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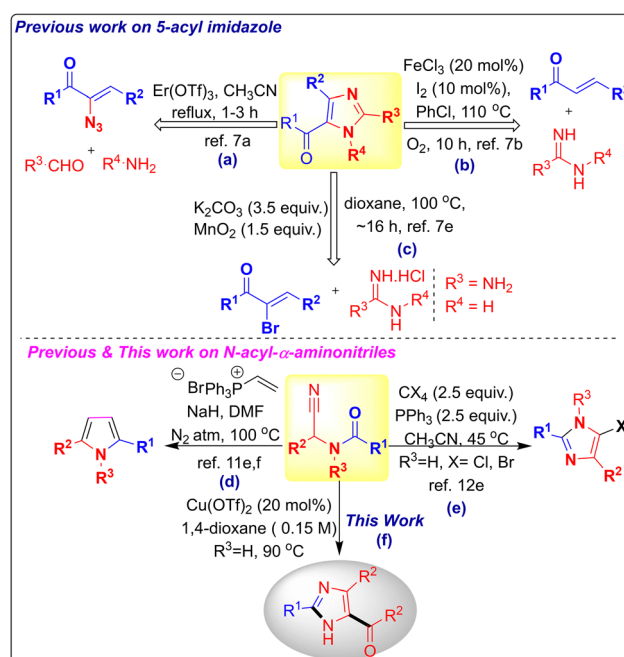
## Cu(OTf)<sub>2</sub>-catalyzed access to 2,4,5-trisubstituted imidazoles from acyclic Reissert compounds

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A Cu(OTf)<sub>2</sub>-catalyzed cascade self-coupling of *N*-acyl- $\alpha$ -aminonitriles (acyclic Reissert compounds) has been developed to afford 2,4,5-trisubstituted imidazoles in moderate to good yields. Single-crystal X-ray diffraction confirmed the structure of a representative 1*H*-2,4-disubstituted-5-acylimidazole, while NMR studies revealed N1/N3 tautomerism in selected cases. The synthetic utility of this protocol was further demonstrated by gram-scale synthesis and carbonyl reduction.

Imidazole, a privileged core structure, finds diverse applications in medicinal chemistry,<sup>1</sup> natural products,<sup>2</sup> and drug discovery.<sup>3</sup> Substitution on the imidazole ring further extends its utility to functional materials,<sup>4a,b</sup> polymers,<sup>4c,d</sup> and coordination chemistry,<sup>4e,f</sup> spurring interest in 2,4,5-trisubstituted imidazoles.<sup>5</sup> Traditional syntheses rely on the Radziszewski multicomponent cyclocondensation of aldehydes, ammonia, and 1,2-diketones,<sup>4g,h</sup> with numerous refinements enabling substituted analogues.<sup>5</sup> However, methods for 5(4)-acylimidazoles bearing ketones or esters remain underexplored.<sup>6,7</sup> For instance, Muthusubramanian and coworkers (2014) reported an Er(OTf)<sub>3</sub>-catalyzed multicomponent reaction of  $\alpha$ -azido chalcones, aryl aldehydes, and anilines (Scheme 1a).<sup>7a</sup> Li and coworkers (2015) developed an FeCl<sub>3</sub>/I<sub>2</sub>-catalyzed aerobic oxidative coupling of amidines and chalcones for regioselective acylimidazoles (Scheme 1b).<sup>7e</sup> Guchhait and coworkers (2017) devised a tandem aza-Michael addition/S<sub>N</sub>2 redox-neutral process from  $\alpha$ -bromo enones (Scheme 1c).<sup>7e</sup> With such limited precedents, substantial opportunities remain for new approaches to C-acylimidazoles.

More than 160 years after their discovery,<sup>8</sup>  $\alpha$ -aminonitriles remain powerful synthetic linchpins, undergoing transformations<sup>9</sup> *via* deprotonation or decyanation to iminium ions, as demonstrated in our amide and 2,4-diarylquinoline syntheses.<sup>10a-c</sup> These findings prompted us to explore *N*-acyl- $\alpha$ -aminonitriles,<sup>10d</sup> an open-chain



Scheme 1 Prior art on acylimidazoles and *N*-acyl- $\alpha$ -aminonitriles, and this work.

class of Reissert analogues. The 1,4- and 1,2-addition reactions of deprotonated Reissert compounds and their open-chain analogues have been widely exploited for the construction of diverse molecular frameworks.<sup>11</sup> The synergistic electrophilicity of the nitrile group and nucleophilicity of the amine functionality has enabled versatile access to *N*-heterocycles from these bifunctional scaffolds. In this context, cyclization reactions incorporating the nitrile moiety,<sup>12a-c</sup> as well as the use of electron-deficient arenes in place of classical electrophiles,<sup>12d</sup> further expanded the synthetic potential of *N*-acyl- $\alpha$ -aminonitriles.

In a seminal contribution, McEwen and co-workers developed a condensation of the conjugate base of *N*-acyl- $\alpha$ -aminonitriles with vinyltriphenylphosphonium bromide for the synthesis of substituted pyrroles (Scheme 1d).<sup>11ef</sup> Later, Zhong *et al.* reported the synthesis of

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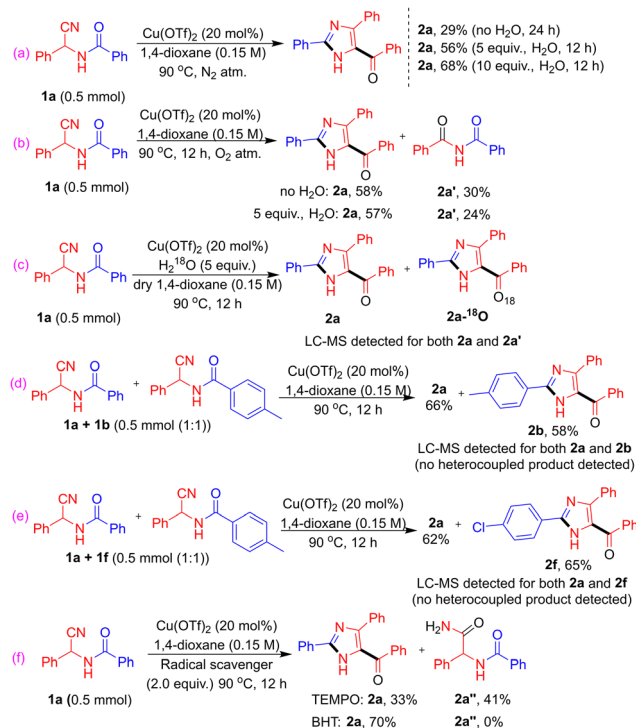
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2,4-disubstituted 5-halo-1*H*-imidazoles from *N*-acyl- $\alpha$ -aminonitriles, which were subsequently converted into 2,4,5-trisubstituted imidazoles *via* Pd-catalyzed cross-coupling (Scheme 1e).<sup>12e</sup> Nearly two decades later, we describe a simple transformation of the same *N*-acyl- $\alpha$ -aminonitriles into C-acylimidazoles in a single step using catalytic Cu(OTf)<sub>2</sub> (Scheme 1f). Our initial hypothesis targeted the synthesis of 5-amino oxazole *via* a Lewis acid-promoted 5-*exo*-dig cyclization; however, the reaction selectively delivered imidazoles through a self-coupling cascade. Given the limited availability of efficient methods for synthesizing 5(4)-acyl-substituted imidazoles, this conversion provides a useful route and highlights a different reactivity pathway of *N*-acyl- $\alpha$ -aminonitriles.

The optimization began with *N*-(cyano(phenyl)methyl)benzamide **1a** as the model substrate. Screening of common metal halides in 1,4-dioxane at 90 °C (Table 1, entries 1–5) delivered the desired product **2a** in modest yields (17–63%). Subsequent evaluation of various metal triflates (Table 1, entries 6–10) identified Cu(OTf)<sub>2</sub> as the most effective catalyst, providing **2a** in 73% yield at 20 mol% loading (Table 1, entry 7). With copper triflate selected, solvent screening was carried out next. Replacing 1,4-dioxane with ethanol, isopropanol (IPA), ethylene glycol, ethyl acetate, or acetonitrile (Table 1, entries 11–15) failed to improve the reaction efficiency. Catalyst loading studies showed that reducing Cu(OTf)<sub>2</sub> to 15 mol% lowered the yield (Table 1, entry 16), while increasing it to 25 mol% offered no further enhancement (Table 1, entry 17). Temperature variation (Table 1, entries 18 and 19) confirmed that 90 °C was optimal for the formation of **2a**.

Control experiments under N<sub>2</sub> and O<sub>2</sub> were performed to probe the reaction pathway (SI, Table S4). Under N<sub>2</sub>, the reaction gave only



Scheme 2 Control experiments to study the reaction pathway.

29% yield of **2a** without water, which increased to 56% and 68% upon addition of 5 and 10 equiv. of H<sub>2</sub>O, respectively, indicating the role of water (Scheme 2a). Under O<sub>2</sub>, the reaction afforded **2a** in 58% yield with 30% of decyanative product **2a'** in the absence of water, while similar yields of **2a** (57%) and reduced **2a'** (24%) were observed in the presence of water, indicating competing oxygen-mediated pathways (Scheme 2b). Next, the reaction was performed<sup>13</sup> in H<sub>2</sub><sup>18</sup>O using dry 1,4-dioxane, and LC-MS analysis showed a mixture of isotopic and non-isotopic mass peaks (SI, Fig. S10). The non-isotopic mass suggests that oxygen may also arise from water generated *in situ* during the course of the reaction and from residual moisture (Scheme 2c). Further, cross-over experiments with **1a/1b** (electron-donating) and **1a/1f** (halogen-substituted) under standard conditions afforded only the corresponding products **2a/2b** and **2a/2f**, respectively (Scheme 2d and e). No heterocoupled products were detected, indicating exclusive homocoupling (SI, Fig. S8 and S9). In the presence of TEMPO, the yield of **2a** decreased to 33%, along with formation of hydrolysed product **2''** in 41% yield likely due to the Cu/TEMPO system. In contrast, BHT afforded **2a** in 70% yield (*cf.* 73% standard). These results suggest that the reaction does not proceed *via* a radical pathway (Scheme 2f).

With the optimized conditions and control studies, the substrate scope of *N*-acyl- $\alpha$ -aminonitriles was examined (Table 2). A range of *para*-substituted phenyl derivatives, including *p*-Me (**1b**), *p*-Et (**1c**), *p*-OMe (**1d**), *p*-F (**1e**), *p*-Cl (**1f**), *p*-Br (**1g**), *p*-COOMe (**1h**), *p*-CF<sub>3</sub> (**1i**), and *p*-CN (**1j**), were well tolerated, affording the corresponding products **2b–2j** in 60–78% yield. *Meta*- and *ortho*-substituted substrates such as *m*-Me (**1k**), *m*-OMe (**1l**), and *o*-Me (**1m**) also reacted smoothly, affording **2k–2n** in 65–66% yield. Whereas *o*-OMe (**2n**) was observed only in trace amounts and could not be isolated. Polysubstituted

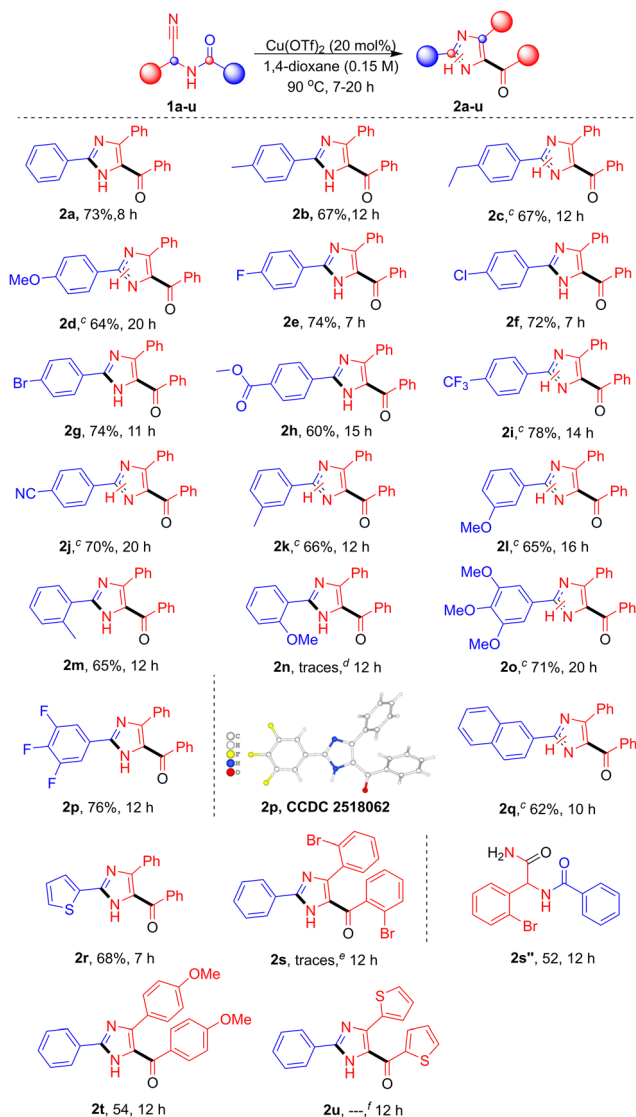
Table 1 Reaction optimization studies<sup>abc</sup>

S. no	Catalyst (x mol%)	Solvent	Temp. (°C)/time (h)	Yield (%)
1	FeCl <sub>3</sub> (20)	1,4-dioxane	90/12	63
2	CoCl <sub>2</sub> ·6H <sub>2</sub> O (20)	1,4-dioxane	90/24	17
3	CuCl <sub>2</sub> (20)	1,4-dioxane	90/24	44
4	CuBr <sub>2</sub> (20)	1,4-dioxane	90/16	56
5	ZnCl <sub>2</sub> (20)	1,4-dioxane	90/24	31
6	Fe(OTf) <sub>2</sub> (20)	1,4-dioxane	90/12	59
7	<b>Cu(OTf)<sub>2</sub> (20)</b>	<b>1,4-dioxane</b>	<b>90/08</b>	<b>73</b>
8	Sm(OTf) <sub>3</sub> (20)	1,4-dioxane	90/24	48
9	AgOTf (20)	1,4-dioxane	90/24	54
10	Yb(OTf) <sub>3</sub> (20)	1,4-dioxane	90/24	51
11	Cu(OTf) <sub>2</sub> (20)	Ethanol	80/24	42
12	Cu(OTf) <sub>2</sub> (20)	IPA	80/24	38
13	Cu(OTf) <sub>2</sub> (20)	Ethylene glycol	100/12	61
14	Cu(OTf) <sub>2</sub> (20)	Ethyl acetate	80/24	34
15	Cu(OTf) <sub>2</sub> (20)	Acetonitrile	80/24	19
16	Cu(OTf) <sub>2</sub> (15)	1,4-dioxane	90/24	64
17	Cu(OTf) <sub>2</sub> (25)	1,4-dioxane	90/8	72
18	Cu(OTf) <sub>2</sub> (20)	1,4-dioxane	70/24	58
19	Cu(OTf) <sub>2</sub> (20)	1,4-dioxane	110/8	74

<sup>a</sup> Reaction conditions: all reactions were carried out using **1a** (0.5 mmol), solvent (0.15 M) and catalyst (x mol%) in a sealed vial at indicated temperature and time unless otherwise noted. <sup>b</sup> Isolated yield. <sup>c</sup> See the SI (Tables S1–S4) for the detailed optimization studies.

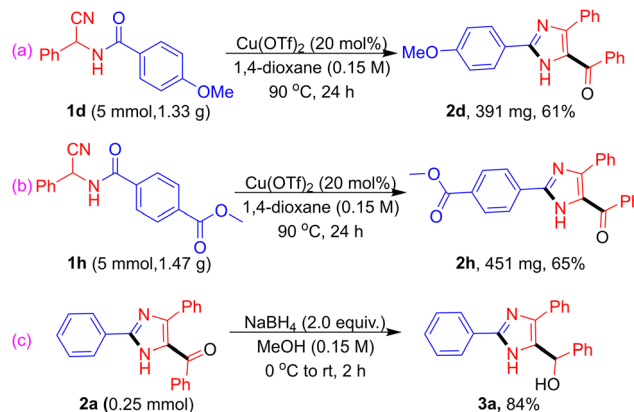


Table 2 Scope and limitations of *N*-acyl- $\alpha$ -aminonitriles to 2,4,5-trisubstituted imidazoles<sup>a,b</sup>



<sup>a</sup> Reaction conditions: Compound **1a** (0.5 mmol),  $\text{Cu}(\text{OTf})_2$  (20 mol %), and 1,4-dioxane (0.15 M) were stirred at 90 °C for 7–20 h. <sup>b</sup> Isolated yields. <sup>c</sup> The presence of N1–N3 tautomeric forms was confirmed by NMR analysis. <sup>d</sup> Detected in trace amounts by TLC; not isolated due to multiple spots. <sup>e</sup> **2s** was detected in trace amounts and not isolated; the corresponding amide was obtained. <sup>f</sup> The mass was confirmed by HRMS analysis; however, isolation for pure NMR characterization was unsuccessful.

aromatics, including 3,4,5-tri-OMe (**1o**) and 3,4,5-trifluoro (**1p**), were compatible, producing **2o** and **2p** in 71% and 76% yield, respectively, with the structure of **2p** confirmed by single-crystal X-ray analysis.<sup>14</sup> Fused aromatics and heteroaryl substrates, such as naphthyl (**1q**) and 2-thienyl (**1r**), furnished **2q** and **2r** in 62–68% yields. Substrates with aryl groups attached to the  $\alpha$ -carbon, including *o*-Br (**1s**), *p*-OMe (**1t**), and 2-thienyl (**1u**), gave **2t** in 54% yield. For **1s**, only traces of **2s** were observed by TLC, and the major isolated product was the corresponding hydrolysed amide **2s''** in 52% yield. Similarly, **2u** was confirmed by HRMS analysis, while its isolation was unsuccessful.



Scheme 3 Synthetic applications and control studies.

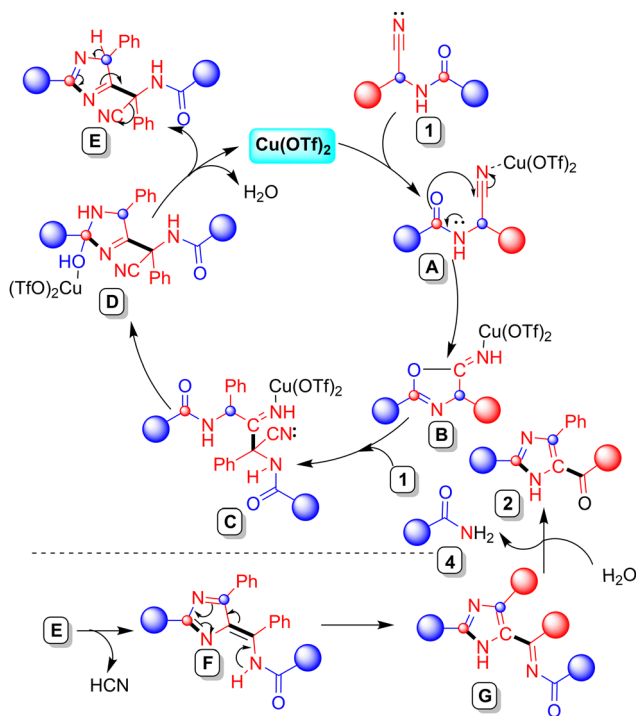
Overall, *para*-substituted substrates generally gave higher yields and shorter reaction times, *meta*-substituents gave moderate results, and *ortho*-substitution lowered yields and required longer reactions, likely due to steric effects.

We further evaluated the scalability of the methodology on a gram-scale using the standard optimized conditions. Representative substrates bearing an electron-donating substituent (**1d**) and an electron-withdrawing substituent (**1h**) furnished the corresponding products **2d** and **2h** in moderate yields of 61% and 65%, respectively (Scheme 3a & b). In addition, reduction of carbonyl functional group in **2a** with  $\text{NaBH}_4$  proceeded smoothly to afford the corresponding secondary alcohol **3a** in 84% yield (Scheme 3c).

A plausible mechanism, supported by control experiments and literature precedent,<sup>11,12,15</sup> is outlined in Scheme 4. Coordination of  $\text{Cu}(\text{OTf})_2$  to the nitrile group of  $\alpha$ -aminonitrile **1** generates intermediate **A**, increasing the electrophilicity of the nitrile carbon and enabling intramolecular 5-*exo*-dig cyclization to form imino-oxazolone **B**. DFT calculations using UB3LYP/def2-TZVP with a 1,4-dioxane solvent model (see SI for computational details) support preferential nitrogen coordination ( $\Delta G = -8.04 \text{ kcal mol}^{-1}$ ) over oxygen ( $\Delta G = -3.35 \text{ kcal mol}^{-1}$ ), with HOMO–LUMO overlap and a smaller band gap (2.13 eV) favouring the nitrile binding pathway (SI, Fig. S13). Further, to assess the ring-closure mechanism and stability of cyclized intermediate **B**, transition state free energy calculations were performed (see SI, Fig. S15). The process proceeds *via* transition state **A** with an activation free energy of  $\Delta G^\ddagger = 23.4 \text{ kcal mol}^{-1}$ , leading to intermediate **B**, which is thermodynamically stabilized by  $-4.46 \text{ kcal mol}^{-1}$  relative to the initial reactant **1**.<sup>16</sup> Next, nucleophilic addition of a second molecule of **1** to **B**, followed by ring opening, affords intermediate **C**. Owing to the lability of  $\text{Cu}(\text{II})$  coordination, intramolecular exchange between imine and amide carbonyl binding facilitates cyclization to imidazoline **D**. Dehydration of **D** regenerates  $\text{Cu}(\text{OTf})_2$  and furnishes intermediate **E**, which upon isomerization and HCN elimination gives **F**. Proton transfer affords aromatic intermediate **G**, and final hydrolysis yields the 2,4,5-trisubstituted imidazole **2** along with amide **4**, confirmed by <sup>1</sup>H NMR spectroscopy (SI, Fig. S57).

In conclusion, a copper-catalyzed synthesis of *C*-acylimidazoles from open-chain analogues of Reissert compound is disclosed. The reaction is proposed to proceed through an imino-oxazolone





Scheme 4 Plausible reaction mechanism.

pathway, enabling access to 5-acylimidazole scaffolds. Broad aryl-substrate tolerance, gram-scale feasibility, and reduction of the carbonyl to the corresponding alcohol demonstrate the practicality of the method. A plausible mechanism was proposed based on control studies and DFT calculations. This work expands the synthetic toolbox for *N*-acyl- $\alpha$ -aminonitriles and provides a useful entry to acylimidazoles.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

The supporting data has been provided as part of the supplementary information (SI). Supplementary information: Tables S1–S4 and Fig. S1 and S2. NMR spectra and further experimental details. See DOI: <https://doi.org/10.1039/d6cc00157b>.

CCDC 2518062 contains the supplementary crystallographic data for this paper.<sup>14</sup>

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- 13 For detailed isotopic studies with H<sub>2</sub><sup>18</sup>O refer supporting information Fig. S10 to Fig. S12.
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