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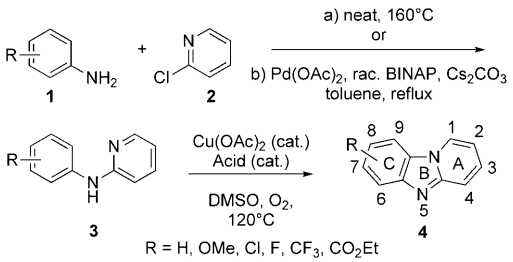
On the Importance of an Acid Additive in the Synthesis of Pyrido[1,2-*a*]benzimidazoles by Direct Copper-Catalyzed Amination

Kye-Simeon Masters,[a] Tom R. M. Rauws,[a] Ashok K. Yadav,[a] Wouter A. Herrebout,[b] Benjamin Van der Veken,[b] and Bert U. W. Maes*[a]

Pyrido[1,2-*a*]benzimidazoles[1,2a] are interesting compounds both from the viewpoint of medicinal chemistry[2–7] (solubility,[7] DNA intercalation[3]) and materials chemistry[8] (fluorescence). Of note among the former is the antibiotic drug Rifaximin,[5] which contains this heteroaromatic core. The classical synthetic approach for the assembly of pyrido[1,2-*a*]benzimidazoles is by [3+3] cyclocondensation of benzimidazoles containing a methylene group at C2 with appropriate bielectrophiles.[2a] However, these procedures are often low-yielding, involve indirect/lengthy sequences, and/or provide access to a limited range of products, primarily providing derivatives with substituents located on the pyridine ring (A ring, Scheme 1).[2–4] Theoretically, a good alternative synthetic method for the synthesis of pyrido[1,2-*a*]benzimidazoles with substituents in the benzene ring (C ring) should be accessible by intramolecular transition-metal-catalyzed C–N bond formation in *N*-(2-chloroaryl)-pyridin-2-amines, based on chemistry recently developed in our research group.[9] These substrates themselves are easily available through S_NAr or selective Pd-catalyzed amination[10] of 2-chloropyridine with 2-chloroanilines.[11] If a synthetic procedure that eliminated the need for preactivation of the 2-position of the 2-chloroarylamino entity could be developed, this would be even more powerful, as anilines are more readily commercially available than 2-chloroanilines. Therefore the synthesis of pyrido[1,2-*a*]benzimidazoles (**4**) by a transition-metal-catalyzed intramolecular C–H amination approach from *N*-arylpyridin-2-amines (**3**) was explored (Scheme 1).



Scheme 1. Cu^{II}-catalyzed intramolecular C–H amination.

Reports on C–N bond formation,[12a] in comparison with C–C bond formation,[12b–p] by transition-metal-catalyzed C–H functionalization are still relatively rare despite the undeniably important role of C–N bond formation in organic synthesis. In comparison with existing methodology, direct transition-metal-catalyzed C–H amination has an advantage over nitrene C–H insertion, since the latter requires preactivation of amine.[12a,13]

There are hitherto two approaches used to attain C–N bond formation by direct C–H bond functionalization.[14] The difference lies in the C–N bond-forming step from the M^{+n} intermediate, which can either be achieved by using an oxidant that delivers a C–$M^{+(n+2)}$–N species allowing C–N bond formation by reductive elimination to reform M^{+n}, or alternatively, the M^{+n} intermediate can directly undergo reductive elimination forming M^0, and an oxidant is required to bring the transition metal back to the M^{+n} oxidation state. The majority of the examples published involve the use of a Pd^{II} catalyst in combination with $Cu^{II}(OAc)_2$ as reoxidant of Pd^0, in either an equimolar amount or catalytic amount when used in combination with O_2. Only two procedures are based on Cu^{II} catalysis, one in the presence and one in the absence of acetic acid.[14g,i] We decided to focus on Cu^{II} catalysis to achieve ring closure of *N*-arylpyridin-2-amine (**3**) as only one transition metal is required and O_2 can be used for the reoxidation. The use of O_2 is beneficial as it is the greenest oxidant available to chemists, and an oxidation of an M^{+n} intermediate would require stronger and less sustainable oxidants.

N-Phenylpyridin-2-amine (**3a**) was chosen as the test substrate for this transformation, using $Cu^{II}(OAc)_2{\cdot}H_2O$ in DMSO in the presence of O_2 at 100 °C to achieve the cyclization (Table 1). A conversion of 43% was achieved (Table 1, entry 1). The addition of acid proved beneficial as one equivalent of acetic acid gave a higher consumption of substrate (53%, Table 1, entry 3). When a catalytic amount of acid (15 mol%) was used, a similar conversion was ob-

[a] Dr. K.-S. Masters, T. R. M. Rauws, Dr. A. K. Yadav, Prof. Dr. B. U. W. Maes
Organic Synthesis, University of Antwerp
Groenenborgerlaan 171, 2020 Antwerp (Belgium)
Fax: (+32) 32653233
E-mail: bert.maes@ua.ac.be

[b] Prof. Dr. W. A. Herrebout, Prof. Dr. B. Van der Veken
Cryospectroscopy, University of Antwerp
Groenenborgerlaan 171, 2020 Antwerp (Belgium)

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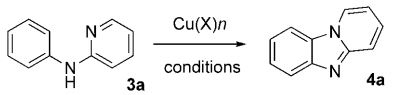
Table 1. Optimization of the intramolecular C–H amination of *N*-phenylpyridin-2-amine (**3a**).



Entry	Solvent	Catalyst	Additive	mol%	*T* [°C]	Conv. [%][a,b]
1	DMSO	$Cu(OAc)_2{\cdot}H_2O$	–	–	100	43
2	DMSO	$Cu(OAc)_2{\cdot}H_2O$	AcOH	15	100	47
3	DMSO	$Cu(OAc)_2{\cdot}H_2O$	AcOH	100	100	53
4	DMSO	$Cu(OAc)_2{\cdot}H_2O$	–	–	120	82
5	DMSO	$Cu(OAc)_2{\cdot}H_2O$	AcOH	15	120	92
6	DMSO	$Cu(OAc)_2$	AcOH	15	120	65
7	DMSO/1% H_2O v/v	$Cu(OAc)_2{\cdot}H_2O$	AcOH	15	120	90
8	DMSO/10% H_2O v/v	$Cu(OAc)_2{\cdot}H_2O$	AcOH	15	120	19
9	DMSO	$Cu(OAc)_2{\cdot}H_2O$	KOAc	100	120	17
10	DMSO	$Cu(OAc)_2{\cdot}H_2O$	Cs_2CO_3	100	120	0
11	DMSO	$Cu(O_2CCF_3)_2$	AcOH	15	120	84
12	DMSO	$Cu(OTf)_2$	AcOH	15	120	28
13	DMSO	$CuSO_4$	AcOH	15	120	29
14	DMSO	$CuCl_2$	AcOH	15	120	5
15	DMSO	$Cu(OH)_2$	AcOH	15	120	0
16	DMSO	$Cu(OAc)_2{\cdot}H_2O$	$PrCO_2H$	15	120	91
17	DMSO	$Cu(OAc)_2{\cdot}H_2O$	PivOH	15	120	92
18	DMSO	$Cu(OAc)_2{\cdot}H_2O$	BzOH	15	120	90
19	DMSO	$Cu(OAc)_2{\cdot}H_2O$	TFA	15	120	95
20	DMSO	$Cu(OAc)_2{\cdot}H_2O$	TFA	100	120	17
21	DMSO	$Cu(OAc)_2{\cdot}H_2O$	NH_4Cl	15	120	92
22	DMSO	$Cu(OAc)_2{\cdot}H_2O$	HCl	15	120	89
23	DMSO	$Cu(OAc)_2{\cdot}H_2O$	HCl	100	120	2
24	DMSO	$Cu(OAc)_2{\cdot}H_2O$	TFBA	15	120	15[c,d,e]

[a] Reactions were performed under an atmosphere of O_2 (ca. 1 atm) at a concentration of 0.5 M in standard (undried) DMSO, unless otherwise indicated with 15 mol% Cu^{II} salt. [b] Conversion of **3a** to **4a** determined by HPLC after 18 h. [c] Under an Ar atmosphere, after 24 h. [d] Confirmed by ^1H NMR spectroscopy of the crude reaction mixture. [e] With AcOH (15 mol%) in either DMSO or DMF under an Ar atmosphere, similar results were obtained.

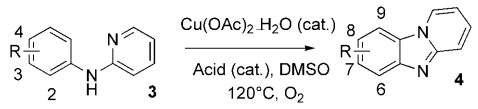
served as with one equivalent (Table 1, entry 2). At higher temperature (120°C) a better conversion was achieved (Table 1, entries 4 and 5). Because the addition of 15 mol% acid was optimal, we decided to perform further optimizations with a catalytic amount of acid. Interestingly, anhydrous $Cu^{II}(OAc)_2$ proved less effective than the monohydrate (Table 1, entry 6), and the reaction proved not to be sensitive to the presence of 1% v/v water (Table 1, entry 7), but a higher amount was detrimental (Table 1, entry 8). The use of dimethoxyethane, dioxane, acetonitrile, 1-propanol, or toluene as solvent failed to effect the cyclization. Only solvents in which a S=O or C=O moiety was present allowed the reaction (DMSO, sulfolane, NMP, DMA, and DMF).[15] Among these DMSO and DMF gave the highest conversions, and the former was arbitrarily chosen for further studies.[15] Interestingly, the use of base instead of acid (acetate and carbonate) had an inhibitory effect on the conversion (Table 1, entries 9 and 10), and bidentate amine ligands[16] completely shut the reaction down. Cu^{II} catalysts with carboxylate counterions performed well (Table 1, entries 5 and 11), whilst those with a sulfonate or sulfate group (Table 1, entries 12 and 13) promoted the reaction to a significantly lesser extent. Other copper salts (Table 1, entries 14 and 15) failed to effect the conversion.

Subsequently, the influence of the structure of the acid additive was investigated (Table 1).[17] Other carboxylic acids such as butyric, pivalic, and benzoic acid gave essentially the same conversion of **3a** to **4a** after a reaction time of 18 h (Table 1, entries 16–18). Stronger acids such as trifluoroacetic acid can also be used but only in a catalytic amount (Table 1, entries 19 and 20). Also non-carboxylic acid containing acids are allowed (Table 1, entries 21 and 22), but again when the acid is strong the use of a stoichiometric amount is detrimental (Table 1, entry 23). As the conversion data in Table 1 do not take into account side reactions of the substrate **3a**, we looked at isolated yields in the presence of acetic acid and several substituted benzoic acids possessing different pK_a values.

Interestingly, a significant difference in the isolated yields and amount of recovered substrate was found for the studied acids (acetic acid: 60% **4a**, 10% **3a**; 4-methoxybenzoic acid (pK_a: 4.47): 52% **4a**, 30% **3a**; benzoic acid (pK_a: 4.17): 75% **4a**, 16% **3a**; 3,4,5-trifluorobenzoic acid (TFBA) (pK_a: 3.46): 92% **4a**, no **3a**).[18] These results indicate that the selectivity of the reaction is dependent on the type of acid additive used. In the case of acetic acid and 4-methoxybenzoic acid, the missing mass balance is 22% and 10%, respectively, in comparison with the experiment involving 3,4,5-trifluorobenzoic acid (Table 2, entry 2). 3,4,5-Trifluorobenzoic acid is clearly a superior additive, additionally providing a faster reaction and full conversion of **3a**. In the case of less acidic additives (acetic, 4-methoxybenzoic, and benzoic acid), starting material was recovered. A similar selectivity trend was observed for *N*-(4-fluorophenyl)pyridin-2-amine (**3b**) with the yield of the desired compound increased with decreasing pK_a value (4-methoxybenzoic acid: 38% **4b**; benzoic acid: 68% **4b**; 3,4,5-trifluorobenzoic acid: 75% **4b**). In this case, however, no starting material remained. Ultra performance liquid chromatography (UPLC) analysis of the crude reaction mixtures showed various amounts of substrate dimers depending on the acid used. We therefore currently believe that the pK_a related selectivity of the acid can be rationalized by the control of competing intra- and intermolecular C–N bond formation. This will be studied in future research.

The results obtained for substrates **3a** and **3b** clearly indicated that the use of a catalytic amount of 3,4,5-trifluorobenzoic acid is superior and therefore the scope was assessed for these optimized reaction conditions [$Cu^{II}(OAc)_2{\cdot}H_2O$ (15 mol%), 3,4,5-trifluorobenzoic acid (15 mol%), DMSO, 120°C] for a set of substituted *N*-phenylpyridin-2-amines (Table 2). Both electron-donating (OMe, entry 8) and electron-withdrawing groups (Cl, entry 11; COOEt, entry 12; CF_3, entry 16) in the *para* position of the benzene ring were tolerated, although the ethoxycarbonyl and trifluoromethyl group required a 20% loading of catalyst (Table 2, entries 13 and 17). With 15 mol% $Cu^{II}(OAc)_2$ at least 15% of substrate **3** could be recovered.

Table 2. Intramolecular C–H amination of *N*-arylpyridin-2-amines (**3**).



Entry	Catalyst and acid loading	Acid	R	Product	R	Yield [%][a,b]
1	15	AcOH	H	**4a**	H	60
2	15	TFBA	H	**4a**	H	92
3	15	TFBA	4-F	**4b**	8-F	75
4	15	TFBA	3-F	**4c + 4c′**	7- + 9-F	58[d]
5	20	TFBA	3-F	**4c + 4c′**	7- + 9-F	79 (12:1)[c,e]
6	15	TFBA	2-F	**4d**	6-F	62[d]
7	20	TFBA	2-F	**4d**	6-F	98
8	15	TFBA	4-OMe	**4e**	8-OMe	60
9	15	TFBA	3-OMe	**4f + 4f′**	7- + 9-OMe	70 (13:1)[c,e]
10	15	TFBA	2-OMe	**4g**	6-OMe	59
11	15	TFBA	4-Cl	**4h**	8-Cl	78
12	15	TFBA	4-CO_2Et	**4i**	8-CO_2Et	46[d]
13	20	TFBA	4-CO_2Et	**4i**	8-CO_2Et	57
14	15	TFBA	3-CO_2Et	**4j + 4j′**	7- + 9-CO_2Et	31[d]
15	20	TFBA	3-CO_2Et	**4j + 4j′**	7- + 9-CO_2Et	55 (26:1)[c]
16	15	TFBA	4-CF_3	**4k**	8-CF_3	71[d]
17	20	TFBA	4-CF_3	**4k**	8-CF_3	80

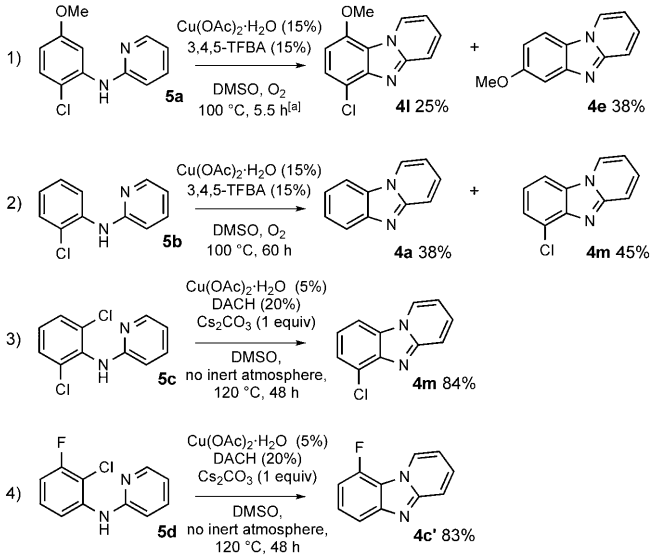
[a] Yields refer to isolated products with a purity of >95% by ^{1}H NMR analysis. [b] $Cu(OAc)_2·H_2O$ (*n* mol%), acid (*n* mol%), DMSO, O_2, 24 h. [c] Regioisomer ratio (7:9). [d] At least 15% substrate could be recovered. [e] The regioisomers were obtained as separate compounds.

All substituents in *meta* or *ortho* positions (Table 2, entries 5, 7, and 15), except the methoxy group (Table 2, entries 9 and 10), also required this higher loading. The *meta*-substituted substrates proved interesting, as in all cases a high regioselectivity for the 7- over the 9-substituted pyrido-[1,2-*a*]benzimidazole was achieved (Table 2, entries 5, 9, and 15).

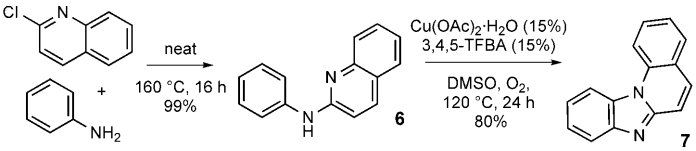
Having developed a satisfactory entry to 6-, 7-, and 8-substituted pyrido[1,2-*a*]benzimidazoles, we envisioned being able to access the minor component from the cyclization of *meta*-substituted substrates (**3**) by blocking one C–H functionalization position with a chloro substituent, which could later be removed by hydrodechlorination (Scheme 2). *N*-(2-Chloro-5-methoxyphenyl)pyridin-2-amine (**5a**) was chosen as the model substrate. A C–Cl amination pathway was found to be competitive under the intramolecular C–H amination reaction conditions (entry 1, Scheme 2). Such cyclizations mediated by copper have been reported, however these are always promoted by basic rather than acidic conditions.[19–20]

With the simplified 2-chloro substrate **5b** (entry 2, Scheme 2) a similar behavior was observed. A substrate with a C–Cl moiety located remotely from the site of the Cu^{II} coordination, as in substrate **3h**, was not effected by the C–H amination reaction conditions (Table 2, entry 11). The intramolecular C2–Cl activation is therefore directed, requiring less energy than an intermolecular process. This rationalizes why a deactivated C–Cl can react so easily without requiring electron-rich ligands. A change of conditions from catalytic acid to stoichiometric base promoted the C2–Cl substitution process exclusively, and only traces of product due to the C–H amination pathway were detectable. Cs_2CO_3 proved more effective than CsOAc, and the use of a Cu^{II}-stabilizing ligand (*trans*-1,2-diaminocyclohexane (DACH))[21] provided a means by which the catalyst loading could be reduced to 5%.[15] Application of these optimal conditions to 2,6-dichloro substrate **5c** gave 6-chloropyrido[1,2-*a*]benzimidazole (**4m**), in good yield (entry 3, Scheme 2), and without observable hydrodechlorination of **5c** and **4m**. The latter conditions also provided the 9-fluoro derivative **4c′** from **5d** (entry 4, Scheme 2) in 83% isolated yield. This compound could only be obtained as a minor compound by the direct amination of **3c** (Table 2, entry 5). The C–Cl and the C–H functionalization process are thus complementary, in conjunction providing selective access to 6-, 7-, 8-, and 9-substituted benzo[1,2-*a*]imidazoles.

We next sought to apply our methodology to the synthesis of the benzimidazo[1,2-*a*]quinoline core **7** (Scheme 3), which has antitumor properties. *N*-Phenylquinoline-2-amine (**6**) was accessed in 99% isolated yield by heating 2-chloroquinoline neat with 1.5 equivalents of aniline. The C–H amination of **6** was performed by using the optimized reaction con-



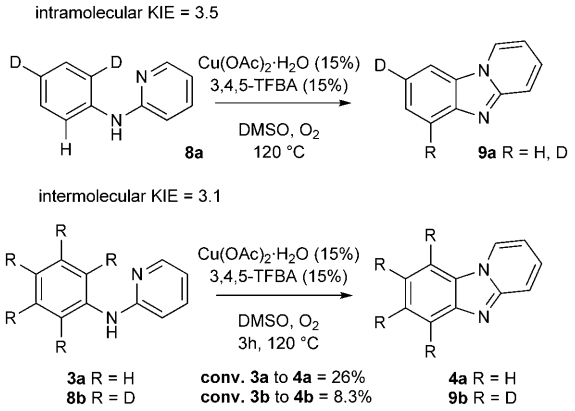
Scheme 2. Cyclization of *N*-(2-chloroaryl)pyridin-2-amines (**5**). [a] Incomplete conversion.



Scheme 3. Synthesis of anti-cancer core **7**.

ditions, smoothly delivering **7**[22,3a] in 80% yield. This cyclization is notable as it takes place at an *o*,*o*-disubstituted nitrogen.

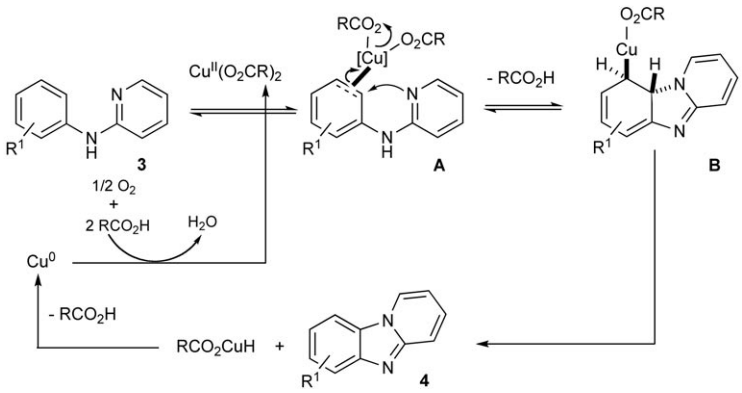
To gain an insight into the mechanism, both intra- and intermolecular kinetic isotope effects (KIEs) were determined (Scheme 4). The intramolecular KIE, determined through



Scheme 4. Determination of intra- and intermolecular KIE.

competitive H/D cyclization from 2,4-dideutero-*N*-phenylpyridin-2-amine (**8a**), was 3.5, showing that the C–H bond rupture is a kinetically relevant process.[23] The intermolecular KIE was determined to be 3.1 through comparison of a reaction of substrate **3a** and the 2,3,4,5,6-pentadeuterated analogue **8b**, revealing that the C–H bond breakage is involved in the rate-determining step of the catalytic cycle.[24]

A possible rationalization of the mechanism is presented in Scheme 5. Coordination of $(RCO_2)_2Cu^{II}$ with substrate **3** (**A**), followed by intramolecular nucleophilic attack of the amidine on the activated arene (η^2 π complex) delivers the σ-alkyl Cu^{II} species **B**.[25] Subsequent β-hydride elimination gives **4** and $RCO_2Cu^{II}H$.[26] Reductive elimination of RCO_2H from $RCO_2Cu^{II}H$ yields Cu^0, which can be reoxidized to $(RCO_2)_2Cu^{II}$ with O_2 and RCO_2H.[27] This mechanism proceeding via a Cu^{II}/Cu^0 catalytic cycle is in agreement with the 1:1 Cu^{II}/product stoichiometry obtained when



Scheme 5. Proposed mechanism for the intramolecular C–H amination of **3**.

the reaction is executed under oxygen-free conditions (Table 1, entry 24). This excludes a mechanism via disproportionation of two Cu^{II} complexes, yielding a Cu^{I} and Cu^{III} species of which only one will act as the catalyst. Occurrence of a disproportionation process therefore would deliver a conversion to product of a maximum of half the copper loading, which is clearly not in accordance with our experimental finding. The observation that reaction product can be formed under an oxygen-free atmosphere shows that oxygen acts as the final electron acceptor (a two electron oxidant) and regenerates the Cu^{II} species.[28] A *syn* β-hydride elimination as 'H'-removal process is consistent with the kinetic isotope effect experimentally observed (Scheme 4).[29] A concerted metallation–deprotonation /CMD) mechanism is unlikely as substrate **3c** containing a *meta* fluoro substituent preferentially cyclizes in C6 of the aniline moiety. Taking into account that a fluorine atom is small, a CMD mechanism would be consistent with a preferential C2 direct functionalization process.[23] A C–H activation process via **B** is in agreement with the higher k_{obsd} value measured for substrate **3b** (0.37) versus **3a** (0.19),[30a] since DFT calculations performed on the respective intermediates **B** clearly point to a lower activation energy for $R^1 = 4$-F (75.6 kJ mol^{-1}) than for $R^1 = H$ (87.0 kJ mol^{-1}).[15,30] The observation that more acidic benzoic acids give faster reactions can be rationalized by taking into account that these give more electrophilic $(RCO_2)_2Cu^{II}$ species, and consequently a higher concentration of **B**, which is involved in the rate-limiting step of the reaction.

While this work was nearing completion Zhu and Zhang reported another catalytic system for the direct intramolecular C–H amination of *N*-arylpyridin-2-amines.[31] They showed the use of a combination of a $Cu(OAc)_2$ and $Fe(NO_3)_3{\cdot}9H_2O$ catalyst to be essential to achieve high yields of the target compounds. The unique role of the Fe^{III} is believed to lie in its ability to form an electrophilic Cu^{III} species, beneficial for the S_EAr mechanism. The catalytic system we disclose here results from a fundamental study of the role of the acid additive on the reaction (rate and selectivity). By using a catalytic amount of 3,4,5-trifluorobenzoic acid, high yields of target compound can be achieved without the requirement of co-catalytic $Fe(NO_3)_3{\cdot}9H_2O$. In contrast to the Cu^{II}/Fe^{III} system, our methodology allows smooth cyclization of electron-deficient substrates, as exemplified by a fluoro group in the *ortho* (**3d**) and *meta* (**3c**) position of the phenyl ring. Substrates with a sterically hindered pyridine nitrogen atom, as in *N*-phenylquinoline-2-amine (**6**), were also viable substrates using 3,4,5-trifluorobenzoic acid additive. The Zhu and Zhang procedure required a stoichiometric amount of $Cu(OAc)_2$ to achieve similar yields for products common to both studies, namely **3c**, **3d**, and **6**. Moreover, for substrates **3c** and **6** a reaction time of more than 65 h was necessary. For other substrates our method requires generally a lower loading of copper catalyst and shorter reaction times to achieve similar yields.

In summary, we have developed new and efficient synthetic protocols for pyrido[1,2-*a*]benzimidazoles based on

C–H and C–Cl functionalization. Together, the two methods represent a 'synthetic kit' for expedient access to 6-, 7-, 8-, and 9-substituted pyrido[1,2-*a*]benzimidazoles in good to excellent yields. In the C–H amination reaction an unprecedented influence of the type of acid on the catalysis has been identified.

Experimental Section

General procedure for the C–H amination (conditions a, b, and c): Substrate **3** (0.50 mmol), $Cu(OAc)_2 \cdot H_2O$ (conditions a and b: 0.075 mmol, 15 mol%; conditions c: 0.1 mmol, 20 mol%), additive (conditions a: acetic acid, 0.075 mmol; conditions b: 3,4,5-trifluorobenzoic acid (3,4,5-TFBA), 0.075 mmol; conditions c: 3,4,5-TFBA, 0.1 mmol), and solvent (DMSO, 1.00 mL) were added to a 10 mL microwave vial. The resulting reaction mixture was stirred under a flow of oxygen for 5 min prior to sealing under oxygen with a pressure cap, then supplied with additional oxygen by a balloon and being heated by a temperature-calibrated aluminum hotplate[15] at 120 °C. Depending on the reaction, samples were taken at the designated times by using a syringe/needle (HPLC/UPLC conversions), or the reaction was run to the stated time and worked up with isolation of reaction product(s) **4** (and recovered substrate **3**). Workup: The vial was unsealed and the reaction mixture taken up in CH_2Cl_2 (50 mL per mmol **3**), then washed with concentrated NH_4OH(aq)/saturated brine (3:2, 50 mL per mmol **3**). The wash was repeated, then the organic phase was dried over $MgSO_4$ and the volatiles removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel by eluting with CH_2Cl_2, then gradient CH_2Cl_2/ammonia in MeOH (7 M) (199:1, 124:1, 99:1, 66:1, 49:1) to deliver the isolated product (and remaining substrate, if applicable).

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Keywords: catalysis · C–H activation · C–H amination · C–H functionalization · copper

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