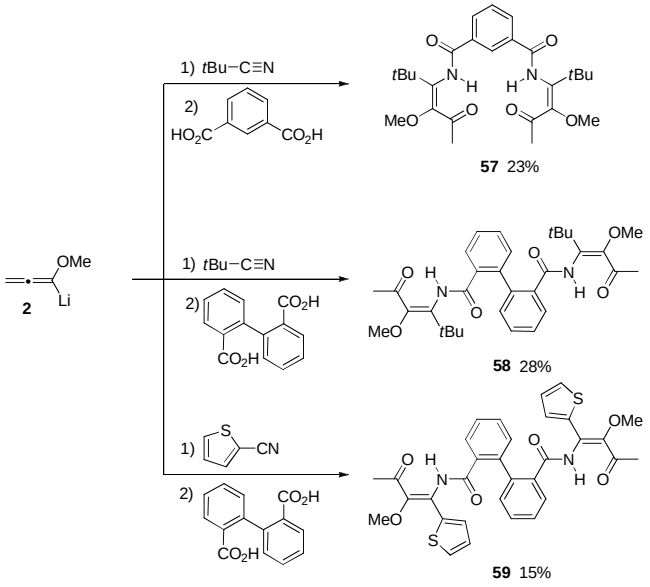
As counterpart to the use of dinitriles (see Scheme 6) we also investigated aromatic dicarboxylic acids as components. The results of Scheme 9 demonstrate that the reactions of lithiated methoxyallene **2** with pivalonitrile and three different dicarboxylic acids provided the expected bisenamides **57**-**59**, however, the low solubility of the diacids allowed only moderate yields. Again, we should stress that during the formation of compounds **57**-**59** six new bonds were generated.[21]

With bisenamides **57** and **58** we studied the subsequent cyclizations and nonaflations (Scheme 10). Compound **57** provided the bispyridin-4-ol derivative **60** and the corresponding bisnonaflate **61** in moderate yields. Under similar reaction conditions the biphenyl derivative **58** was only partially converted into the biscyclization product **62** (60%); the monocyclization product **64** was also isolated in 18% yield, which offered the option to perform other condensation reactions with the remaining enamide moiety (see Scheme 36). Compounds **62** and **64** were smoothly converted into the corresponding nonaflates **63** and **65**.[21]

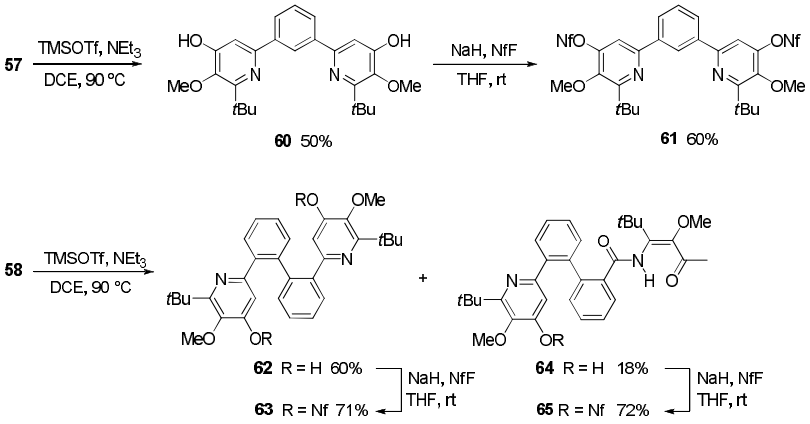
5. Chiral carboxylic acids and nitriles in the pyridin-4-ol synthesis

Having demonstrated that the scope is very broad with respect to nitrile and carboxylic acid components we investigated the use of chiral compounds in our route to pyridin-4-ols.[22,23] The resulting products could be useful ligands for metal-catalyzed asymmetric transformations.

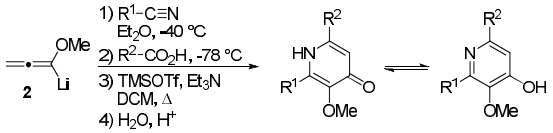
Scheme 11 and Table 4 summarize the reactions executed with chiral carboxylic acids. Our results reveal that also a broad range of simple (entries 1 and 2) or functionalized chiral carboxylic acids (entries 3-8) can be employed and that the efficacy of the three-component reactions is moderate to good.



Scheme 9. Use of aromatic dicarboxylic acids in the synthesis of bisenamides **57**-**59**.



Scheme 10. Cyclizations of bisenamides **57** and **58** providing compounds **60**-**65**.

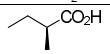
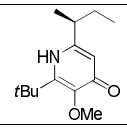
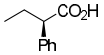
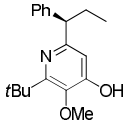
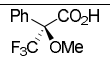
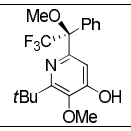
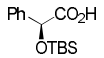
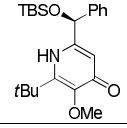
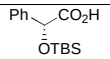
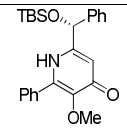
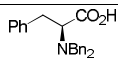
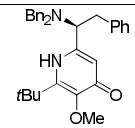
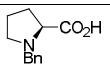
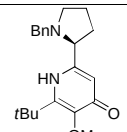
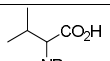
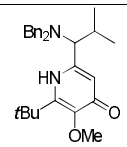


Scheme 11. Synthesis of pyridin-4-ones/pyridin-4-ols using chiral nitriles and/or carboxylic acids.

Of particular interest are compounds such as **71** (entry 3) derived from Mosher´s acid, compounds **73** and **74** (entries 4 and 5) derived from protected mandelic acid or pyridin-4-one **76** with an amino acid-

derived substituent (entry 6). The reaction of lithiated methoxyallene **2**, pivalonitrile and protected proline unfortunately failed to give the expected product (entry 7), possibly due to steric hinderance.[22]

Table 4. Scope of the synthesis of pyridin-4-ones/pyridin-4-ols using chiral carboxylic acids (see Scheme 11).

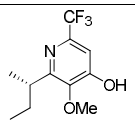
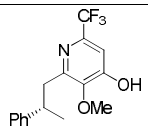
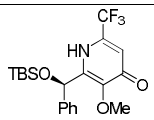
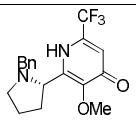
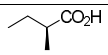
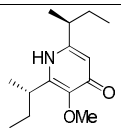
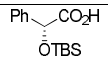
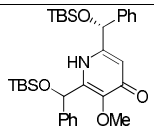
Entry	R^1-CN	R^2-CO_2H	Product[a]	Yield[b]
1	*t*Bu-CN	 **66**		**67**, 24%
2	*t*Bu-CN	 **68**		**69**, 45%
3	*t*Bu-CN	 **70**		**71**, 30%
4	*t*Bu-CN	 (*S*)-**72**		**73**, 50%
5	Ph-CN	 (*R*)-**72**		**74**, 24%
6	*t*Bu-CN	 **75**		**76**, 45%
7	*t*Bu-CN	 **77**		--
8	*t*Bu-CN	 *rac*-**78**		**79**, 50%

[a] Only the predominating tautomer in $CDCl_3$ is shown; [b] Yields are based on the nitrile.

The analogous reactions of chiral nitriles provided similar results (Table 5). Lithiated methoxyallene **2**, simple nitriles such as **80** or **82** and trifluoroacetic acid as third component provided the expected pyridine derivatives **81** and **83** (entries 1 and 2). Similarly, enantiopure mandelonitrile derivative **84** gave the pyridin-4-one **85** in moderate yield (entry 3). Again a proline derived component such as **86** failed to give the desired product that was assumed to be a particular interesting ligand for catalysis (entry 4). We also

combined two chiral components (entry 5) to obtain compound **87** in excellent yield. The two mandelic acid-derived precursors of entry 6 also furnished the expected product **88**, however, as a separable 1:1 mixture of the two diastereomers, since the nitrile **84** was used as racemic mixture in this experiment. All examples investigated did not show an erosion of the enantiopurity of the products. In most of the cases the pyridin-4-one tautomer was the predominating species in the ^{1}H NMR spectra recorded in $CDCl_3$; we speculate that hydrogen bridges of the proton at the pyridin-4-one nitrogen to the heteroatoms in α-position at C-1 or C-6 play an important role in determining these tautomerization equilibria.[22,23]

Table 5. Scope of the synthesis of pyridin-4-ones/4-hydroxypyridines using chiral nitriles (see Scheme 11).

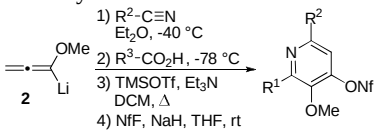
Entry	R^1-CN	R^2-CO_2H	Product[a]	Yield[b]
1	 **80**	CF_3CO_2H		**81**, 56%
2	 **82**	CF_3CO_2H		**83**, 28%
3	 **84**	CF_3CO_2H		**85**, 37%
4	 **86**	CF_3CO_2H		--
5	 **80**	 **66**		**87**, 85%
6	 *rac*-**84**	 (*R*)-**72**		**88**, 26% (1:1 mixture of separable diastereomers)

Finally, enantiopure lactic acid derivatives **89** and **92** were studied in the four-component version of our pyridine synthesis leading to the corresponding pyridin-4-yl nonaflates (Table 6).[23] Entries 1 and 2 describe the conversion of TBS-protected lactic acid **89** that furnished the 6-*tert*-butyl- and phenyl-substituted pyridin-4-yl nonaflates **90** and **91** in moderate yield. The combination of enantiopure lactic acid derived nitrile **92** with three carboxylic acids delivered the pyridin-4-yl nonaflates **93**-**95** in 36-46% overall yield. The two chiral components **92** and **89** opened an access to pyridine derivative **96** with stereogenic centers at C-2 and C-6 (entry 6).

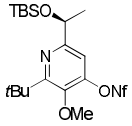
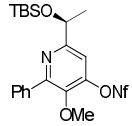
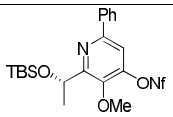
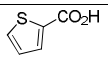
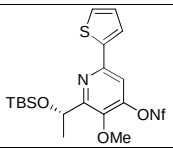
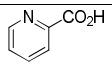
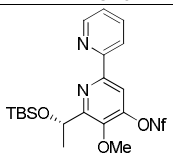
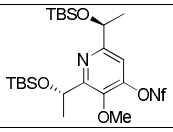
Although the yields of the syntheses of these pyridin-4-yl nonaflates were in part not very high there is certainly room for optimization to improve the very rapid access to these chiral compounds. It should be

mentioned that many of the enantiopure pyridine derivatives collected in Tables 4-6 (or compounds derived thereof) are promising ligands in asymmetric catalysis. The chiral bipyridine derivative **95** may be a particularly interesting candidate.

Table 6. Synthesis of pyridin-4-yl nonaflates **90**-**96** derived from lactic acid derivatives.



90-**96**

Entry	R^1-CN	R^2CO_2H	Product	Yield[a]
1	*t*Bu-CN	 **89**		**90**, 35%
2	Ph-CN	 **89**		**91**, 32%
3	 **92**	Ph-CO_2H		**93**, 46%
4	 **92**			**94**, 36%
5	 **92**			**95**, 37%
6	 **92**	 **89**		**96**, 13%

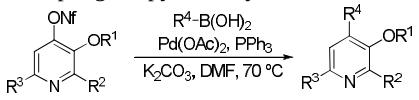
[a] Overall yield.

Overall, the many examples presented in chapters 3-5 demonstrate the very broad scope of the serendipitously discovered new three-component reaction to functionalized pyridin-4-ols. Almost all types of nitriles and carboxylic acids can be used as components and flexibility with respect to the alkoxy substituent at C-3 of the pyridines is also guaranteed due to the different lithiated alkoxyallenes employed. The use of this group as well as that of other substituents at the pyridine core for functionalizations is described in the following chapters.

6. Palladium-catalyzed reactions of pyridin-4-yl nonaflates

Among the palladium-catalyzed reactions the Suzuki-Miyaura coupling is probably the most flexible and efficient method to introduce new substituents to sp^2-hybridized centers. We also experienced excellent behavior of typical pyridin-4-yl nonaflates examined, that were coupled with a variety of boronic acids under standard conditions to give the expected 4-aryl- or 4-alkenyl-substituted pyridine derivatives **97**-**111** (Table 7). With a few exceptions, the yields were in a range of 80 to 95% confirming the high efficacy of this type of coupling reactions with pyridin-4-yl nonaflates. The tetrasubstituted pyridine derivative **103** was employed for an approach to the potent HMG-CoA inhibitor Glenvastatin.[17]

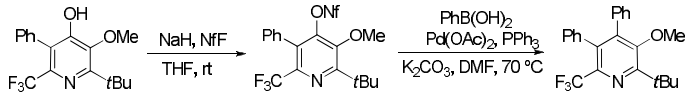
Table 7. Suzuki-Miyaura couplings of pyridin-4-yl nonaflates with different boronic acids.



97-111

Precursor	R^1	R^2	R^3	R^4	Yield	Ref.
20	Me	*t*Bu	CF_3	4-MeO-C_6H_4	**97**, 84%	11
20	Me	tBu	CF_3	4-NC-C_6H_4	**98**, 81%	13
20	Me	*t*Bu	CF_3	4-Ac-C_6H_4	**99**, 98%	18
20	Me	*t*Bu	CF_3		**100**, 88%	13
40	Me	*t*Bu	2-Py	4-Ac-C_6H_4	**101**, 78%	18
23	Me	*n*Oct	CF_3	4-Ac-C_6H_4	**102**, 81%	18
36	Me	*i*Pr	Ph	4-F-C_6H_4	**103**, 92%	17
25	Me	Ph	CF_3	4-MeO-C_6H_4	**104**, 74%	13
38	Me	*t*Bu	Me		**105**, 92%	17
43	Me	*t*Bu			**106**, 81%	19
49	Me	Ph	2-Py	4-Ac-C_6H_4	**107**, 82%	18
49	Me	Ph	2-Py		**108**, 89%	17
21	Bn	*t*Bu	CF_3	Ph	**109**, 99%	13
21	Bn	*t*Bu	CF_3	4-MeO-C_6H_4	**110**, 60%	13
22	TMSE	*t*Bu	CF_3	Ph	**111**, 69%	13

We also tested pyridin-4-yl nonaflate **112** obtained from the corresponding pyridin-4-ol **34** (see Scheme 7) in a Suzuki-Miyaura coupling with phenyl boronic acid. The expected pentasubstituted pyridine derivative **113** was isolated in very good yield (Scheme 12). The steric hindrance to be assumed in this transformation did not hamper the efficacy of this coupling.[13]

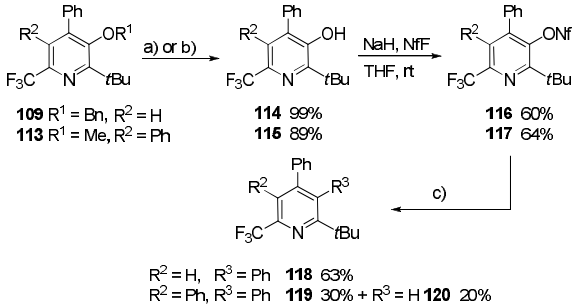


34 **112** 38% **113** 84%

Scheme 12. Suzuki-Miyaura coupling of nonaflate **112** to pentasubstituted pyridine derivative **113**.

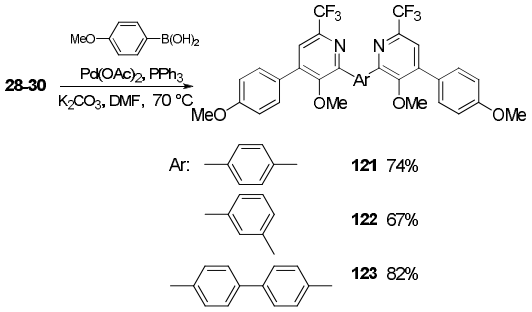
With compounds **109** and **113** the suitability of the dealkylation of the 3-alkoxy group at the pyridine core, the activation of this position by nonaflation and the subsequent Suzuki-Miyaura couplings were examined.[13] The removal of the benzyl or methyl groups required treatment with TFA or with trimethylsilyl iodide at 80 °C, but provided the desired 3-hydroxy-substituted pyridine derivatives **114** and **115** in good

yield. Nonaflation under standard conditions followed by coupling of **116** and **117** with phenyl boronic acid under standard conditions afforded the expected products **118** and **119**. Whereas compound **118** was formed in reasonable yield without detected side-products, the pentasubstituted pyridine derivative **119** was only isolated in 30% yield together with the reduced product **120** in 20% yield. In this example, the coupling between the 2-*tert*-butyl and 4-phenyl group is apparently slow due to the steric hindrance and hence reductive removal of the nonafloxy group can compete (Scheme 13).



Scheme 13. Dealkylation and nonaflation at C-3 of pyridine derivatives **109** and **113** and Suzuki-Miyaura couplings of compounds **116** and **117** to 3-substituted pyridine derivatives **118** and **119**. Reagents and conditions: a) TFA, DCE,80 °C; b) TMSI, DCE, 80 °C; c) $PhB(OH)_2$, $Pd(OAc)_2$, PPh_3, *i*Pr_2NH, DMF, 70 °C.

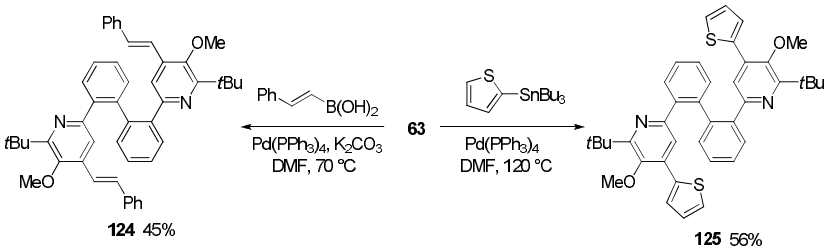
The bisnonaflates **28**-**30**, prepared employing aromatic dinitriles (see Scheme 6), were also excellent substrates for the palladium-catalyzed couplings and they efficiently led to compounds **121**-**123** containing highly extended π-systems (Scheme 14).[15] The structure of compound **121** was unequivocally confirmed by an X-ray crystal structure analysis.[24]



Scheme 14. Suzuki-Miyaura coupling of bisnonaflates **28**-**30** derived from aromatic dinitriles leading to compounds **121**-**123**.

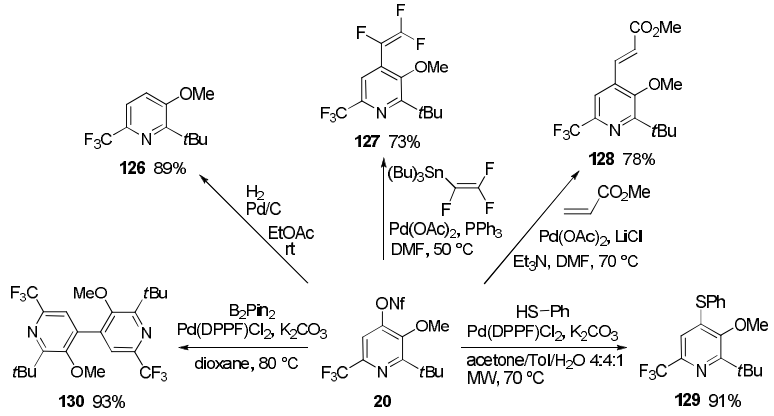
Related products were obtained starting with bisnonaflate **63** that is derived from diphenic acid (see Schemes 9 and 10). The Suzuki-Miyaura reaction of this compound with an α,β-unsaturated boronic acid provided compound **124** in moderate yield, whereas the Stille coupling of **63** with 2-(tributylstannyl)thiophene gave the expected thiophenyl-substituted product **125** in 56% yield (Scheme

15).[21] All these examples demonstrate that the route via pyridin-4-yl nonaflates such as **28**-**30** or **63** derived from dinitriles or dicarboxylic acids allow a very rapid access to compounds with highly extended π-systems in a fairly flexible fashion.



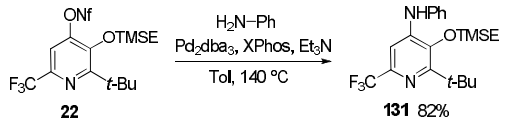
Scheme 15. Palladium-catalyzed couplings of bisnonaflate **63** derived from diphenic acid affording **124** and **125**.

With the numerous presented Suzuki-Miyaura couplings and one Stille reaction we demonstrated the versatility of pyridin-4-yl nonaflates as substrates in this type of processes leading to highly substituted pyridine derivatives with broad diversity. Scheme 16 summarizes other palladium-catalyzed reactions employing the model nonaflate **20** as precursor. The reductive removal of the nonafloxy group smoothly furnished trisubstituted pyridine **126** and a Stille coupling with a stannane provided the trifluorovinyl-substituted compound **127** in satisfying yield. The Heck reaction to methyl acrylate derivative **128** and the thiolation to **129** also proceeded with reasonable efficacy. Finally, the reductive coupling employing a diboron reagent opened an access to compounds such as the highly substituted 4,4´-bipyridine derivative **130** in excellent yield.[3c,13]



Scheme 16. Palladium-catalyzed reactions of nonaflate **20** to pyridine derivatives **126**-**130**.

The palladium-catalyzed amination of the analogous TMSE-substituted nonaflate **22** with aniline provided the expected product **131** in excellent yield (Scheme 17).[13]



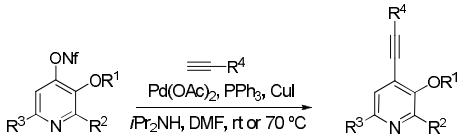
22 **131** 82%

Scheme 17. Palladium-catalyzed amination of nonaflate **22** with aniline to 4-amino-substituted pyridine **131**.

7. Sonogashira reactions of pyridin-4-yl nonaflates and synthesis of furopyridines

Sonogashira couplings of pyridin-4-yl nonaflates worked equally well and provided under standard conditions a series of 4-alkynyl-substituted pyridine derivatives (Table 8). The examples demonstrate that different combinations of substituents are possible and that the yields range from 60-99%. 3-Methoxy-, 3-benzyloxy- and 3-TMSE-substituted pyridin-4-yl nonaflates behave comparable well and form the coupling products **134**, **139**, and **140** in good yields. With respect to the terminal alkyne there seems to be no limitation and even compound **136** with an unprotected hydroxyl group was obtained in excellent yield.

Table 8. Sonogashira couplings of pyridin-4-yl nonaflates with different alkynes to alkynyl-substituted pyridine derivatives **133-140**.

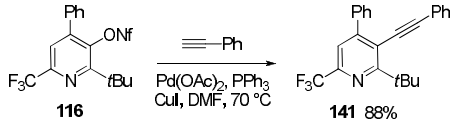


133-140

Precursor	R^1	R^2	R^3	R^4	Yield	Ref.
132[a]	Me	Et	CF_3	Ph	**133**, 72%	25
20	Me	*t*Bu	CF_3	Ph	**134**, 72%	11
20	Me	*t*Bu	CF_3	*n*Bu	**135**, 61%	25
20	Me	*t*Bu	CF_3	CMe_2OH	**136**, 96%	25
50	Me	Ph	2-Thienyl	Ph	**137**, 58%	17
21	Bn	*t*Bu	CF_3	CH_2OMe	**138**, 75%	25
21	Bn	*t*Bu	CF_3	Ph	**139**, 99%	25
22	TMSE	*t*Bu	CF_3	Ph	**140**, 78%	25

[a] Obtained from **8** by the standard nonaflation protocol.

The example of Scheme 18 demonstrates that the Sonogashira coupling of the pyridin-3-yl nonaflate **116** (see Scheme 13) also works with excellent efficacy providing the 3-substituted compound **141** in 88% yield.[13]



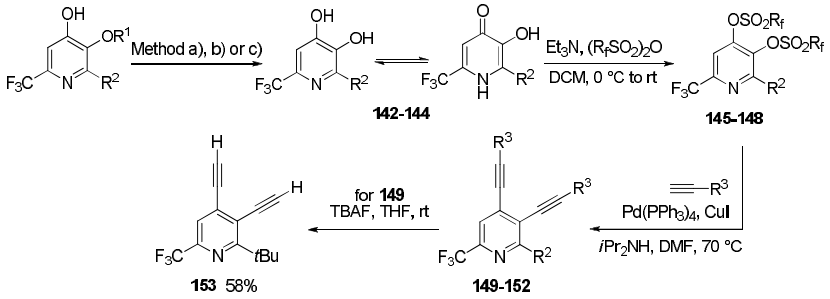
116 **141** 88%

Scheme 18. Sonogashira coupling of pyridin-3-yl nonaflate **116** with phenylacetylene to 3-alkynyl-substituted pyridine derivative **141**.

With a series of pyridin-3,4-diols, we examined the feasibility of twofold Sonogashira reactions. For this purpose the primary products of the three-component reaction **16**, **19** and **25** were converted into the corresponding pyridin-3,4-diols **142-144** by appropriate dealkylation procedures (Scheme 19, Table 9). By

hydrogenolysis benzyloxy-substituted compound **16** was converted into product **142** under mild conditions, whereas the TMSE-substituted pyridine derivative **19** was treated with trifluoroacetic acid to quantitatively provide **143**.

The methoxy-substituted compound **25** gave the desired pyridin-3,4-diol **144** in excellent yield by employing BBr_3 as Lewis acid.[16] The pyridin-3,4-diols are in equilibrium with the corresponding 3-hydroxypyridin-4-one tautomer. For compound **143** an X-ray crystal structure analysis revealed a very interesting network of hydrogen bond-connected molecules with two pyridin-3,4-diol molecules in one plane and two pyridinone molecules in a perpendicular plane. Three of these derivatives were converted into the corresponding bistriflates **145**, **146** and **148** or the bisnonaflate **147**. This double activation allowed the planned Sonogashira reactions with different alkynes to furnish the dialkynyl-substituted pyridine derivatives **149**-**152** in moderate yields.



Scheme 19. Generation of pyridin-3,4-diols **142**-**144** and Sonogashira couplings of pyridin-4-yl bis-sulfonates with alkynes to dialkynyl-substituted pyridine derivatives **149**-**152** and desilylation of **149** to **153**. Reagents and conditions: Method a) Pd/C, H_2, MeOH, rt; Method b) TFA:DCM (1:2), rt; Method c) BBr_3, DCM, 0 °C to rt.

Table 9. Synthesis of pyridin-3,4-diols **142**-**144** and Sonogashira couplings of **146**-**148** with alkynes to pyridines **149**-**152** (see Scheme 19).

Precursor	R^1	R^2	Yield	R_f	Yield	R^3	Yield
16	Bn[a]	Me	**142**, 74%	CF_3	**145**, 78%	--	--
19	TMSE[b]	*t*Bu	**143**, quant.	CF_3	**146**, 90%	TIPS	**149**, 35%
19	TMSE[b]	*t*Bu	**143**	CF_3	**146**	Ph	**150**, 44%
19	TMSE[b]	*t*Bu	**143**	C_4F_9	**147**, 59%	Ph	**151**, 30%
25	Me[c]	Ph	**144**, 94%	CF_3	**148**, 47%	Ph	**152**, 40%

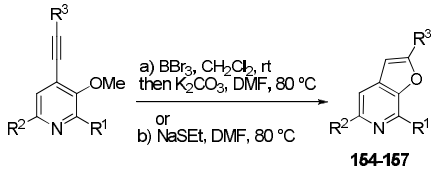
[a] Method a) Pd/C, H_2, MeOH, rt; [b] Method b) TFA:DCM (1:2), rt; [c] Method c) BBr_3, DCM, 0 °C to rt.

The TIPS-protected product **149** was desilylated with fluoride and afforded the bis(ethynyl)-substituted pyridine derivative **153** in 58% yield. Compounds such as **149**-**153** might be interesting candidates to examine Bergman cyclizations that should generate isoquinoline derivatives, but this option was not examined. The bis(2-phenylethynyl)-substituted compounds **150** and **151** are fluorescent, emitting light in the violet region.[16]

During an attempt to convert the methoxy group of 4-alkynyl-substituted pyridines such as **20** by treatment with BBr_3 into the hydroxyl group Jyotirmayee Dash discovered an unexpected formation of furo[2,3-c]pyridines, e.g. of **154**.[25] The method was further optimized and turned out to be an excellent route to this class of heterocycles.[26] Simple examples are summarized in Table 10 showing that the dealkylations

were possible either under basic conditions with sodium ethanethiolate or with Lewis acids such as BBr_3. The resulting pyridin-3-ol derivatives underwent the 5-*endo*-dig cyclization in part spontaneously, a reaction generally completed by treatment with potassium carbonate, that gave the products **154**-**157** in moderate to very good yields.[25]

Table 10. Formation of furo[2,3-c]pyridines **154**-**157** from 4-alkynyl-substituted 3-methoxypyridines.

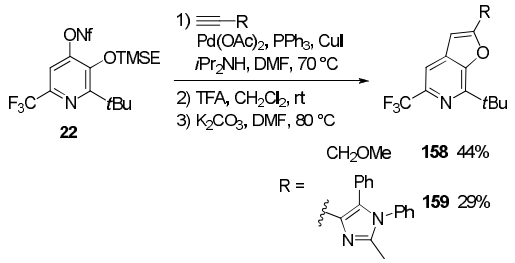


154-**157**

Precursor	R^1	R^2	R^3	Yield
20[a]	*t*Bu	CF_3	Ph	**154**, 73%
20[a]	*t*Bu	CF_3	*n*Bu	**155**, 85%
50[b]	Ph	2-Thienyl	Ph	**156**, 41%
25[b]	Ph	CF_3	Ph	**157**, 40%

[a] Method a); [b] Method b).

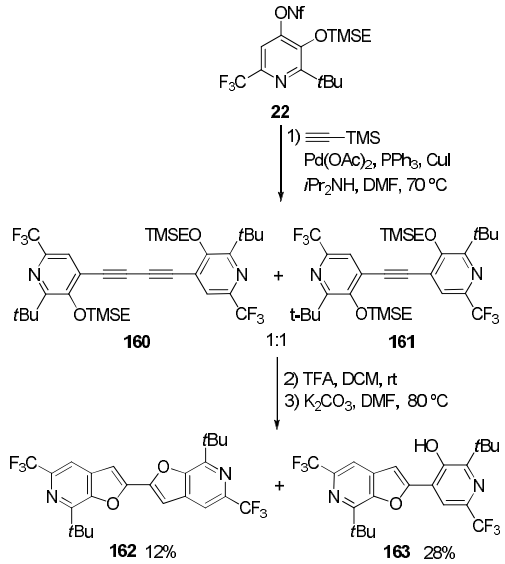
With the TMSE-substituted pyridin-4-yl nonaflate **22** two one-pot reactions involving the sequence Sonogashira coupling/dealkylation/cyclization were performed (Scheme 20).



Scheme 20. Sonogashira couplings of pyridin-4-yl nonaflate **22** and conversions to furo[2,3-c]pyridines **158** and **159**.

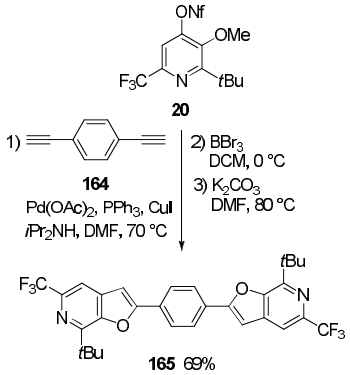
The coupling of **22** with a propargyl methyl ether followed by dealkylation employing acid and cyclization with potassium carbonate furnished the furo[2,3-c]pyridine derivative **158** in moderate yield. Analogously, **22** was converted into **159** by combining it with an imidazol-4-yl-substituted alkyne (itself a product derived from lithiated methoxyallene);[6] although the yield in this multi-step process is rather low, the product is remarkable since it contains two alkoxyallene-derived moieties.[25]

The model compound **22** and trimethylsilylethyne were employed to examine the one-pot conversion into bispyridyl-substituted alkyne **161**.[25] Not only the expected product **161** was formed but in equal amounts the product of a Glaser coupling generating the butadiynyl system **160** (Scheme 21). The compounds could not be separated, however, removal of the TMSE group and subsequent treatment with base delivered the two separable cyclization products **162** and **163**. The bis(furo[2,3-c]pyridine) **162** was isolated in 12% yield and compound **163** in 28% yield.



Scheme 21. Sonogashira reaction of nonaflate **22** with trimethylsilylethyne providing **160** and **161** and their conversion into furo[2,3-c]pyridines **162** and **163**.

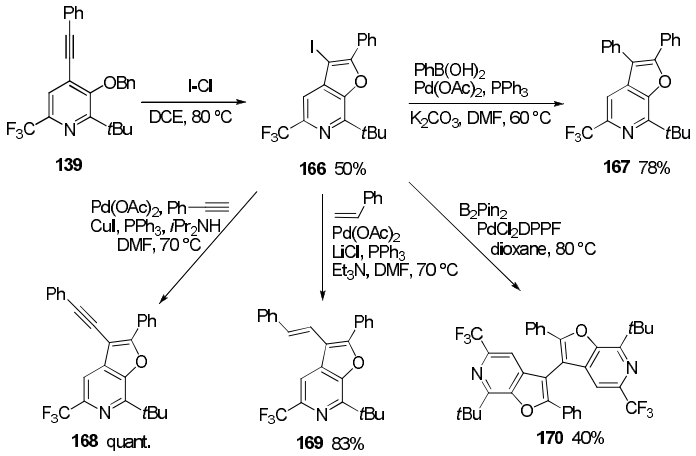
A similar approach to a bis(furo[2,3-c]pyridine) system is depicted in Scheme 22. The twofold Sonogashira reaction of dialkyne **164** with pyridin-4-yl nonaflate **20** followed by BBr_3-promoted demethylation and cyclization with base provided the target compound **165** in 69% overall yield. The structure of this compound and its conformation were established by an X-ray crystal structure analysis.[25]



Scheme 22. One-pot synthesis of the bis(furo[2,3-c]pyridine) derivative **165**.

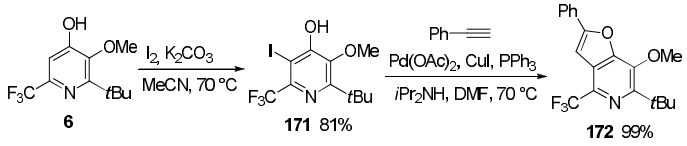
An alternative option to prepare a library of furo[2,3-c]pyridine derivatives was offered by the iodine monochloride induced cyclization[27] of 3-benzyloxy-4-alkynyl-substituted pyridine derivative **139** (Scheme 23). This cyclization occurred under *O*-debenzylation and afforded 3-iodofuro[2,3-c]pyridine **166** in 50% yield. The introduced iodine substituent allowed all types of palladium-catalyzed reactions as demonstrated by the Suzuki-Miyaura coupling to **167**, the Sonogashira reaction to **168**, the Heck coupling to styrene

derivative **169** and the reductive dimerization employing a diboron reagent that furnished bis(furo[2,3-c]-pyridine) derivative **170**.[25] All these examples show the enormous potential of alkynyl-substituted pyridines such as **139** to provide highly substituted furo[2,3-c]pyridines. Compounds **167**-**170** are strongly fluorescent.



Scheme 23. Iodine monochloride induced cyclization of alkynyl-substituted pyridine **139** to 3-iodofuro[2,3-c]pyridine **166** and subsequent palladium-catalyzed couplings leading to **167**-**170**.

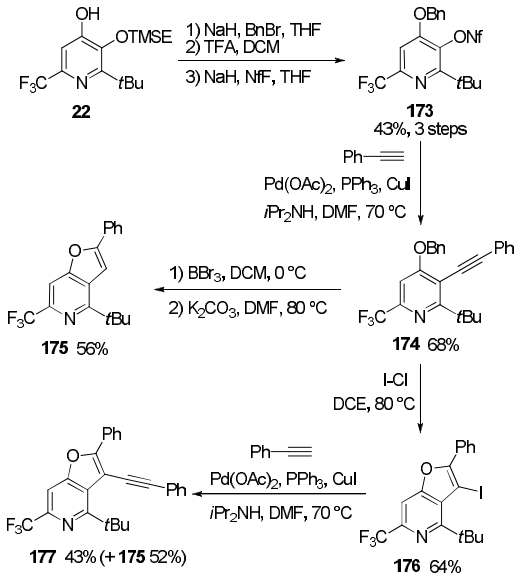
Another variation examined with one example only, gave access to alkoxy-substituted furo[2,3-c]-pyridines of type **172** (Scheme 24), but it should be of general applicability. Pyridin-4-ol **6** was treated with iodine under basic conditions to introduce the halogen atom at C-5 of the pyridine ring giving **171**. A Sonogashira reaction of this substrate with phenylacetylene directly provided the target compound **172** in quantitative yield. It is obvious that other palladium-catalyzed reactions are possible with easily prepared 5-iodo-pyridine derivatives such as **171**.[25,28]



Scheme 24. Iodination of pyridin-4-ol **6** and subsequent Sonogashira reaction of **171** leading to methoxy-substituted furo[2,3-c]pyridine **172**.

The synthesis of the regioisomeric furo[3,2-c]pyridines was achieved by exchanging the role of the two oxygen functions of 3-alkoxy-pyridin-4-ols such as **22**. Protection of the free hydroxyl group of **22**, removal of the TMSE-group by acid and subsequent nonaflation under standard conditions provided pyridine **173** with a nonafloxy group at C-3 in reasonable overall yield (Scheme 25). Sonogashira reaction at this position introduced the 3-alkynyl group of compound **174** that was either *O*-dealkylated by BBr_3 and subsequently treated with base to deliver the target furo[3,2-c]pyridine **175**. Alternatively, compound **174** was treated with iodine monochloride to give the 3-iodo furo[3,2-c]pyridine **176**. The Sonogashira reaction of this product gave the desired alkynyl-substituted furo[3,2-c]pyridine **177** (43%) together with the reduced

product **175** (52%).[25] This single example shows again the potential of this route to prepare the regioisomeric furo[3,2-c]pyridines, since other pyridin-4-ols, various terminal alkynes and different final coupling components should be applicable and provide all kind of highly substituted compounds of type **177**.



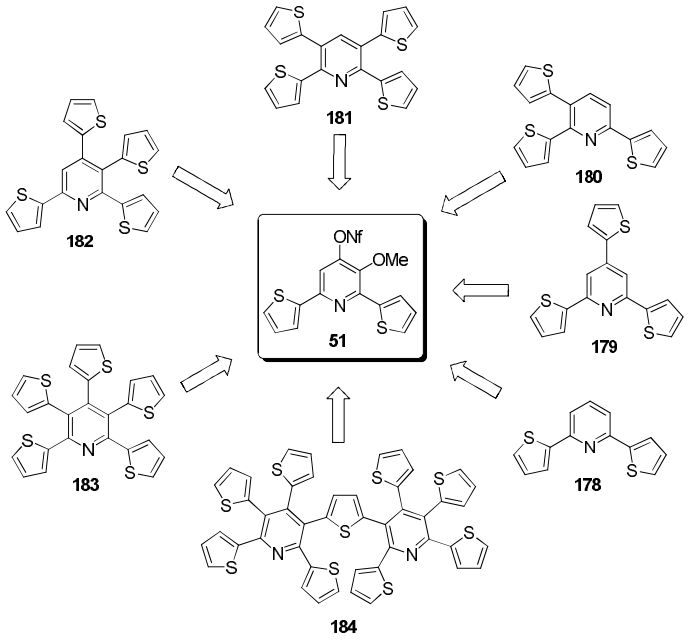
Scheme 25. Synthesis of regioisomeric pyridin-3-yl nonaflate **173**, Sonogashira reaction to **174** and subsequent transformations into furo[3,2-c]pyridines **175**, **176** and **177**.

8. Synthesis of oligo(thiophen-2-yl)-substituted pyridine derivatives

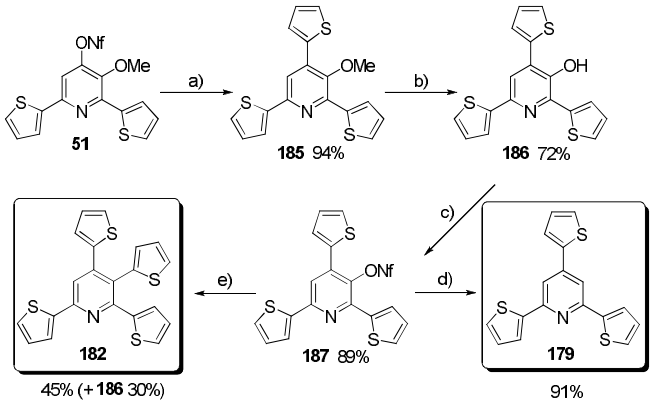
For curiosity and in order to demonstrate the applicability and versatility of our three-component route to highly substituted pyridines we planned to prepare a series of compounds, in which the number of a certain substituent increases from two to five in different positions of the pyridine core. We selected thiophen-2-yl as substituent due to the relevance of heterocycles containing this group in organic electronics or for other applications.[29] Our plan was to start with pyridin-4-yl nonaflate **51** that is very easily available (see Table 3, entry 16), also in 10 g quantities, and to convert **51** by reduction, functionalizations and couplings into pyridine derivatives with two (**178**), three (**179** and **180**), four (**181** and **182**) and finally into the compound **183** with five thiophen-2-yl substituents (Scheme 26). A further goal was the preparation of compounds such as the thiophen-2,5-diyl-bridged system **184** containing altogether nine thiophene moieties. The photophysical and electrochemical properties of these pyridine derivatives should be studied and compared. Although the methods employed to synthesize these compounds are essentially standard coupling reactions these have to demonstrate their efficacy in a sterically encumbered situation.

We started our endeavor by the preparation of tri- and tetrasubstituted compounds **179** and **182** by converting precursor nonaflate **51** into the tri(thiophen-2-yl)-substituted pyridine **185** through very efficient Suzuki-Miyaura coupling with thiophene-2-boronic acid (Scheme 27). Compound **185** was *O*-dealkylated

with sodium ethanethiolate to give **186** and a subsequent nonaflation furnished the crucial pyridin-3-yl nonaflate **187** in good overall yield.



Scheme 26. Retrosynthetic analysis to oligo(thiophen-2-yl)-substituted pyridine derivatives **178**-**184** based on 2,6-di(thiophen-2-yl)-substituted pyridin-4-yl nonaflate **51**.

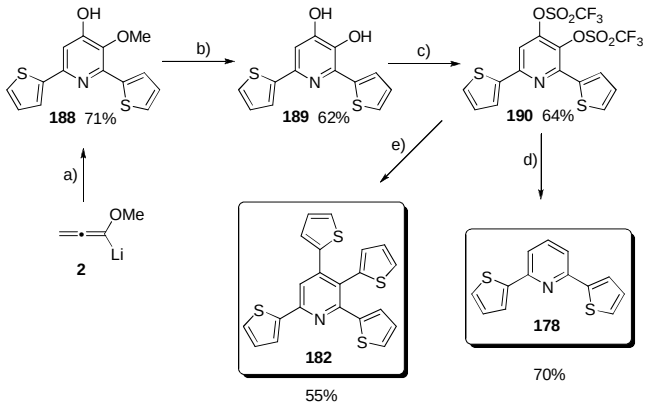


Scheme 27. Conversion of 2,6-di(thiophen-2-yl)pyridin-4-yl nonaflate **51** into tri- and tetrasubstituted pyridine derivatives **179** and **182**. Reagents and conditions: a) thiophene-2-boronic acid, $Pd(PPh_3)_4$, K_2CO_3, DMF, 70 °C; b) NaSEt, DMF, 90 °C; c) NaH, NfF, THF, rt; d) $Pd(OAc)_2$, DPPP, Et_3N, HCO_2H, DMF, 90 °C; e) thiophene-2-boronic acid, $Pd(PPh_3)_4$, K_2CO_3, DMF, 80 °C.

The reductive removal of the nonafloxy group with formic acid/base/palladium acetate afforded the symmetric target compound **179** in excellent yield. The nonaflate **187** was also employed to introduce a

fourth thiophene moiety by a Suzuki-Miyaura coupling. The desired unsymmetrical 1,2,3,5-tetra(thiophen-2-yl)pyridine **182** was isolated in 45% yield together with the *O*-desulfonylated product **186** whose formation indicated the difficulties associated with the coupling between two existing substituents at the pyridine core.[20]

Scheme 28 summarizes the preparation of targets **178** and **182**. Pyridin-4-ol derivative **188** was smoothly available in large quantities by the three-component reaction of lithiated methoxyallene **2** with thiophene-2-carbonitrile and thiophene-2-carboxylic acid and subsequent cyclization. After *O*-demethylation with $AlCl_3$ in an ionic liquid the resulting pyridin-3,4-diol **189** was then converted into the corresponding bis(triflate) **190** that undergoes a twofold Suzuki-Miyaura reaction to furnish the desired tetrasubstituted unsymmetrical pyridine derivative **182** in decent overall yield. Alternatively, the two trifloxy groups were reductively removed from **190** affording 2,6-dithiophen-2-yl-pyridine **178** in good yield.[20]

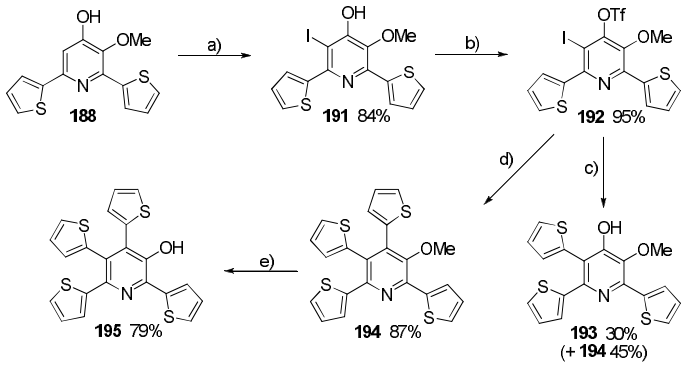


Scheme 28. Synthesis of pyridin-4-ol **188** and of di- and tetrasubstituted pyridine derivatives **178** and **182**. Reagents and conditions: a) i: thiophene-2-carbonitrile, ii: thiophene-2-carboxylic acid, iii: TMSOTf/NEt_3; b) 1 M ionic liquid (2 $AlCl_3$/Me_3N·HCl) in DCM, rt; c) Tf_2O, Et_3N, DMAP, DCM, 0 °C to rt; d) $Pd(OAc)_2$, DPPP, Et_3N, HCO_2H, DMF, 90 °C; e) thiophene-2-boronic acid, $Pd(OAc)_2$, K_2CO_3, PPh_3, DMF, 80 °C.

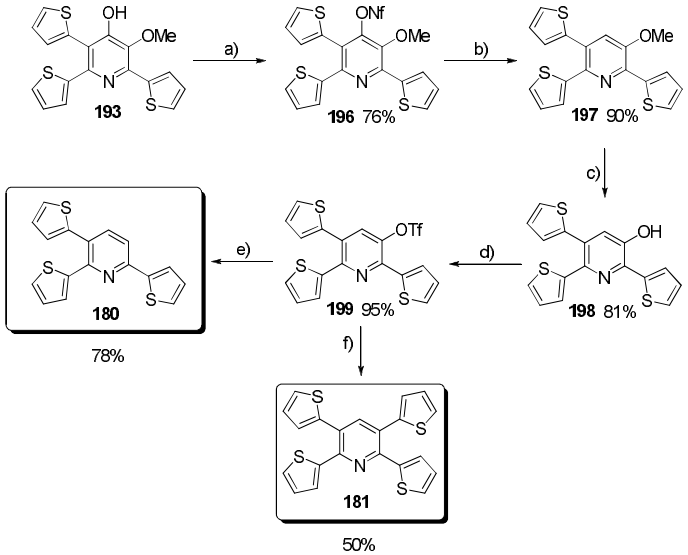
To achieve an activation of C-5 of the pyridine derivatives we iodinated pyridin-4-ol **188** (Scheme 29). The resulting product **191** was then converted into pyridin-4-yl triflate **192** that was first subjected to a Suzuki-Miyaura reaction with thiophene-2-boronic acid. The twofold coupling reaction proceeded to give the expected product **194**, however, the mono-substitution product **193** with a free hydroxyl group at C-4 was also formed. This compound was very useful as shown below. Compound **194** was exclusively obtained by a Stille reaction of **192** with 2-(tributylstannyl)thiophene and was *O*-demethylated with sodium ethanethiolate to give the desired pentasubstituted pyridin-3-ol **195** in good overall yield, that was planned to be the key building block for fully thiophen-2-yl-substituted pyridines.[20,30]

Compound **193** was a useful starting material to prepare the tri- and tetrasubstituted pyridine derivatives **180** and **181** (Scheme 30). The steps involved are essentially self-explanatory and employ reactions already discussed above. The crucial precursor of the two target compounds, pyridin-3-yl triflate **199**, was obtained in good yield over four steps. Its reduction provided the unsymmetrical trisubstituted

pyridine derivative **180** and the Suzuki-Miyaura reaction gave the symmetrical tetrasubstituted pyridine **181** in 50% yield (not optimized).[20]



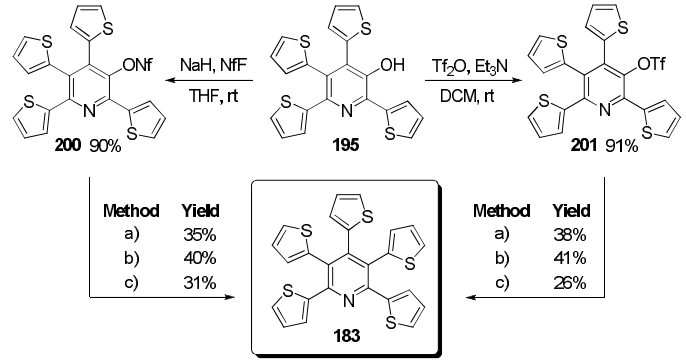
Scheme 29. Synthesis of key building blocks **193** and **195**. Reagents and conditions: a) I_2, Na_2CO_3, THF/H_2O, rt; b) Tf_2O, Et_3N, DCM, 0 °C, rt; c) thiophene-2-boronic acid, $Pd(PPh_3)_4$, K_2CO_3, PPh_3, DMF, 70 °C; d) 2-(tributylstannyl)thiophene, $Pd(PPh_3)_4$, DMF, 90 °C; e) NaSEt, DMF, 90 °C.



Scheme 30. Synthesis of tri- and tetrasubstituted pyridine derivatives **180** and **181**. Reagents and conditions: a) NaH, NfF, THF, rt; b) $Pd(OAc)_2$, DPPP, Et_3N, HCO_2H, DMF, 90 °C; c) BBr_3, DCM, 0 °C to rt; d) Tf_2O, Et_3N, DMAP, DCM, 0 °C to rt; e) $Pd(OAc)_2$, DPPP, Et_3N, HCO_2H, DMF, 90 °C; f) thiophene-2-boronic acid, $Pd(PPh_3)_4$, K_2CO_3, DMF, 70 °C.

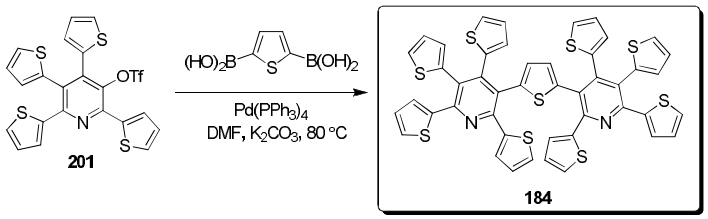
With 2,4,5,6-tetra(thiophen-2-yl)pyridin-3-ol **195** in hand we could try the synthesis of the challenging pentasubstituted pyridine derivative **183** (Scheme 31). This pyridin-3-ol was smoothly converted into nonaflate **200** and triflate **201** under standard conditions. Gratifyingly, both activated compounds could be converted into the desired product **183**, either by Suzuki-Miyaura reaction with the boronic acid, or by Stille

reaction employing the stannane, or by Negishi reaction by coupling the *in situ* generated zinc reagent. The yields are in the range of 25-40%, with the Stille conditions giving the highest efficacies. The moderate yields certainly reflect the considerable steric hindrance in the coupling processes. Nevertheless, we were very pleased to reach the ultimate goal of our synthetic exercise. The UV/Vis spectra and fluorescence spectra of compounds **178**-**183** in neutral and protonated form were studied. In part we could also investigate the (irreversible) electrochemical oxidation of these thiophen-2-yl-substituted pyridine derivatives.[20,30]



Scheme 31. Synthesis of 2,3,4,5,6-penta(thiophen-2-yl)pyridine **183**. Reagents and conditions: a) thiophene-2-boronic acid, $Pd(PPh_3)_4$, K_2CO_3, DMF, 80 °C; b) 2-(tributylstannyl)thiophene, $Pd(PPh_3)_4$, DMF, 90 °C; c) thiophene, *n*BuLi, $ZnBr_2$, $Pd(PPh_3)_4$, THF, 60 °C.

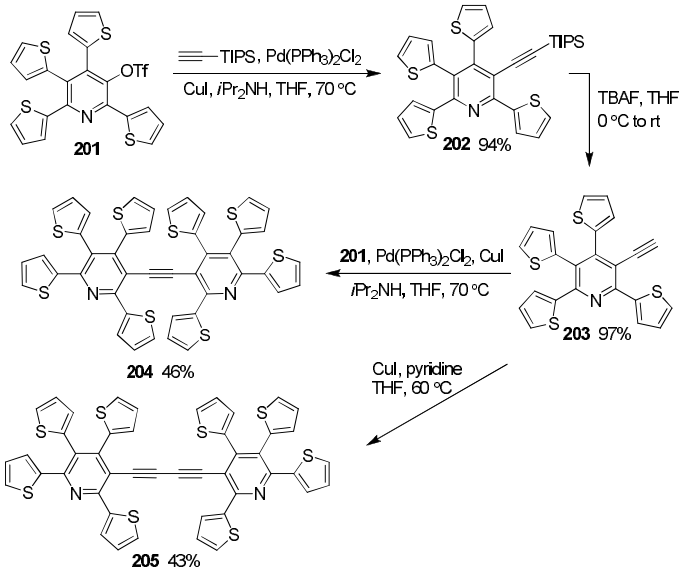
Compounds such as **200** and **201** allow also the synthesis of more extended π-systems. When triflate **201** was coupled with thiophene-2,5-diboronic acid the expected coupling product **184** containing nine thiophene units was formed in reasonable yield (Scheme 32).[30]



Scheme 32. Synthesis of pyridine derivative **184** containing nine thiophene units.

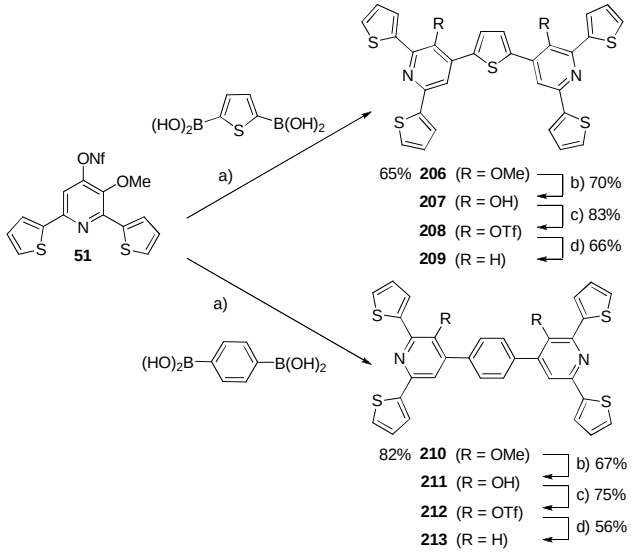
Triflate **201** was similarly used for the preparation of symmetrical compounds with central alkyne moieties (Scheme 33). Sonogashira reaction of triflate **201** gave **202** and desilylation of this intermediate furnished 3-ethynyl-substituted pyridine derivative **203** in excellent yield. A second Sonogashira coupling with **201** provided compound **204** with an ethyne bridge, whilst the oxidative dimerization under Glaser conditions delivered **205** with a 1,3-butadiyne center.[30]

The thiophen-2-yl-substituted building blocks shown in the Schemes above can obviously be used for a variety of other reactions, in particular for other coupling methods.



Scheme 33. Synthesis of oligo(thiophen-2-yl)-substituted pyridine derivatives **204** and **205** with an ethyne or 1,3-butadiyne center.

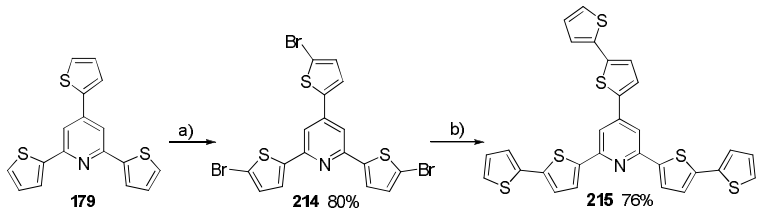
Scheme 34 shows two applications leading again to symmetrical polyheterocyclic systems.



Scheme 34. Suzuki-Miyaura couplings of nonaflate **51** with aromatic diboronic acids to compounds **206** and **210** and their further transformations. Reagents and conditions: a) $Pd(PPh_3)_4$, K_2CO_3, DMF, 70 °C; b) NaSEt, DMF, 90 °C; c) pyridine, DMAP, Tf_2O, DCM, 0 °C to rt; d) $Pd(OAc)_2$, DPPP, Et_3N, HCO_2H, DMF, 90 °C.

The preparation of compound **206** from nonaflate **51** and thiophene-2,5-diboronic acid was simple and the remaining oxygen function of **206** was used for additional couplings or reductively removed as illustrated. Analogous transformations have been performed with compound **210** that was available from **51** and its Suzuki-Miyaura reaction with benzene-1,4-diboronic acid.[31]

The thiophen-2-yl substituents of all compounds offer various possibilities for further functionalizations leading to even higher diversity of products. The 5-position is particularly reactive and can, for instance, easily be brominated (Scheme 35). Under optimized conditions trisubstituted pyridine derivative **179** and *N*-bromosuccinimide provided the tris(5-bromothiophen-2-yl)-substituted pyridine **214** in good yield. The bromo substituent could be used for further coupling reactions, e.g. for a threefold Suzuki-Miyaura reaction with thiophene-2-boronic acid to furnish product **215** with three 2,2'-bithiophen-5-yl groups. Similar reactions of other thiophen-2-yl-substituted pyridines have also been studied.[31]



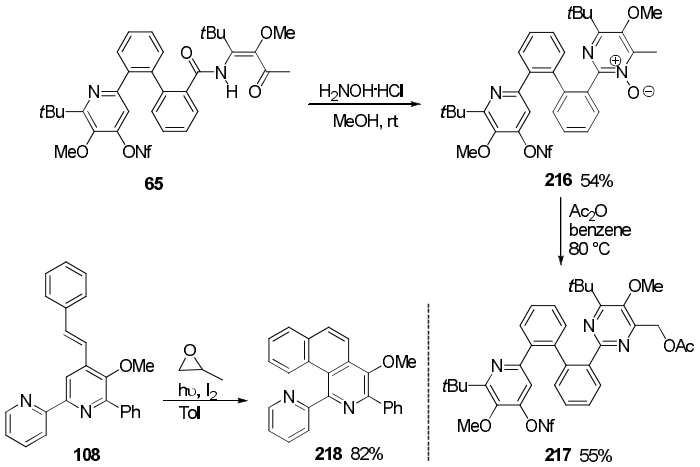
Scheme 35. Bromination of **179** and coupling of **214** to tris(2,2´-bithiophen-5-yl)-substituted compound **215**. Reagents and conditions: a) 4 equiv. NBS, DMF, -20 °C to rt; b) thiophene-2-boronic acid, $Pd(PPh_3)_4$, K_2CO_3, DMF, 80 °C.

9. Miscellaneous reactions of pyridin-4-ol-derived compounds

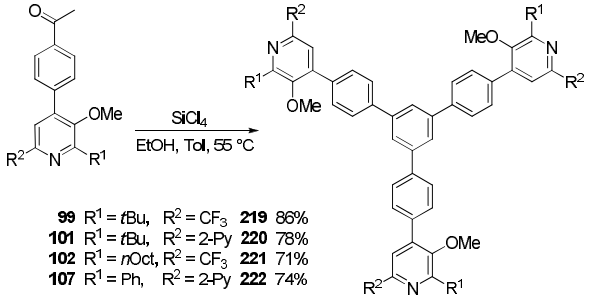
In this short chapter we briefly sketch useful reactions that do not fit in the discussed topics above. Due to the untouched enamide moiety the monocyclization product **65** (Scheme 10) allowed the synthesis of pyridine/pyrimidine hybrids such as **217** (Scheme 36). For this purpose **65** was condensed with hydroxylamine hydrochloride to give the corresponding pyrimidine-*N*-oxide **216**.[32] This intermediate was heated with acetic acid anhydride to undergo a Boekelheide rearrangement delivering acetoxymethyl-substituted compound **217** in 55% yield.[21] The photoirradiation of 4-styryl bipyridine derivative **108** in the presence of iodine and propylene oxide with a 150 W medium pressure lamp afforded pyridin-2-yl-substituted benzoisoquinoline **218** in 82% yield.[17] These examples demonstrate the potential of pyridin-4-yl nonaflates and their subsequent products for further elaboration to more complex heterocyclic compounds.

The 4-acetylphenyl-substituted pyridine and bipyridine derivatives **99**, **101**, **102** and **107** (Table 7) were synthesized to have a fast access to C_3-symmetric star-shaped molecules. These are generated by an acid-promoted cyclocondensation reaction of three acetyl groups to generate a new central benzene ring. The reaction conditions involved $SiCl_4$ in the presence of ethanol, a convenient way to generate dry hydrochloric acid.[33] By this method the compounds **219**-**222** were obtained in good to excellent yields, but it should be mentioned that this protocol did not work in all cases investigated (Scheme 37). Precipitating intermediates probably prevent full conversion of the compounds. Solutions of star-shaped molecules **219**-**222** were studied by STM (scanning tunnel microscopy) on highly ordered pyrolytic graphite and they showed quite

interesting two-dimensional self-assembly (Figure 2). The arrangement of molecules at the solution surface interface is strongly dependent on the substitution pattern of the compounds.[18]



Scheme 36. Reaction of pyridin-4-yl-substituted enamide **65** with hydroxylamine hydrochloride to **216**, rearrangement to pyridine/pyrimidine hybrid **217** and photolytic transformation of bipyridine derivative **108** into benzoisoquinoline **218**.



Scheme 37. Cyclocondensation of 4-acetylphenyl-substituted pyridine and bipyridine derivatives to C_3-symmetric star-shaped pyridine derivatives **219**-**222**.

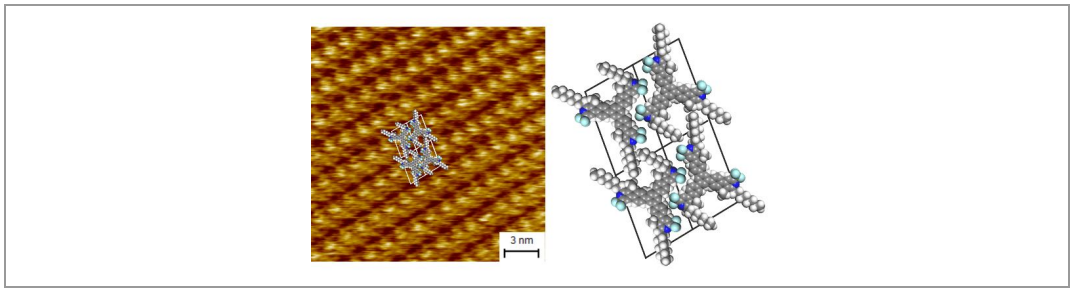


Figure 2. Scanning tunneling microscopy height image at the interface between a 1-phenyloctane solution of compound **221** and the basal plane of highly oriented pyrolytic graphite showing a lamellae arrangement and the proposed detailed molecular model (taken from ref. 18).

10. Conclusions

The serendipitously discovered three-component reaction of alkoxyallenes, nitriles and carboxylic acids led to a new and exciting direction of our research. The scope of the reaction is extremely broad and the efficacy is generally good, furnishing an extensive library of highly substituted pyridin-4-ol derivatives or their corresponding pyridin-4-yl nonaflates. Our approach impressively confirms the advantages of multi-component reactions.[34] All types of 2,6-disubstituted pyridine derivatives are available and the different oxygen functionalities at C-3 and C-4 permit regioselective substitution reactions in these positions. Furthermore, C-5 can be activated by iodination thus also allowing coupling reactions in this position. All kinds of palladium-catalyzed reactions have been examined and proved to be well suited to access specifically substituted pyridine derivatives. Sonogashira reactions followed by cyclizations allowed a new and flexible route to furo[2,3-c]pyridines and furo[3,2-c]pyridines. The impressive capability of our flexible approach to highly substituted pyridine derivatives was demonstrated by the synthesis of a series of oligo(thiophen-2-yl)-substituted pyridines, with compounds such as **183** with five thiophene groups or compound **184** with nine thiophene units as highlights. In general, our developed methods allow a very rapid entry to extended π-systems as shown by the synthesis of symmetrical compounds such as **123** or **222**. It should also be noted that the crucial enamide intermediates of type **L** can also undergo condensation reactions with ammonia sources or with hydroxylamine hydrochloride to deliver highly substituted pyrimidine derivatives.[32,35] Alternatively, enamides prepared from TMSE-substituted allenes, nitriles and carboxylic acids were converted into functionalized oxazole derivatives by treatment with TFA.[36] Furthermore, the condensation of enamides of type **L** to pyridinol derivatives caused the search for an access to enamides by alternative routes that also allowed the preparation of specifically substituted pyridine, bipyridine and terpyridine derivatives.[37] In summary, functionalized enamides obtained by the unexpected three-component reaction are an excellent starting point to approach heterocyclic compounds of high diversity.

List of abbreviations

DCE = 1,2-dichloroethane
DCM = dichloromethane
DMAP = 4-(*N*,*N*-dimethylamino)pyridine
DMF = dimethylformamide
DPPF = 1,1'-bis(diphenylphosphino)ferrocene
DPPP = 1,3-bis(diphenylphosphino)propane
MW = microwave
NBS = *N*-bromosuccinimide
NfF = nonafluorobutanesulfonyl fluoride
Nf_2O = nonafluorobutanesulfonic acid anhydride
TFA = trifluoroacetic acid
Tf_2O = trifluoromethanesulfonic acid anhydride
TIPS = tris(*i*-propyl)silyl
TMSE = (2-trimethylsilyl)ethoxy
TMSOTf = trimethylsilyl trifluoromethanesulfonate
Tol = toluene

XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

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