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Ruthenium-Porphyrin-Catalyzed [4 + 2] Cycloaddition of α,β-Unsaturated Imines and Aldehydes

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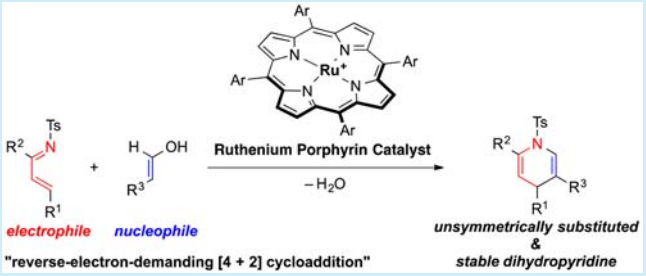
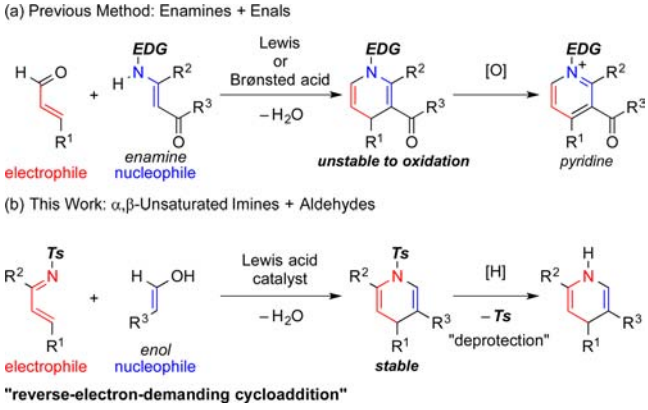
Supporting Information

ABSTRACT: A new efficient synthetic route to unsymmetrically substituted dihydropyridine scaffolds via dehydrative [4 + 2] cycloaddition of *N*-tosylated α,β-unsaturated imines with aldehydes has been developed. This transformation is enabled by (i) the remarkable catalytic ability of the cationic Ru(IV) porphyrin complex to activate both the imino and carbonyl groups and (ii) the hydrophobic nature of the porphyrin ligand, which helps realize robust Lewis acidity in the dehydrative cycloaddition.



An essential role in biological processes through NADH regeneration is played by 1,4-dihydropyridine scaffolds. Furthermore, they show specific and significant medicinal properties, i.e., they function as L-type calcium channel blockers in the treatment of hypertension.[1] Moreover, because of their reducing nature, dihydropyridines have attracted considerable attention as potential biomimetic reductants in combination with organocatalysts.[2] Following Hantzsch's report on the most convenient route to symmetrically substituted dihydropyridines,[3] the medicinal and synthetic applications of these compounds have seen a notable increase. However, for effective control of the chemical properties of dihydropyridines, reliable synthetic routes to *unsymmetrically substituted* or more complicatedly substituted dihydropyridines must be designed. Several modifications of Hantzsch's method have been proposed for the synthesis of unsymmetrical dihydropyridine derivatives via [3 + 3] cycloaddition of electrophilic enals with nucleophilic enamines (Scheme 1 (a)).[4] However, the electron-donating groups on the nitrogen atoms, which are required to enhance the nucleophilicity of the enamines, may induce oxidation of the resulting products to form pyridine scaffolds. This phenomenon leads to poor modifiability in the synthesis of structurally diverse dihydropyridines.

Scheme 1. Synthetic Routes to Dihydropyridine Derivatives



To solve the underlying problems in dihydropyridine synthesis, we chose to design a new synthetic route to unsymmetrically substituted dihydropyridines. We hypothesized the following: *N*-tosylated α,β-unsaturated imines can be used as nitrogen sources and electrophiles in the presence of Lewis acid catalysts, so that dehydrative [4 + 2] cycloaddition with aldehydes, which provide enol-type nucleophiles *in situ*, affords the desired dihydropyridine. The resulting product would be stable to undesired oxidation owing to the electron-withdrawing tosyl groups. The imine used can be considered as *a reverse-electron-demanding nitrogen atom source component*, as opposed to the conventional approach (Scheme 1 (b)). Furthermore, the tosyl groups can be removed under reductive conditions, so that oxidation-sensitive unprotected dihydropyridines can be obtained. Herein, we report that the intermolecular reaction of α,β-unsaturated imines with aldehydes affords dihydropyridines in a single step.

Porphyrins have emerged as useful ligands for transition-metal catalysts in organic synthesis, when the use of other ligands is infeasible.[5] During the course of our recent study on metalloporphyrin-catalyzed cycloaddition to afford various heterocycles, we postulated that metalloporphyrins also catalyze the cycloaddition of α,β-unsaturated imines with aldehydes to afford dihydropyridines.

To prove our hypothesis, we examined the reaction with an *N*-tosylated α,β-unsaturated imine **1a** and a highly enolizable

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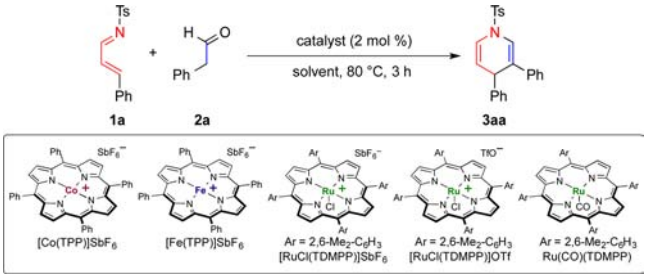
aldehyde **2a** as model substrates (Table 1), using various catalysts and solvents.[6] In this reaction, we first chose the

Table 1. Dehydrative [4 + 2] Cycloaddition of α,β-Unsaturated Imines 1a and Aldehydes 2a[a]



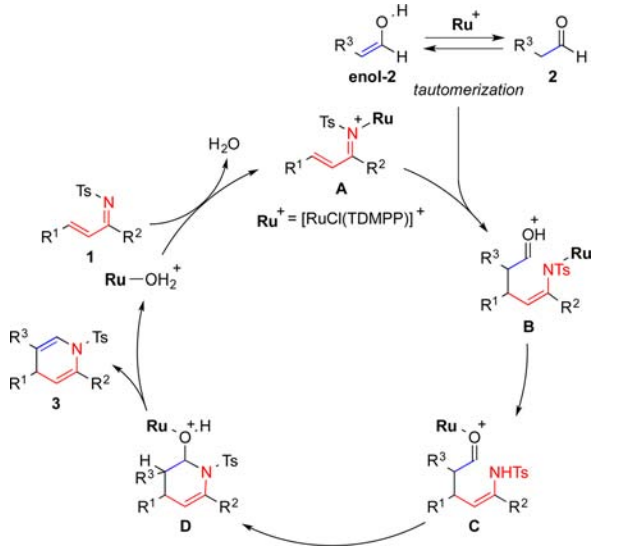
entry	catalyst	solvent	yield (%)[b]
1	$[Co(TPP)]SbF_6$	toluene	17
2	$[Fe(TPP)]SbF_6$	toluene	24
3	$[Co(TPP)]SbF_6$+$[Fe(TPP)]SbF_6$[c]	toluene	44
4	$[RuCl(TDMPP)]SbF_6$	toluene	62
5	$[Mn(TPP)]SbF_6$	toluene	<1
6	$[Cr(TPP)]SbF_6$	toluene	14
7	$[Ru(TDMPP)](SbF_6)_2$	toluene	62
8	$[RuCl(TDMPP)]BF_4$	toluene	62
9	[RuCl(TDMPP)]OTf	toluene	79[d]
10	Ru(CO) (TDMPP)	toluene	<1

[a]Reactions were carried out using catalysts (2 mol %), **1a** (0.6 mmol, 3 equiv), and **2a** (0.2 mmol) in 2 mL of toluene (80 °C) for 3 h. [b]Determined by ^1H NMR analysis using TCE (1,1,2,2-tetrachloroethane) as internal standards. [c]1 mol % of each metal porphyrin complex was used. [d]Isolated yields. TDMPP: 5,10,15,20-tetrakis(2,6-dimethylphenyl)porphyrinato. TPP: 5,10,15,20-tetraphenylporphyrinato.

cationic cobalt(III) porphyrin complex as the Lewis acid catalyst. We have previously reported that such a catalyst efficiently activates *N*-tosylated imines to undergo the aza-Diels–Alder reaction with unactivated dienes;[7] hence, we believed that it might be a good catalyst for the present cycloaddition as well. Indeed, the reaction of **1a** and **2a** in the presence of $[Co(TPP)]SbF_6$ (2 mol %) afforded the desired product **3aa** in 17% yield (entry 1).[8] The reaction with $[Fe(TPP)]SbF_6$ (2 mol %), which is an efficient catalyst for aldehyde activation,[9] also afforded the product in 24% yield (entry 2). The yield of **3aa** improved to 44% when a combination of $[Co(TPP)]SbF_6$ (1 mol %) and $[Fe(TPP)]SbF_6$ (1 mol %) was used as the catalyst (entry 3). This result suggests that *ability to activate both the imino group and the aldehyde group* is a requisite for the catalyst. Motivated by this result, we next selected ruthenium porphyrins, which are well-known to show remarkable reactivity,[10] as catalysts for the reaction. We also had previously demonstrated that cationic Ru porphyrins are effective catalysts for carbonyl and *N*-tosylated imino activation.[11,12] In the present study, the cationic Ru(IV) porphyrin catalyst $[RuCl(TDMPP)]SbF_6$ afforded **3aa** in yields as high as 62% (entry 4). Other metal porphyrins such as manganese(III) and chromium(III) porphyrins were unreactive for the cycloaddition (entries 5, 6).[13] Thus, Ru porphyrin catalyst was identified as the best Lewis acid catalyst for the cycloaddition. Notably, nonporphyrin-ligated acid catalysts such as ruthenium chloride and iron chloride showed lower catalytic activity than did the ruthenium porphyrin catalyst or failed to catalyze the reaction (Table S1). These results unambiguously show that specific characteristic of the porphyrin ligands is crucial to this reaction. The dicationic catalyst did not bring about any change in the yield of **3aa** (entry 7). The ruthenium porphyrin catalyst possessing BF_4^- instead of SbF_6^-, too, had no drastic effect on the reaction (entry 8). Eventually, ruthenium porphyrin with a ^-OTf counteranion, [RuCl(TDMPP)]OTf, was found to be the best Lewis acid catalyst that gave the highest isolated yield, 79% (entry 9). Interestingly, ruthenium carbonyl porphyrins, which are known to be efficient catalysts for the activation of various heterocompounds,[14] did not catalyze the reaction at all (entry 10). This result emphasized the importance of the cationic feature of the catalyst for this catalysis.

The reaction mechanism proposed based on these observations is outlined in Scheme 2. First, the *N*-tosylated

Scheme 2. Plausible Reaction Mechanism



unsaturated imine **1** is activated by the Ru porphyrin catalyst to give the cationic intermediate **A**. In a parallel step, the catalyst isomerizes aldehyde **2** to its enol form **enol-2**. We previously reported that the cationic ruthenium porphyrin complex has a unique property in which it enolizes carbonyl compounds;[11] this feature might play a critical role in the present reaction. The 1,4-addition of **enol-2** to **A** affords **B**, followed by intramolecular proton transfer to **C**. Sequential nucleophilic attack of the nitrogen atom onto the activated carbonyl carbon of intermediate **C** affords cyclic adduct **D**. Finally, elimination of water from **D** gives the unsymmetrically substituted dihydropyridine scaffolds. The water molecule coordinating onto the Ru center is removed by the hydrophobic environment of the porphyrin ligand,[10,14f] thus regenerating the catalyst and promoting the reaction.

With the optimized reaction conditions in hand, we investigated the effects of substituents on the *N*-tosylated α,β-unsaturated imines (Figure 1). The reaction of **1b** with **2a** afforded **3ba** in good yield. Importantly, the sterically more hindered *o*-methylphenyl group on the substrate **1c** did not affect the reactivity. The electron-donating methoxy group (**1d**), as well as the electron-withdrawing trifluoromethyl, fluoro, cyano, and nitro groups (**1e**, **1f**, **1g**, and **1h** respectively), were tolerated in this catalytic system. The substrate with a heteroaryl group such as a thienyl group was transformed to

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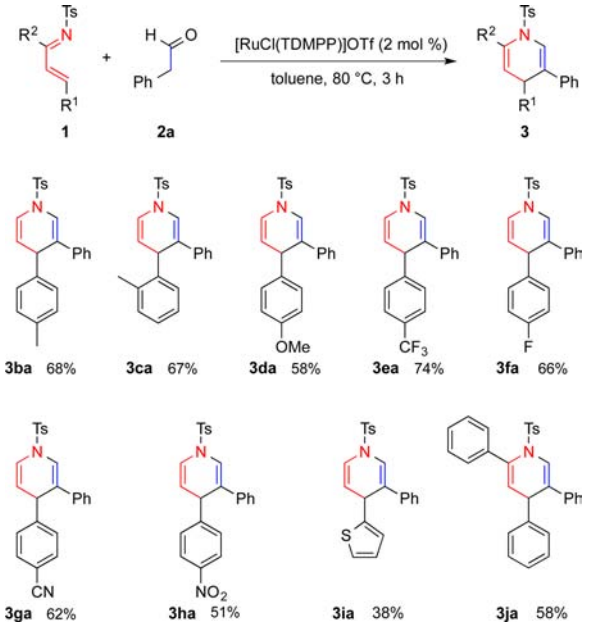

Figure 1. Cycloaddition of imines **1** and **2a**. [a]Reactions were carried out using [RuCl(TDMPP)]OTf (2 mol %), **1** (0.6 mmol, 3 equiv), and **2a** (0.2 mmol) in 2 mL of toluene (80 °C) for 3 h. [b]Isolated yields.

3ia, although the yield was low (38%). When the unsaturated ketimine **1j** was used in the reaction, the trisubstituted dihydropyridine **3ja** was obtained in good yield.

Next, the reaction scope of the aldehydes was examined (Figure 2). Aryl acetaldehydes with electron-donating func-

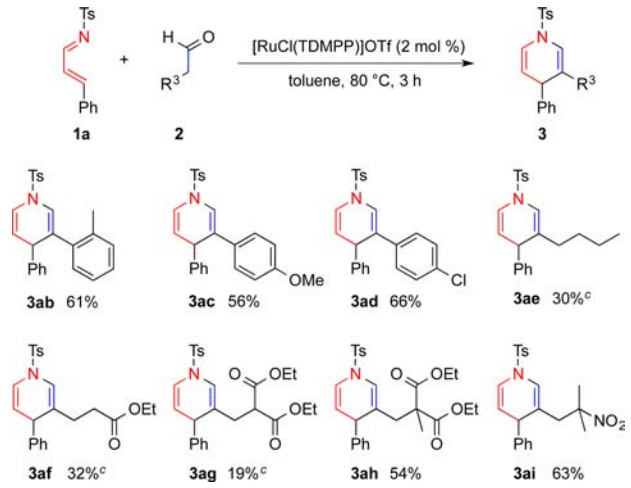

Figure 2. Cycloaddition of **1a** and aldehydes **2**. [a]Reactions were carried out using [RuCl(TDMPP)]OTf (2 mol %), **1a** (0.6 mmol, 3 equiv), and **2** (0.2 mmol) in 2 mL of toluene (80 °C) for 3 h. [b]Isolated yields. [c]Determined by ^{1}H NMR analysis using TCE as internal standards.

tional groups reacted with the unsaturated imines to give the desired products in satisfactory yields (**2b**,**2c**). Similarly, the substrate with the electron-withdrawing moiety, *p*-chlorophenylacetaldehyde **2d**, was converted to **3ad** in 66% yield. On the other hand, aliphatic aldehydes such as **2e** resulted in a very low product yield of 30%. This low reactivity of the aliphatic aldehyde was thought to be derived from its low enolizability and weak coordinating ability toward the catalyst. Therefore, we attempted to enhance the reactivity of aliphatic aldehydes by introducing electron-withdrawing coordinating groups into the alkyl chains. Introduction of mono- and diester groups at the γ-positions of the aliphatic aldehydes with active α-protons failed to promote the reaction and gave unidentifiable byproducts (**2f**, **2g**).[15] This result urged us to test the reaction of a diester-substituted aliphatic aldehyde without α-protons (**2h**). Indeed, the reaction of **2h** with **1a** afforded the desired product **3ah** with the acceptable yield. In the same way, 4-methyl-4-nitropentanal **2i** was transformed to dihydropyridine **3ai** in 63% yield. These results suggest that aliphatic aldehydes can be used with this catalytic system by effective introduction of the appropriate functional groups into the alkyl chains.

To demonstrate the synthetic utility of the reaction, we briefly examined the detosylation of the cycloadduct to prepare an unprotected dihydropyridine. Indeed, detosylation was accomplished by the use of samarium iodide as a reductant.[16]

In summary, we have developed a novel synthetic route to unsymmetrically substituted dihydropyridine derivatives via dehydrative [4 + 2] cycloaddition of *N*-tosylated α,β-unsaturated imines and aldehydes catalyzed by cationic Ru(IV) porphyrin complexes. The proposed methodology was employed for the successful synthesis of various *N*-tosylated dihydropyridine derivatives with unprecedented substitution patterns, and the cycloadducts could be converted to nontosylated dihydropyridines by reduction with samarium iodide. The proposed strategy is expected to pave the way for the construction of structurally diverse dihydropyridines, which cannot be prepared via conventional methods, and thus contributes to the design of pharmaceuticals and reductants for organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02654.

Experimental procedures, spectroscopic (FID), and analytical data for new compounds (PDF)
Crystallographic data (CIF)
Crystallographic data (CIF)
Crystallographic data (CIF)
Crystallographic data (CIF)
Additional files (ZIP)

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Notes

The authors declare no competing financial interest.

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