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Dual Heterogeneous Catalysis for a Regioselective Three-Component Synthesis of Bi- and Tri(hetero)arylpyridines

Christophe Allais,[a] Frédéric Liéby-Muller,[a] Thierry Constantieux,[a,*] and Jean Rodriguez[a,*]

[a] Aix-Marseille Université, UMR CNRS 7313 iSm2, Campus Saint Jérôme, service 531, 13397 Marseille, France
Fax: (+33)-(0)491-289-187; phone: (+33)-(0)491-288-933; e-mail: thierry.constantieux@univ-amu.fr or jean.rodriguez@univ-amu.fr

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Abstract: We have designed a new, user-friendly oxidative dual heterogeneous catalytic system capable of promoting polysubstituted pyridines as unique products from simple activated Michael acceptors, 1,3-dicarbonyls and ammonium acetate. This metal-free environmentally-respectful and totally regioselective domino reaction proved to be a great strategy to access bi- and triaryl-type pyridines as well as challenging bi- and triheteroaryl-type pyridines in a single operation.

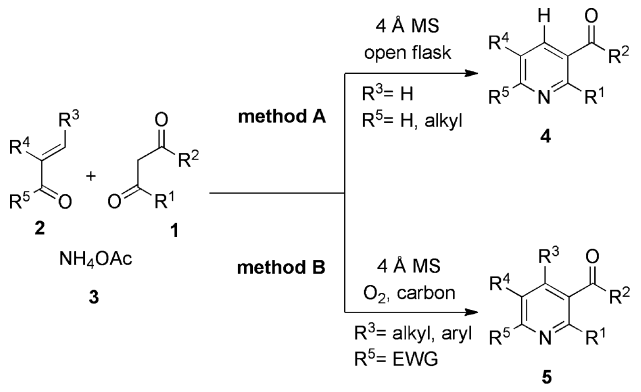
Keywords: biaryls; 1,3-/1,2-dicarbonyls; dual heterogeneous catalysis; multicomponent recations; pyridines

Introduction

Since its discovery 166 years ago,[1] pyridine has become one of the most studied nitrogen-containing heterocycles. This important building block is found in numerous natural biological systems such as vitamin B6 or nicotine. Pyridines and their derivatives have gained considerable attention due to their central roles in the biological activity of natural substances, as well as in the design of therapeutic agents.[2] Moreover, the pyridine ring is recurrent in numerous drugs with a large panel of bioactivities.[3] These scaffolds are also of widespread interest in agrochemistry,[4] coordination[5] and supramolecular[6] chemistry, material sciences,[7] polymers,[8] catalysis,[9] organocatalysis[10] and synthesis of natural products.[11] Because of this large spectrum of fascinating applications, the selective synthesis of highly functionalized pyridine derivatives remains an attractive challenge in modern synthetic organic chemistry.[12] Currently the metal-catalyzed [2+2+2] cycloisomerization of alkynes with nitriles largely leads the way for the synthesis of pyridines.[13] However, despite recent spectacular advances,[14] the low availability of some catalysts and substrates associated with the lack of regioselectivity[15] constitute major drawbacks of this methodology. Alternatively, bimolecular or multicomponent metal-free synthetic methods based on the direct condensation of carbonyl compounds with a source of ammonia constitute an interesting complement but still suffer from substrate limitations,[16] require an oxidative agent,[17] or an elimination step.[18] In this context, the development of new one-pot regiodefined syntheses of highly substituted pyridine nuclei from simple starting materials is of significant value.

For several years, our group has been strongly involved in the development of new molecular sieves (MS)-promoted domino[19] multicomponent reactions (MCRs)[20] providing high molecular complexity and diversity[21] while combining economical[22] and environmental aspects,[23] to reach, in a stereoselective manner, polyfunctionalized nitrogen-containing heterocycles[24] from 1,3-dicarbonyls.[25] Among these methodologies, we recently reported preliminary results on the regioselective metal-free three-component access to pyridine derivatives (Scheme 1).[26]

This flexible environmentally-friendly strategy involved the direct open flask condensation of 1,3-dicarbonyls **1** with Michael acceptors **2** and ammonium acetate **3** under heterogeneous catalysis by 4 Å MS in its "classical conditions" (Scheme 1, method A). More recently, we successfully extended this reaction to the first use of β,γ-unsaturated-α-keto carbonyl derivatives as Michael acceptors in an MCR.[27] The success of this transformation relied on the development of "dual heterogeneous catalysis", i.e., combination of molecular sieves with activated carbon under an oxygen atmosphere, allowing the incorporation of great molecular diversity at strategic C-2[28] and C-4[29] positions (Scheme 1, method B).



Scheme 1. 4 Å MS-promoted three-component reaction (3-CR) synthesis of polysubstituted pyridines.

The purpose of this article is to present how this methodology proved to be a great strategy to access bi- and triaryl-type pyridines as well as challenging bi- and triheteroaryl-type pyridines in a single operation. Currently, metallo-catalyzed cross-coupling[30] and oxidative C–H functionalization[31] reactions lead the way in the synthesis of aryl-substituted pyridines. However, the use of metal catalysts combined with the production of halogenated waste is not compatible with sustainable chemistry, and regioselectivity in direct C–H arylation is not always satisfying.[32] Consequently, we strongly thought that our methodology may be a robust complementary synthetic route to access biaryl- or triaryl-type pyridines in a single operation, from easily accessible substrates, without the use of any metal.

Results and Discussion

Application of "Dual Heterogeneous Catalysis" to the Synthesis of Bi- and Triaryl-Type Pyridines 5

We focused our efforts on the synthesis of 4-arylpyridines that are less accessible from metal-catalyzed protocols. For this purpose, we prepared (see Figure 1 and Experimental Section)[33–35] a series of β,γ-unsaturated-α-keto esters **6**, α-ketophosphonate **7** and α-keto amides **8**[36] bearing an aryl substituent at the terminal position.

A library of 4-arylpyridines **5** was synthesized between these activated Michael acceptors and various 1,3-dicarbonyl derivatives **1** (Figure 1). The efficiency of this method to access such challenging biaryl derivatives is clearly demonstrated by the results reported in Figure 2. Thus, 4-phenyl-substituted pyridine **5a** was efficiently formed from α-keto ester **6a** and methyl acetoacetate (**1a**). Gratifyingly, this metal-free transformation proved to be very tolerant in regard to the substitution on the phenyl ring. Indeed, both electron-donating (4-MeO, **5b**) and electron-withdrawing

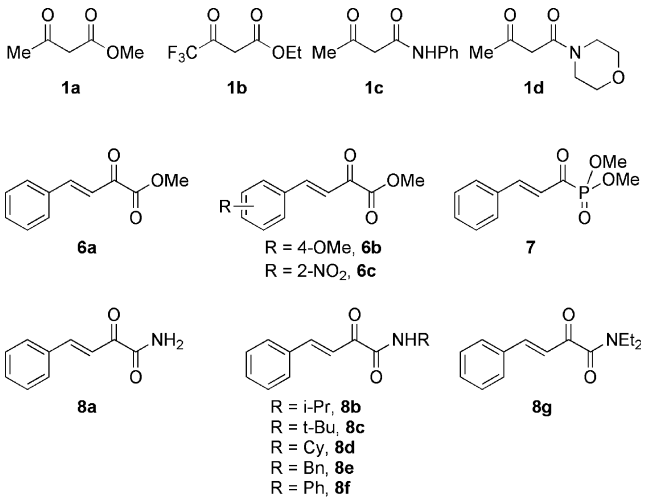


Figure 1. 1,3-Dicarbonyls **1** and γ-arylated activated Michael acceptors **6–8** used in the MCRs.

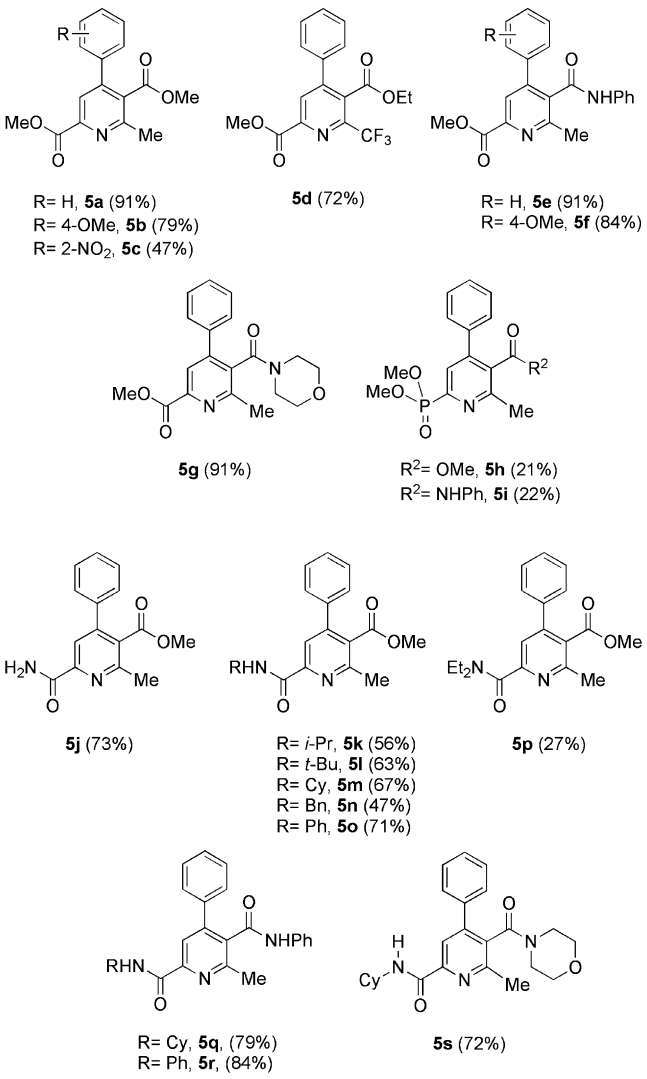


Figure 2. 4-Arylpyridines obtained from the 3-CR.

(2-NO_2, **5c**) functionalities were tolerated in the reaction although a moderate yield was obtained for **5c**, presumably due the *ortho*-steric hindrance provided by the nitro group. 2-Trifluoromethylated biarylpyridine **5d** was also isolated in good yield when **1b** was the Michael donor. 4-Arylnicotinamide derivatives such as **5e** and **5f** were successfully obtained from secondary β-keto amide **1c** and β,γ-unsaturated-α-keto esters **6a** and **6b**, respectively. Finally, the tertiary amide **1d** gave **5g** in excellent yield. The use of γ-phenyl-β,γ-unsaturated α-ketophosphonate **7** was not as successful as expected, and the corresponding phosphorus-containing 4-phenylpyridines **5h** and **5i** were obtained from methyl acetoacetate (**1a**) and acetoacetanilide (**1c**) with a yield that does not exceed 22%. Finally, we used β,γ-unsaturated α-keto amides **8** in this MCR, allowing the rapid generation of an important panoply of pyridines **5j–s** bearing an amide function on position 2, known as picolinamide derivatives. In addition to their great biological significance, these pyridine scaffolds are of widespread interest in coordination chemistry,[37] catalysis[9b] and organocatalysis.[10a,c] Furthermore, the application of such activated Michael acceptors in this transformation increased the functional diversity introduced at the C-2 position of the pyridine ring. In combination with methyl acetoacetate (**1a**), substrates **8a–g** allowed the formation of 4-phenylpicolinamides bearing primary **5j** or secondary **5k–o** amide functionalities. The yield significantly dropped when tertiary α-keto amide **8g** reacted with **1a** to form pyridine **5p**, highlighting the dramatic role of the NH moiety in the activation process. Finally, this methodology proved to be a short and efficient way to polyfunctionalized picolinamide-nicotinamide hybrid derivatives **5q–s** in good yields from secondary or tertiary β-keto amides **1c** and **1d**.

To further demonstrate the high synthetic potential of this methodology, we prepared a series of triaryl-type pyridines **5t–x**. When 1,3-dicarbonyl substrates **1** and activated Michael acceptors **6** or **8** were judiciously chosen, triaryl products were formed by construction of the central pyridine ring (Figure 3). Indeed, α-keto esters **6** could be combined with β-keto ester **1e** or β-keto amide **1f** to lead regioselectively to triarylpyridines **5t** and **5u** in 70% and 92% yields, respectively. Additionally, when α-keto amides **8** were used, triaryl-type picolinamide-nicotinamide hybrid derivatives **5v–x** were easily accessed in synthetically useful yields starting from **1e** and **1f**.

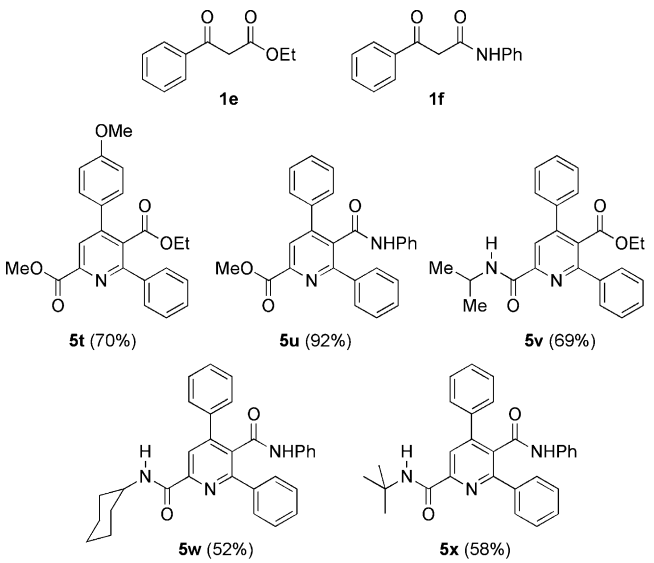
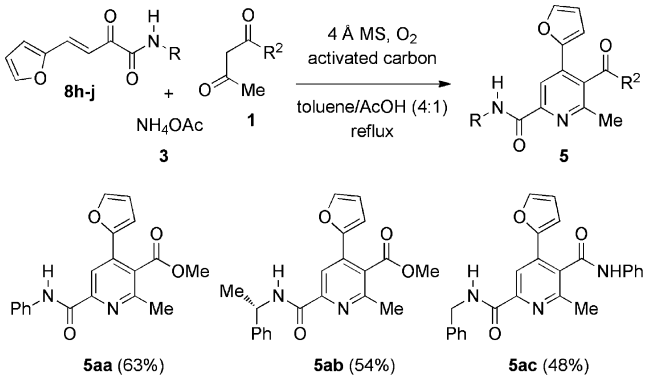


Figure 3. 2,4-Biarylpyridines obtained from β-keto ester **1e** or β-keto amide **1f**.

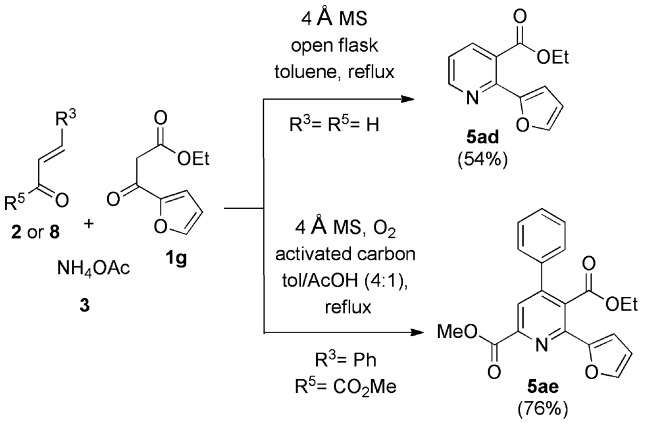
Application of Optimized "Dual Heterogeneous Catalysis" to the Synthesis of Bi- and Triheteroaryl-Type Pyridines 5

Heteroaromatic biaryl compounds are of great interest in many areas including pharmaceuticals, agrochemicals and material sciences and have been encountered in some natural products. Consequently, the straightforward access to these scaffolds remains a great challenge in modern organic synthesis.[38] In this field, cross-coupling reactions between heteroaryl halides and metallated heteroaryl substrates have been described[39] and C–H bond functionalization has been studied over the past few years.[40] However, the currently preferred synthetic route to biheteroaryl compounds is the selective metal-catalyzed dehydrogenative cross-coupling reaction between heteroarenes, which avoids formation of halogen-containing waste.[41] Nonetheless, in the particular case of pyridines, we feel this elegant transformation still suffers from several drawbacks: (i) use of transition metal catalysts does not completely fulfil sustainable chemistry demands, (ii) electron-poor pyridine *N*-oxides have to be used in this process, requiring an additional deprotection step, (iii) several equivalents of pyridine *N*-oxides are usually involved; and (iv) only the activated 2-position of the pyridine ring can be substituted by another heterocycle. We thus envisioned extending the three-component reaction to the synthesis of valuable bi- and triheteroaryl-type pyridines to answer this challenge and provide a viable metal-free alternative.

To reach this goal, heteroaryl substituents have to be introduced in the correct position either in the substrate of the acceptor structure for biheteroaryl targets, or in both reactants for triheteroaryl products.[42] With the appropriate substrates in hand, we first studied the synthesis of 4-heteroaryl-substituted pyridines that are not accessible from dehydrogenative cross-coupling transformations. We thus used furan-containing α-keto amides **8h–j** in the user-friendly metal-free MCR (Scheme 2).



Scheme 2. 4-Furylpyridines **5aa–ac** obtained from the 3-CR.

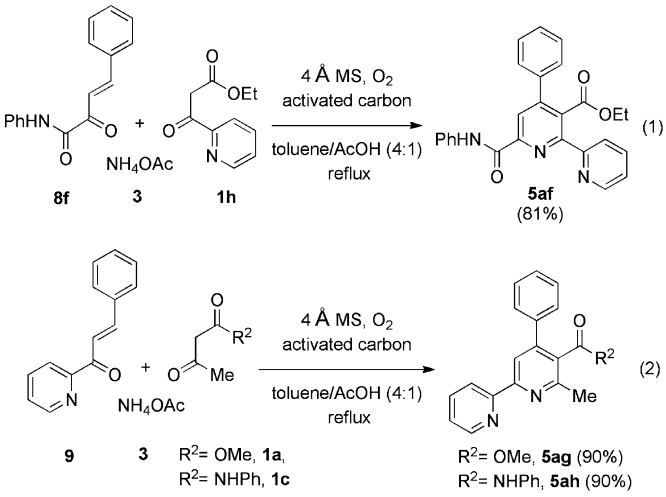


Scheme 3. Synthesis of 2-furylpyridines under "classical" and "dual heterogeneous catalysis" conditions.

Gratifyingly, the totally regioselective process allowed the formation of pyridines **5aa–ac** bearing a furyl substituent at the C-4 position in 48% to 63% yield. Once again, the sequence tolerated both β-keto ester **1a** (R^2 = OMe) and β-keto amide **1c** (R^2 = NHPh).

Efforts were also made to rapidly synthesize 2-heteroaryl-substituted pyridines by adequately choosing the 1,3-dicarbonyl derivative **1** or the Michael acceptors **2** and **8**. Thus, "classical conditions" were only suitable for the synthesis of 2-furylpyridine **5ad** from β-keto ester **1g** and β-unsubstituted enal **2**, whereas it was necessary to apply "dual heterogeneous catalysis" when starting from pyruvate derivative **8** for the synthesis of pyridine **5ae** (Scheme 3).

Stimulated by these results, we then extended the functional diversity of the methodology to several other heterocycles starting with the metal-free synthesis of 2,2′-bipyridines. To elaborate these extremely useful scaffolds, notably in organometallic chemistry,[5a,43] two synthetic routes proved to be highly efficient (Scheme 4).



Scheme 4. Synthetic routes to 2,2′-bipyridines from this 3-CR.

The first one was the construction of the pyridine ring by using β-keto ester **1h** [Scheme 4, Eq. (1)]. Under the optimized conditions, we were pleased to obtain the 2,2′-bipyridine **5af** from activated Michael acceptor **8f** in a satisfactory 81% yield. The second strategy involved the β,γ-unsaturated α-ketopyridine **9** as reaction partner in combination with β-keto ester **1a** or β-keto amide **1c** [Scheme 4, Eq. (2)]. These transformations provided 2-pyridinylpyridines **5ag** and **5ah** in excellent yields, supporting that nitrogen-containing heterocycles could be great activators of the Michael acceptor.

Rewardingly, other heterofunctionalized Michael acceptors **10a** and **10b** provided access to a new class of heterocyclic biaryl products by this methodology. Thus, 2-imidazoyl-4-arylpyridines **5ai**–**ak** were synthesized in a single operation from methyl acetoacetate (**1a**) and acetoacetanilide (**1c**) (Figure 4).

To further demonstrate the versatility of this metal-free MCR in biheteroaryl synthesis while highlighting the remarkable functional diversity at the C-2 posi-

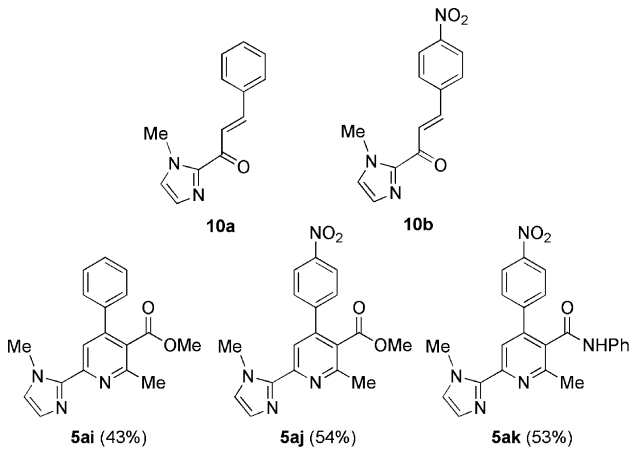
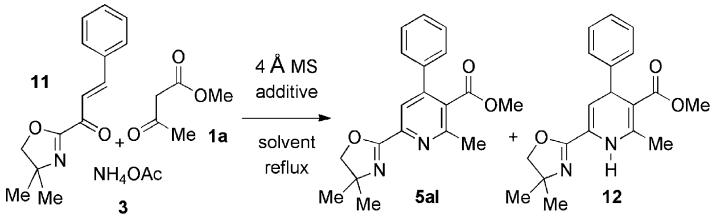


Figure 4. 2-Imidazoylpyridines **5ai–5ak** obtained from the metal-free 3-CR.

Table 1. Optimization of experimental conditions to access 2-oxazoline-pyridine **5al**.



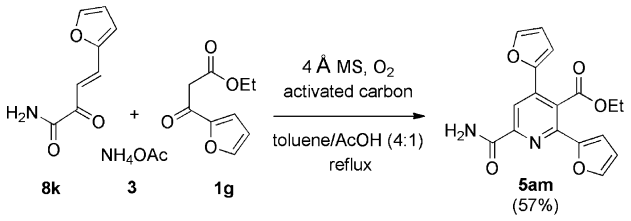
Entry	Solvent	Additive	Atmosphere[a]	Time [h]	**5al** [%][b]	**12** [%][b]
1	toluene/AcOH (4/1)	act. C[c]	O_2	48	–	–
2	toluene	–	air	16	8	50
3	toluene	act. C[c]	O_2	29	47	14
4	toluene	MnO_2[d]	air	6	57	–

[a] Reaction conducted under air or oxygen atmosphere.
[b] Yield after purification by flash chromatography on silica gel.
[c] Activated carbon 50% weight.
[d] One equivalent.

tion of the pyridine ring, we successfully extended the process to the use of α-ketooxazoline **11**. However, a slight improvement of the procedure was necessary because of the instability of the oxazoline ring under acidic conditions (Table 1).

Indeed, in the presence of acetic acid, neither the pyridine mono-oxazoline **5al** nor the corresponding dihydropyridine **12** were observed by NMR analysis (Table 1, entry 1). We then switched to the "classical conditions" of the MCR that allowed the formation of **12** in 50% yield whereas pyridine **5al** was obtained with a poor 8% yield (entry 2). When optimized "dual heterogeneous catalysis" conditions were employed in this transformation without acetic acid as co-solvent (i.e., activated carbon 50% weight under oxygen atmosphere), pyridine **5al** was isolated as the major product in a mixture with a non-negligible amount of corresponding DHP (Entry 3). The yield of this 2-oxazoline pyridine **5al** was ultimately increased to 57% without any trace of **12** when one equivalent of manganese dioxide was added to the mixture of the three partners in refluxing toluene (entry 4). Moreover the reaction time was considerably shortened under these optimized conditions. Despite the moderate yield, a quick access to this type of pyridine mono-oxazoline is not trivial since they are useful ligands commonly synthesized in several steps. Pyridine bis-oxazoline (PYBOX) is certainly the most popular class in this ligand family and is widely involved in organometallic chemistry.[44] Notably, various other ligands with a similar structure to **5al** have been recently utilized in highly enantioselective Fujiwara–Moritani annelations, but were synthesized in six steps.[45]

Finally, the challenging metal-free construction of heterocyclic triaryl compounds was also possible through this versatile methodology as demonstrated



Scheme 5. Synthesis of 2,4-triheteroaryl-type picolinamide **5am** from this 3-CR.

by the formation of pyridine **5am** (Scheme 5). When a mixture of β-keto ester **1g**, β,γ-unsaturated α-keto amide **8k** and ammonium acetate (**3a**) was submitted to our optimized "dual heterogeneous catalysis" conditions, 2,4-bisfuryl-picolinamide **5am** was obtained in a single operation in 57% yield. This result further demonstrated the high synthetic potential of this regioselective and user-friendly methodology.

Conclusions

We have developed a new, metal-free, three-component reaction from 1,3-dicarbonyl derivatives, Michael acceptors and ammonium acetate, allowing the access to polyfunctionalized pyridines with a total control of regioselectivity. This environmentally-friendly approach is in accordance with many stringent criteria of sustainable chemistry such as step- and atom-economy. The transformation proved to be extremely tolerant in regard to reaction partners, leading either to pyridines from β-keto esters or to nicotinamide derivatives from β-keto amides and to picolinamides with α-keto amides.

We clearly demonstrated the high potential of this strategy with the straightforward synthesis of bi- and tri(hetero)aryl-type pyridines without the use of any metal-based catalyst. This provides access to new and potentially useful ligands in coordination chemistry. Advances in this field will be reported in due course.

Experimental Section

General Procedure for the Multicomponent Synthesis of Pyridines 5 in "Dual Heterogeneous Catalysis" Conditions (Example of Pyridine 5a)

To a 50-mL, two-necked, round-bottom flask equipped with reflux condenser, were introduced methyl acetoacetate **1a** (100 mg, 0.86 mmol, 1 equiv.), γ-phenyl-β,γ-unsaturated α-keto-methyl ester **6a** (1 equiv.), ammonium acetate **3** (2 equiv.), activated carbon (50 mg, 50 wt%) and 4 Å molecular sieves (3 g) in a mixture AcOH/toluene (1/4 v/v) (15 mL). The flask was then placed under an oxygen atmosphere. The mixture was stirred at reflux until complete consumption of starting materials (monitored by TLC and MS). The heterogeneous mixture was then filtered on a short pad of celite and thoroughly washed with toluene. Sometimes, an acetate salt is formed after filtration on celite. In this case, a second filtration is needed. The solvent was then removed by evaporation under reduce pressure to afford crude **5a** which was purified by chromatography on silica gel (EtOAc/petroleum ether 1/3; $R_f = 0.18$). Pyridine **5a** was obtained as an orange solid; yield: 91%; mp 118–119 °C). MS (ESI): *m/z* (%) = 308 $[M+Na]^+$ (100), 286 $[M+H]^+$ (14); HR-MS (ESI): *m/z* = 286.1075, calcd. for $C_{16}H_{16}NO_4^+$ $[M+H]^+$: 286.1074; ^{1}H NMR ($CDCl_3$, 300.13 MHz): $\delta = 7.80$ (s, 1H), 7.19 (br s, 5H), 3.77 (s, 3H), 3.44 (s, 3H), 2.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.47 MHz): $\delta = 167.9$, 164.5, 155.6, 148.3, 147.1, 136.8, 130.4, 128.5, 128.2, 127.2, 122.6, 52.4, 51.8, 22.4.

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