Synthesis of Benzenes from Pyridines via N to C switch

Aífe Conboy and Michael F. Greaney*

ABSTRACT: The transformation of pyridines into benzene derivatives is described, using a one-pot ANRORC process with soft nucleophiles such as malonate. Triflic anhydride activates the pyridine to ANRORC synthesis of a carbocyclic β-aminoester intermediate, which aromatizes on heating. The reaction has been exemplified with a room temperature protocol, along with direct syntheses of biologically active, tertiary-alkylated and isotopically-labelled benzoates.

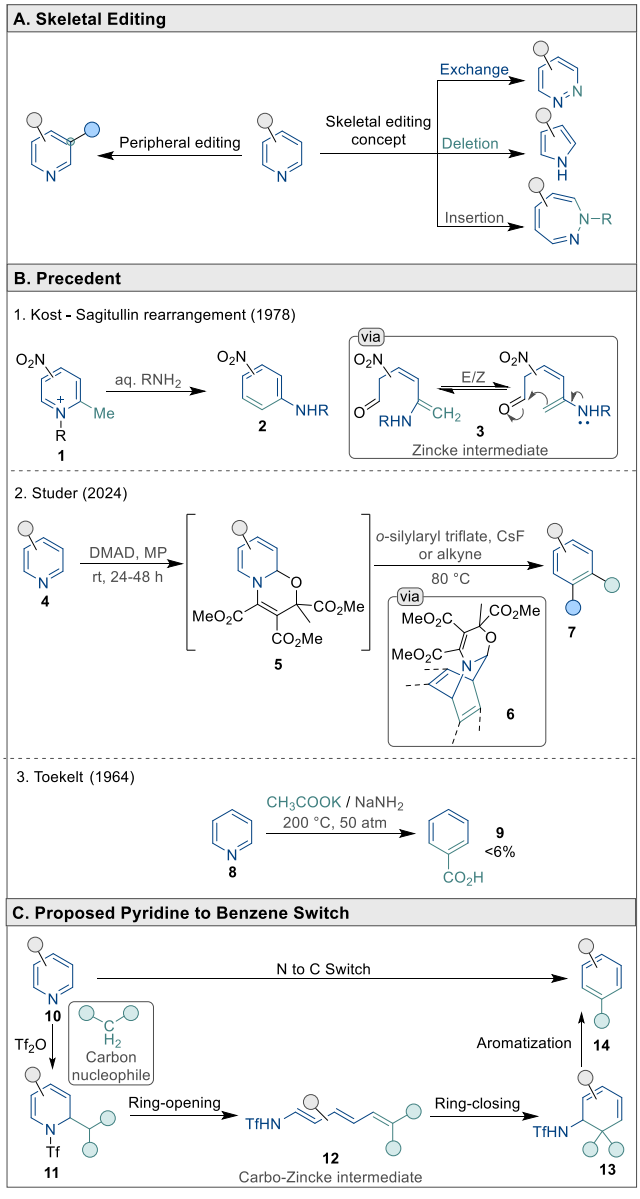
The exchange of arene carbon atoms with nitrogen atoms, and *vice versa*, has recently come into focus as a powerful approach to alter molecular structure at a deep-seated level. This skeletal-editing concept[1] has been demonstrated in a number of modes (*e.g.* single atom exchange, atom deletion and insertion) for skeletal alterations of systems such as indoles, indazoles, pyrimidines, and quinolines.[2,3] These challenging disconnections have stimulated new retrosynthetic thinking, with immediate applications to scaffold-hopping in medicinal chemistry and isotope-labelling.[4]

The importance of pyridines and their derivatives in pharmaceuticals makes them prime candidates for skeletal editing. Recently, the groups of Burns and Levin explored this idea through the conversion of aryl azides to pyridines *via* a nitrene approach.[5] The converse reaction, making benzenes from pyridines, represents a potentially powerful interchange that is challenging for current synthetic methods. The chemistries of benzene and the π-deficient pyridine heterocycle are highly contrasting, creating the possibility of applying distinct pyridine functionalizations to access otherwise difficult to make benzenes, *via* an N – C switch. Further, the central role occupied by pyridines in drug discovery campaigns makes study and quantification of their pharmacology highly important. A precision skeletal edit of biologically active pyridines through N / C switch would create opportunities to rapidly assess SAR on functionalized molecules.

Pyridine to benzene rearrangements are known in the literature primarily through Zincke pyridinium chemistry.[6] The Russian school of Kost and Sagitullin established the rearrangement of 2-methylpyridinium salts **1** to anilines **2** in the 1970s (Scheme 1B) under basic conditions, *via* the Zincke intermediate **3**.[7,8] Work from Kano and co-workers has described a modern variation of this approach under milder conditions, manipulating streptocyanine intermediates.[9] Very recently, Studer and co-workers described a novel approach to the pyridine N/C switch using cycloaddition chemistry.[10] Formation of the dihydropyridine **5** sets up a Diels-Alder reaction (intermediate **6**), with subsequent retro-cycloaddition affording the benzenes **7** (Scheme 1B). Other approaches include direct titanium alkylidyne insertion to pyridine to make *t*-butylbenzenes,[11] and a recent disclosure from Sorensen and co-workers on addition of sulfur ylides to pyridine *N*-oxides.[12]

We were interested in developing a general pyridine / benzene switch that would not rely on rearrangement of a pre-existing carbon substituent. Instead, a nucleophilic addition ring-opening ring closing (ANRORC) process would offer significant advantages in terms of substrate scope and versatility of the carbon nucleophile.

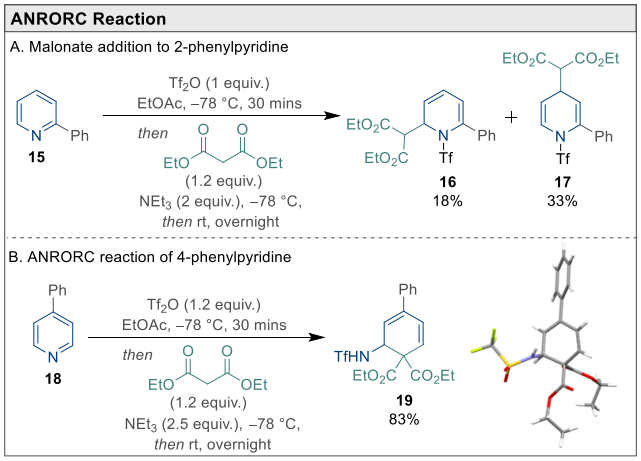
Scheme 1. Background and Proposal.



Such a direct transformation was reported in 1964 by Schmerling and Toekelt, who described very low yields (< 6%) of benzoic acid on treatment of pyridine with KOAc and $NaNH_2$ at 200 °C at 50 atm pressure (Scheme 1B).[13] While these conditions are extreme, they provide historical precedent for a direct ANRORC approach to the problem. We planned the sequence shown in Scheme 1C, whereby intermolecular addition of an acidic methylene component would facilitate the entire ANRORC process via two deprotonation steps. The resultant carbocycle **13** is at the arene oxidation level, and could potentially undergo aromatization through elimination, depending on our choice of nucleophile structure. Recent work from McNally, Paton and co-workers has exploited the facility of triflic anhydride for *in situ* Zincke imine generation from pyridines under mild conditions,[14] and we have employed this method for the Pd-catalyzed arylation of pyridines.[15] Accordingly, we envisaged that direct triflation of pyridine and addition of a compatible carbon nucleophile could access the carbo- Zincke analog **12**, with subsequent recyclization and aromatization.

We began by examining diethylmalonate as the nucleophile with 2-phenylpyridine and 4-phenylpyridine substrates.[16] Treatment with Tf_2O at -78 °C, followed by malonate / Et_3N and warming to room temperature, gave a mixture of the two simple addition products **16** and **17** for 2-phenylpyridine, with the undesired 4-substituted dihydropyridine **17** as the major product (Scheme 2A). 4-Phenylpyridine, by contrast, successfully underwent the desired ANRORC reaction to give the carbocyclic product **19** in an initial 52% yield (Scheme 2B). Compound **19** could be purified by column chromatography and the structure was confirmed by X-ray analysis. Further optimizations (see Supporting Information for full details) led to an enhanced yield of 83%, using triflic anhydride, malonate and Et_3N in a 1.2: 1.2: 2.5 ratio relative to the pyridine substrate.

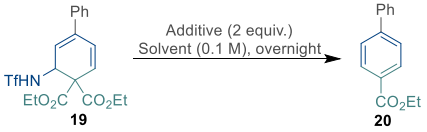
Scheme 2. Initial ANRORC Observations



With an efficient ANRORC process in hand, we then investigated the aromatization step. This could in principle proceed via deprotonation of the triflamide group in **19** with a weak base, and subsequent attack at the adjacent ester group. Ejection of the TfNHCOEt moiety would then give the desired arene product. Initially, we simply heated the isolated carbocycle **19** to reflux with Et_3N and were pleased to observe small amounts of the benzoate **20**, validating the approach (Table 1 entry 1). Moving to higher temperatures in DMF gave better conversions, and a reaction temperature of 140 °C successfully yielded the benzoate product **20** in high yield (Table 1 entry 7).

We could put the two processes together in a one pot operation by performing a solvent change to DMF upon completion of the ANRORC process and heating the reaction for 3 hours to give benzoate **20** in 50% yield (Table 2 entry 1). Further optimization established K_2CO_3 was more effective in the second step for the one pot procedure, affording benzoate **20** in 71% overall yield (Table 2 entry 7).

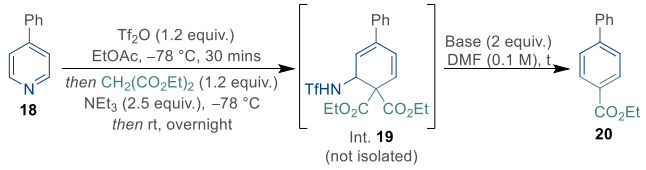
Table 1. Aromatization Optimization



Entry	Solvent	Additive	Temp. (°C)	Conversion (%)[a]	Yield (%)[a]
1	EtOAc	NEt_3	80	15	2
2	EtOAc	DBU	80	66	9
3	Toluene	NEt_3	100	27	11
4	DMF	NEt_3	100	81	13
5	DMF	TsOH[b]	100	18	-
6	DMF	DBU	100	93	-
7	DMF	NEt_3	140	100	80
8	Mesitylene	NEt_3	140	67[c]	36[c]
9	DMF	K_2CO_3	140	100	79
10	DMF	DBU	140	100	69

Reactions were performed on a 0.2 mmol scale. [a]Determined by ^{1}H NMR using mesitylene as an internal standard. [b]20 mol%. [c]1,3,5-Trimethoxybenzene was used as an internal standard.

Table 2. Optimization of a One-Pot Protocol

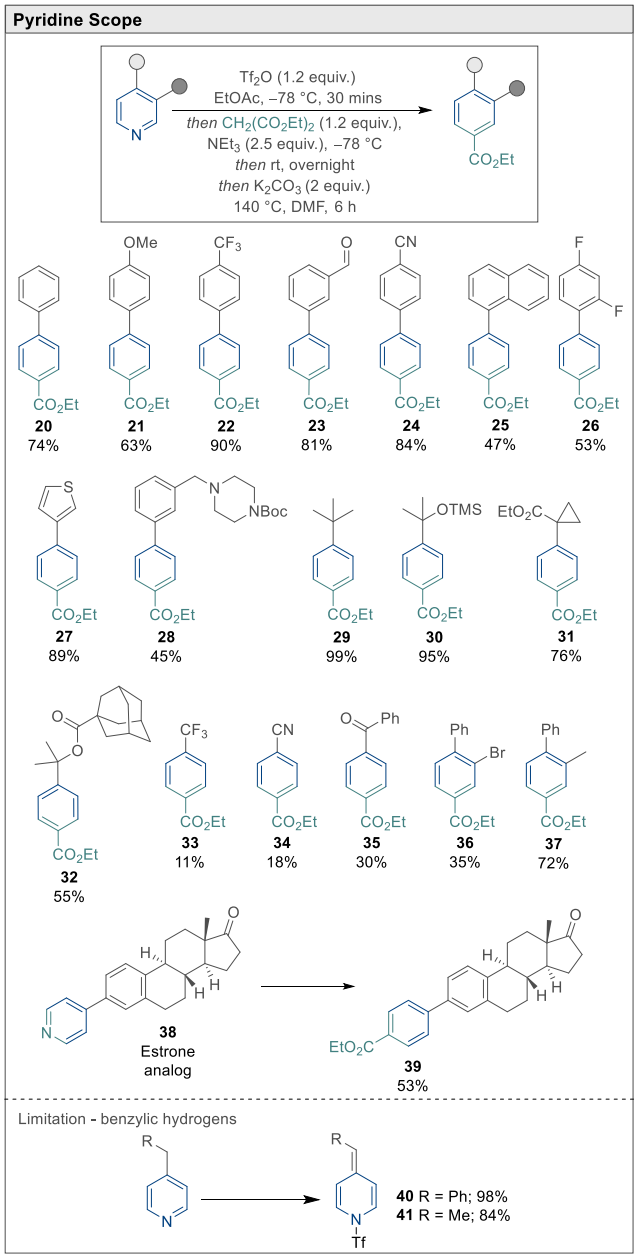


Entry	Base	Time (h)	Int. (%)[a]	Yield (%)[a]
1	NEt_3	3	-	50
2	-	3	66	38
3	DIPEA	3	-	60
4	Collidine	3	3	57
5	Cs_2CO_3	3	17	60
6	K_2CO_3	3	18	56
7	K_2CO_3	6	-	71

Reactions were performed on a 0.2 mmol scale. [a]Determined by ^{1}H NMR using mesitylene as an internal standard.

With a one-pot process in hand, we were pleased to find the reaction was general for a wide variety of 4-arylpyridine substrates (Scheme 3). Functional group tolerance was good, including aldehyde, tertiary amine substitution, and a thiophene heteroarene, with yields generally being good to excellent (**21** – **28**).

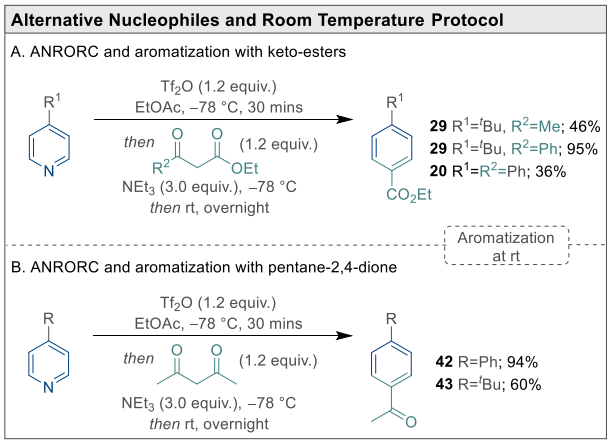
Scheme 3. Pyridine Scope



Reactions were performed on a 0.2 mmol scale. Isolated yields after chromatographic purification.

Turning to alkyl substitution, we were aware that benzylic hydrogen atoms at the 4-position could be problematic, due to rapid elimination to the dihydropyridine on triflation.[17] This proved to be the case, with, for example, compound **41** being formed from 4-ethylpyridine and undergoing no further reaction. Tertiary alkyl substrates, however, proved very effective in the reaction. Both the *t*-butylpyridine and the protected tertiary alcohol derivative were transformed in near quantitative yield to the benzoates **29** and **30**. The adamantyl ester and cyclopropyl compounds were likewise effectively converted to arenes **31** and **32**. Direct substitution of electron withdrawing groups at the 4-position such as CF_3, CN, and PhCO, however, were very de-activating in the reaction. Low yields of the arene products could be obtained (**33** – **35**), but with substantial starting pyridines remaining. Additional 3-substitution could be tolerated, with the bromo and methyl compounds affording the tri-substituted arene products **36** and **37**. See supporting information for further details of unsuccessful substrates. We could demonstrate the nitrogen deletion for the steroidal pyridine **38**, a biologically active estrone analog, forming the arene **39** in 53% yield. Pyridine-estrane derivatives such as **38** display inhibitory activity against cytochrome P450 $_1B_1$, an important therapeutic target, and the ability to perform an N-C switch on such substrates has the potential to enable rapid SAR studies.[18]

Scheme 4. Use of Alternative 1,3-Dicarbonyl Nucleophiles

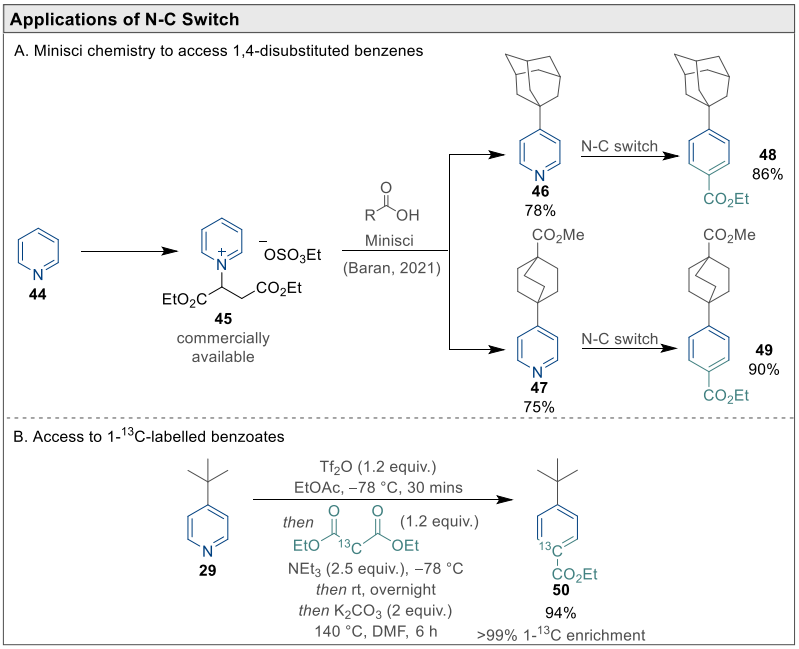


Keto-ester alternatives to malonate were investigated as nucleophiles, with ethyl acetoacetate and ethyl benzoylacetate successfully undergoing ANRORC reaction and aromatization in good to excellent yield (Scheme 4A). Significantly, the aromatization step was much more facile in the case of ketone elimination compared to ester, proceeding at room temperature. The side-product *N*-triflylbenzamide could be isolated from the preparation of **29** using ethyl benzoylacetate, supporting the proposed elimination pathway for aromatization (see Supporting Information for further discussion of this step). Extending this protocol to pentane-2,4-dione gave the acetophenone derivatives **42** and **43** in good yield, *via* the simple expedient of warming to room temperature following triflation (Scheme 4B).

We were interested in using the nitrogen carbon switch to harness some orthogonal aspects of pyridine and benzene reactivity. Using functionalization chemistry distinct to pyridines, we could in principle make benzenes that would be difficult or impossible to directly access through conventional aromatic chemistry. To illustrate this concept we applied a recent Minisci alkylation developed by Baran and co-workers, which uses a succinate activating group to achieve highly selective pyridine 4-substitution, to the synthesis of tertiary-alkylated pyridines **46** and **47 (**Scheme 5A).[19] Both were excellent substrates for the N-C switch, affording benzenes **48** and **49** in high yield.

Finally, the formal swapping of a nitrogen for a carbon atom in an aromatic system creates the possibility for installation of an isotopic label, essential tools in diverse fields such as metabolism, kinetics, and structural characterization.[4] The synthesis of *ipso* ^{13}C-labelled benzenes is traditionally accomplished via laborious multi-step routes, making these labelled compounds expensive. A recent report from Levin and co-workers described an expedient route to 1-^{13}C-labelled phenols

Scheme 5. Pyridine Functionalization and N-C Switch and Labelling Studies



through lithium-halogen exchange of 1,4-dibromo-1,5-pentadiene substrates, followed by [5+1] cyclization with ^{13}C-labelled dibenzyl carbonate.[4a] We envisioned that our protocol could be applied directly for the provision of 1-^{13}C-labelled benzoates. Using commercially available diethyl malonate-2-^{13}C in the reaction, we were able to synthesize the labelled benzoate **50** with >99% incorporation in a single operation from *t*-butylpyridine (Scheme 5B).

In conclusion, we have developed an N to C switch that converts 4-substituted pyridines into benzenes using ANRORC chemistry. This protocol has been successfully applied to a range of 4-aryl and alkyl substituted pyridines, including 3,4-disubstituted and biologically active examples, with broad functional group tolerance demonstrated. The synthetic utility of the process has been further exemplified through the provision of otherwise difficult to prepare benzene products, including 1-^{13}C-labelled benzoates.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge at http://pubs.acs.org. Synthetic methods, optimization studies, preparative procedures, characterization data, and copies of ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra are available in the Supplementary Information. Crystallographic data are available from the Cambridge Crystallographic Data Centre for CCDC deposition number 2327936.

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ACKNOWLEDGMENTS

We acknowledge the EPSRC for funding a studentship for AC (Centre for Doctoral Training in Integrated Catalysis, grant EP/023755/1). Dr George Whitehead and Dr Avantika Hasija (University of Manchester) are thanked for X-Ray crystallographic analysis.

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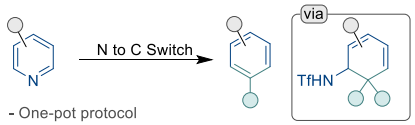

- One-pot protocol
- Up to 99% yield
- Pyridine to benzene switch via ANRORC