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Letter

Synthesis of Polysubstituted Pyrroles via Silver-Catalyzed Oxidative Radical Addition of Cyclopropanols to Imines

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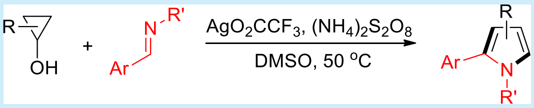
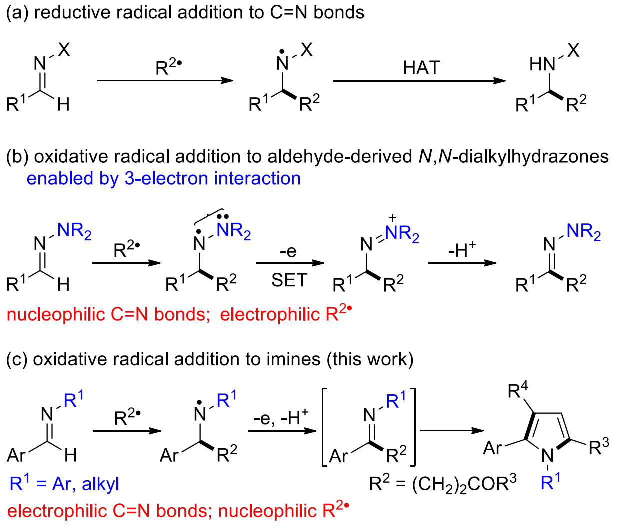
ABSTRACT: A silver-catalyzed formal [3 + 2] cycloaddition reaction, with cyclopropanols as a C3 subunit and imines as a two-atom subunit, is developed. The reaction takes place under mild conditions and produces a broad array of polysubstituted pyrroles in medium to high yields. It represents the first example of oxidative radical addition to imines, thus offering a new choice for the direct C−H functionalization of imines.



Radical addition reactions have become a very important synthetic tool in organic synthesis, since they can assemble carbon−carbon and carbon−heteroatom bonds under mild and nonbasic conditions that may be compatible with various functional groups.[1] With the fast development of this field, the continuous expansion of the scope of radical acceptors is in high demand. So far, C═C bonds are the most common radical acceptors. In contrast, C═N bonds have been much less utilized as acceptors for radical addition. Traditional methods focus on the reductive radical addition to C═N bonds, in which an aminyl radical is generated, followed by hydrogen atom abstraction (HAT) from the solvent or other hydrogen atom sources to give α-branched amines as final products (Scheme 1a).[2,3] Due to the high electronegativity of the nitrogen atom, the oxidation of an aminyl radical is more difficult than its reduction, and consequently, the oxidative radical addition (ORA) to C═N bonds remains a significant challenge in organic chemistry.

Scheme 1. Background and Summary of This Work



Recently, the ORA to aldehyde-derived *N*,*N*-dialkylhydrazones has been successfully developed, providing an efficient access to the direct C−H functionalization of hydrazones (Scheme 1b).[4−8] In this reaction manifold, the electron-donating dialkylamine groups (NR_2) can activate the carbon atom of azomethine (CH═N) toward electrophilic substitution. Therefore, the intermolecular addition is limited to electrophilic radicals, such as fluoroalkyl,[5] nitrogen,[6] phosphine,[7] and α-carbonyl alkyl ones.[8a,b] Moreover, the presence of three-electron π-bonding interactions[5d,e] may stabilize the aminyl radical intermediate and facilitate the subsequent single electron transfer (SET) oxidation. Despite this important progress, this strategy only works for aldehyde-derived hydrazones, while the more common and readily available imines, an important class of building blocks for the assembly of synthetically attractive nitrogen-containing compounds, are still unable to undergo the ORA reaction.

We have recently developed a new methodology for the synthesis of cyclic or acyclic ketones via the ORA to aldehydes.[9] Inspired by this work, we would like to explore the ORA reaction of imines. In view of the electrophilic properties of iminyl C═N bonds, we envisioned that nucleophilic carbon radicals might serve as a good coupling partner. Previous reports,[10] including our work,[11] indicated that nucleophilic carbon-centered radicals could be efficiently generated via the radical ring-opening of cyclopropanols. Herein, we report a novel Ag-catalyzed formal [3 + 2] cycloaddition reaction using cyclopropanols as a C3 subunit

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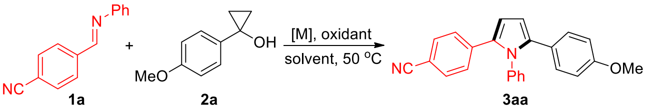
and imines as a two-atom subunit, in which a wide range of polysubstituted pyrroles can be efficiently synthesized from readily attained starting materials under mild conditions (Scheme 1c). The reaction constitutes the first example of ORA to imines, thus providing a new strategy for the radical transformation of imines.

To verify the feasibility, the 4-cyanobenzaldehyde-derived imine **1a** and cyclopropanol **2a** were chosen as the model substrates for screening the reaction parameters. Initially, the reaction was evaluated at 50 °C with 10 mol % of $AgNO_3$ as the catalyst, 3 equiv of $Na_2S_2O_8$ as the oxidant, and dimethyl sulfoxide (DMSO) as the solvent. To our delight, the 1,2,5-trisubstituted pyrrole **3aa** was isolated in 71% yield (Table 1, entry 1). A couple of silver catalysts were then screened under the selected conditions (entries 2−5). When AgO_2CCF_3 was employed as the catalyst, the yield was increased to 77% (entry 5). Afterward, the effect of oxidants was examined, which showed $(NH_4)_2S_2O_8$ to be the most suitable choice, delivering **3aa** in 81% yield (entry 7). Running the reaction in other solvents, such as *N*,*N*-dimethylformamide (DMF), acetonitrile (MeCN), and *N*-methylpyrrolidinone (NMP), led to reduced efficiencies (entries 8−10). The control experiment demonstrated that AgO_2CCF_3 is crucial for this Ag-catalyzed formal [3 + 2] cycloaddition reaction (entry 12).

Table 1. Optimization of Reaction Conditions[a]

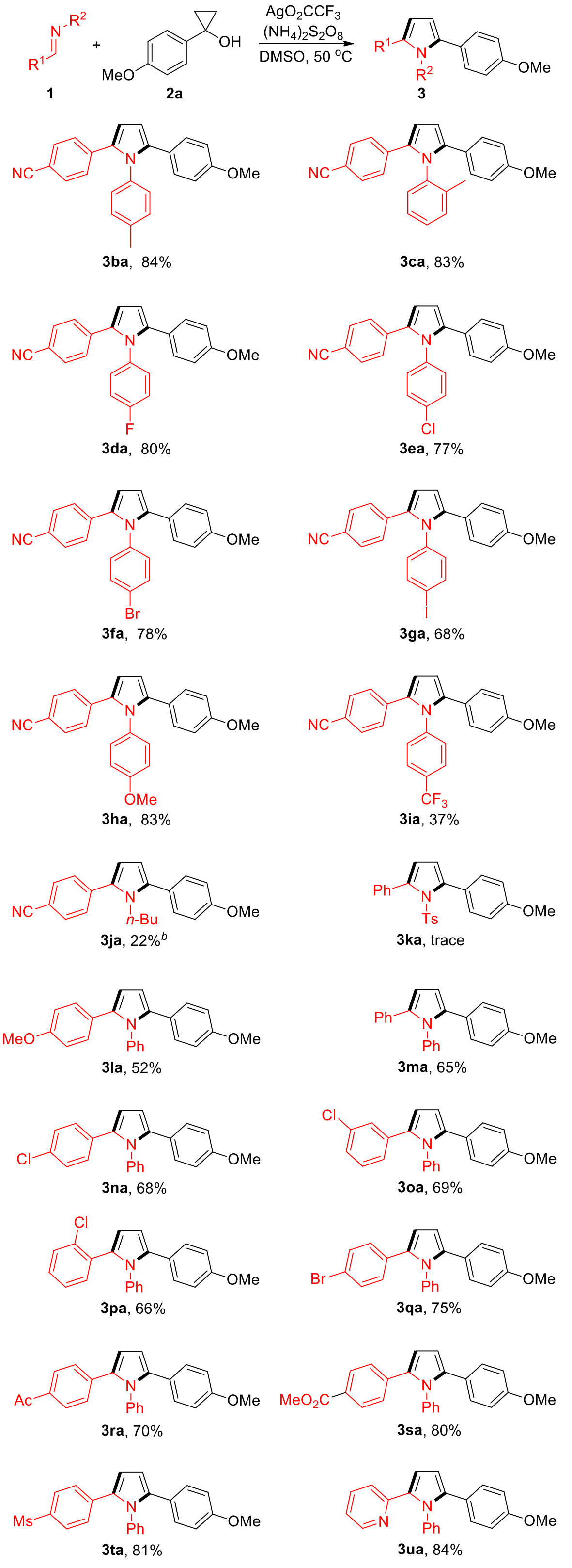


entry	[M]	oxidant	solvent	yield[b] (%)
1	$AgNO_3$	$Na_2S_2O_8$	DMSO	71
2	AgOAc	$Na_2S_2O_8$	DMSO	65
3	Ag_2CO_3	$Na_2S_2O_8$	DMSO	32
4	$AgBF_4$	$Na_2S_2O_8$	DMSO	43
5	AgO_2CCF_3	$Na_2S_2O_8$	DMSO	77
6	AgO_2CCF_3	$K_2S_2O_8$	DMSO	40
7	AgO_2CCF_3	$(NH_4)_2S_2O_8$	DMSO	81 (76)[c]
8	AgO_2CCF_3	$(NH_4)_2S_2O_8$	DMF	trace
9	AgO_2CCF_3	$(NH_4)_2S_2O_8$	MeCN	22
10	AgO_2CCF_3	$(NH_4)_2S_2O_8$	NMP	trace
11	AgO_2CCF_3	$(NH_4)_2S_2O_8$[d]	DMSO	49
12	none	$(NH_4)_2S_2O_8$	DMSO	15

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), [M] (10 mol %), oxidant (0.75 mmol), solvent (6 mL), 50 °C, 10 h. [b] Isolated yield. [c] Yield on a 1.0 mmol scale. [d] 0.5 mmol of $(NH_4)_2S_2O_8$ was used.

After determining the optimized reaction conditions, the scope of this reaction was explored in the context of various imines using **2a** as the coupling partner (Scheme 2). The 4- and 2-methyl benzenamine-derived imines **1b** and **1c** afforded the expected pyrroles **3ba** and **3ca** in comparable yields, suggesting that the steric hindrance of the R^2 group has little impact on the reaction. *N*-Arylimines bearing Me, F, Cl, Br, I, OMe, and CF_3 were all competent substrates, furnishing the corresponding 1,2,5-trisubstituted pyrroles in moderate to high yields (**3ba**−**3ia**). 4-Methoxyaniline-derived imine **1h** afforded the anticipated product **3ha** in 83% yield, while 4-trifluoromethylaniline-derived imine **1i** delivered the corresponding pyrrole **3ia** in 37% yield. These results indicated that substitution of the nitrogen atom of imines with an electron-deficient benzene ring is unfavorable for the reaction.

Scheme 2. Scope with Respect to the Imines[a]

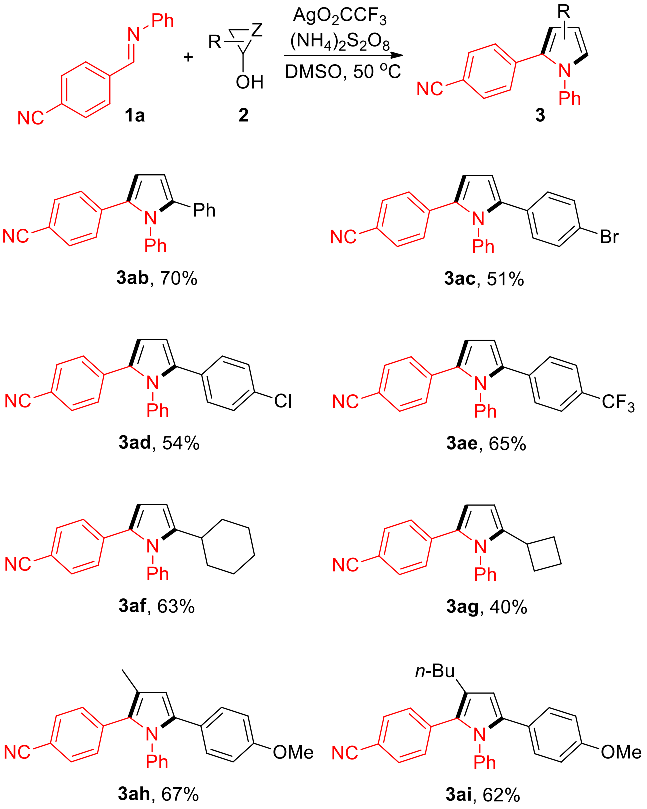


[a] Reaction conditions: **1** (0.25 mmol), **2a** (0.5 mmol), AgO_2CCF_3 (10 mol %), $(NH_4)_2S_2O_8$ (0.75 mmol), DMSO (6 mL), 50 °C, 10 h. Yields of isolated products are given. [b] $AgNO_3$ (10 mol %) and $Na_2S_2O_8$ (0.75 mmol) were used.

In addition to *N*-aryl imines, we also examined the reaction of *N*-alkyl imines. The coupling of *N*-*n*-Bu imine **1j** with **2a** occurred as well, albeit in a low yield (**3ja**). In contrast, this reaction could not be extended to the *N*-sulfonyl imine **1k**. Modulation of the aryl ring of R^1 group with various substituents was feasible. Both the electron-donating (**1l**) and electron-withdrawing groups (**1r**−**1t**) were well tolerated under the reaction conditions, and relatively higher yields were observed for the latter cases (**3ra**−**3ta**). Additionally, imines with heteroaryl groups like pyridine underwent the reaction uneventfully to produce the desired pyrrole in high yield (**3ua**). The imine **1v** (R^1 = *n*-Bu, R^2 = 4-tol), derived from an aliphatic aldehyde, failed to provide the expected product under the conditions.

Subsequently, we focused on investigation of the effects of the cyclopropanol structure. As shown in Scheme 3, the reaction of both 1-aryl- and 1-alkyl-substituted cyclopropanols proceeded smoothly to form the desired 1,2,5-trisubstituted pyrroles in reasonable yields (**3ab**−**3ag**). 2-Substituted cyclopropanols such as **2h** and **2i** were also amenable to this reaction, which produced the 1,2,3,5-tetrasubstituted pyrroles **3ah** and **3ai** in 67% and 62% yield, respectively, thus providing an attractive method for the direct synthesis of polysubstituted pyrroles from readily attained starting materials. It should be noted that halogen atoms, such as bromine and chlorine, were well tolerated for this [3 + 2] cycloaddition process, which may offer a useful handle for further elaboration of the pyrrole products.

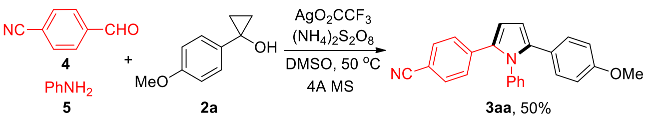
Scheme 3. Scope with Respect to the Cyclopropanols[a]



[a]Reaction conditions: **1a** (0.25 mmol), **2** (0.5 mmol), AgO_2CCF_3 (10 mol %), $(NH_4)_2S_2O_8$ (0.75 mmol), DMSO (6 mL), 50 °C, 10 h. Yields of isolated products are given.

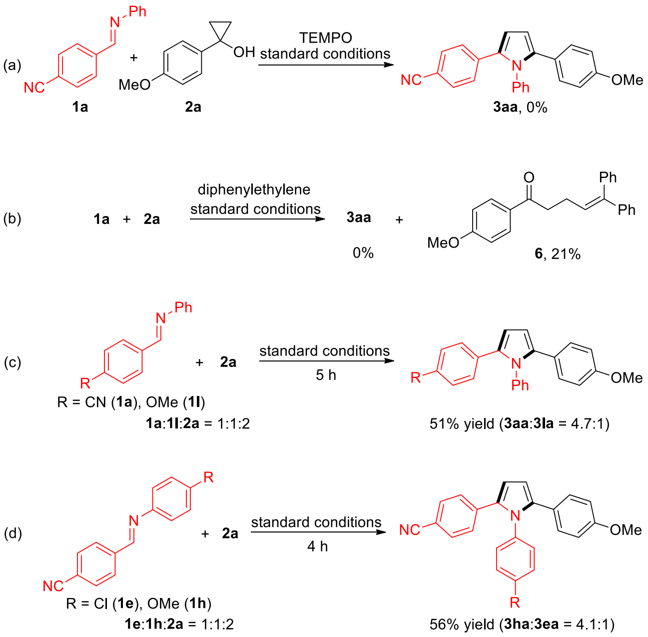
To make this method more practical, a one-pot, three-component reaction of **4**, **5**, and **2a** was conducted, which successfully delivered the expected product **3aa** in a reasonable yield (not optimized) (Scheme 4). As such, the method presented here represents an operationally simple, mild, and efficient process for the assembly of pyrroles, which are important heteroaromatic compounds and versatile structural motifs found in natural products, functional material, pharmaceuticals, and agrochemicals.[12]

Scheme 4. Three-Component Reaction



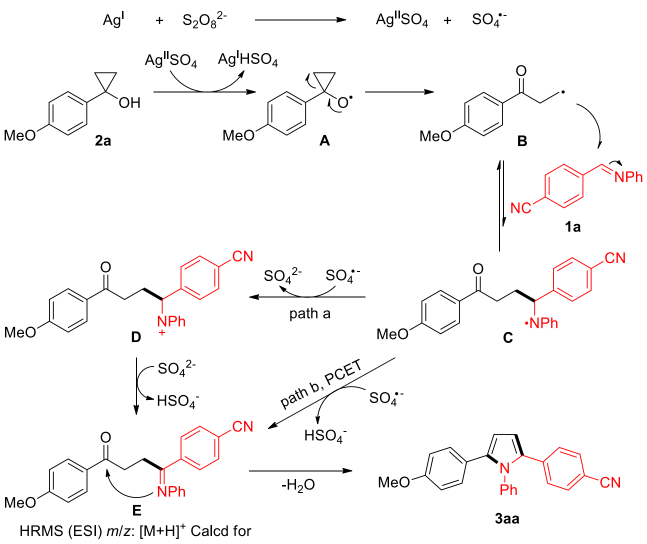
Some experiments were conducted to probe the reaction mechanism of this Ag-catalyzed ORA of cyclopropanols to imines (Scheme 5). The formation of **3aa** was completely suppressed by adding 2 equiv of 2,2,6,6-tetramethylpiperidinooxy (TEMPO) to the standard reaction conditions (Scheme 5a). The addition of 1,1-diphenylethylene also shut down the reaction and produced the alkenyl product **6a** in 21% yield (Scheme 5b). These results indicated that the radical ring-opening of cyclopropanols was feasible under the reaction conditions. The competitive reaction between **1a** and **1l** afforded a 4.7:1 mixture **3aa** and **3la** in 51% yield (Scheme 5c), suggesting that the electron-deficient aldehyde-derived imines are better radical acceptors. A 1:1 mixture of **1e** and **1h** was subjected to the reaction conditions. After being stirred at 50 °C for 4 h, a 4.1:1 mixture of **3ha** and **3ea** was obtained (Scheme 5d), which demonstrated that electron-rich amine-derived imines are better coupling partners.

Scheme 5. Mechanistic Studies



On the basis of the above results and previous reports,[5d,e] a possible reaction mechanism is depicted in Scheme 6 using substrates **1a** and **2a**. Initially, the oxidation of cyclopropanol **2a** by $AgSO_4$, generated from Ag(I) and $S_2O_8^{2-}$, produces a

Scheme 6. Proposed Mechanism



HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{21}N_2O_2$ 369.1598; Found 369.1606

cycloalkanoxyl radical **A**.[11] The ring-opening of **A** followed by the intermolecular radical addition to **1a** affords an aminyl radical **C**. SET oxidation of **C** by sulfate radical ($SO_4^{\bullet-}$) and a subsequent deprotonation (path a) or a concerted proton-coupled electron transfer (PCET, path b) between **C** and $SO_4^{\bullet-}$ may produce the ketone-imine intermediate **E**, which undergoes the intramolecular addition of nitrogen atom to carbonyl group followed by release of H_2O to generate the pyrrole **3aa** as the final product.[13] Although the isolation of intermediate **E** was unsuccessful under the reaction conditions, its intermediacy could be confirmed by the HRMS analysis. The p−π conjugating effect between the phenyl group and aminyl radical **C** or aminyl cation **D** may facilitate the transformation.

In conclusion, a novel method for the direct synthesis of polysubstituted pyrroles has been established via a Ag-catalyzed formal [3 + 2] cycloaddition reaction, featuring the use of cyclopropanols as a C3 subunit and imines as a two-atom subunit. The pyrrole motif is constructed from two readily available components in a convergent fashion, thus offering a highly efficient and attractive approach to access polysubstituted pyrroles. This reaction constitutes the first example of the ORA to simple imines, which provides a new approach for the direct C−H functionalization of imines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02735.

Detailed experimental procedures; characterization data for the products **3** and **6** (PDF)

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Notes

The authors declare no competing financial interest.

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