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Enabling Catalytic Arene C−H Amidomethylation via Bis(tosylamido)methane as a Sustainable Formaldimine Releaser

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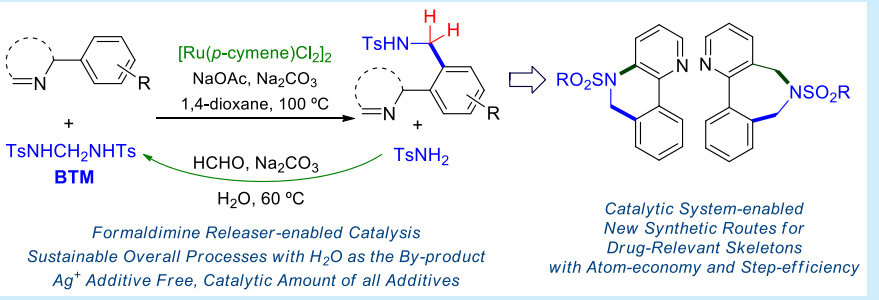
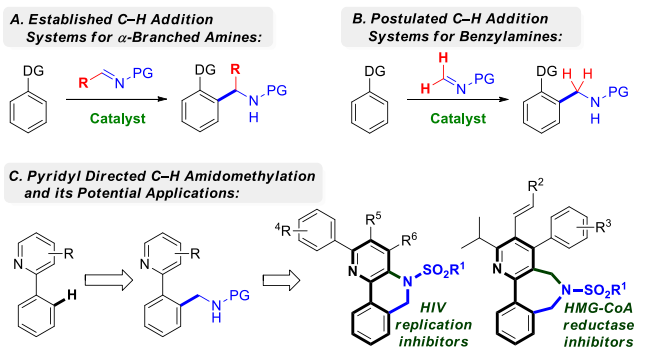
Supporting Information



ABSTRACT: Addition of catalytic arene C−H to formaldimines has been enabled by Ru(II)-catalyzed amidomethylation with bis(tosylamido)methane as a catalytic formaldimine releaser. The new process provides an atom-efficient and sustainable solution to address the challenges of formaldimines in this type of transformation. Furthermore, new synthetic routes based on this catalytic system have been developed for step-efficient access to N-heterotricyclic core structures that are pharmaceutically relevant.

Transition metal-catalyzed additions of unactivated C−H bonds to polarized π bonds represent an efficient and powerful approach for constructing molecules bearing heteroatom-based functionality.[1] Among different systems, the catalytic addition of C−H to C═N bonds is particularly applicable for making various amine products, which are closely related to biologically active molecules and pharmaceuticals.[2] In recent years, a wide spectrum of aldimines with various C substituents, including alkyl, aryl, and electron-withdrawing groups, has been developed for the synthesis of α-branched amine derivatives (Scheme 1A).[3] However, direct addition of C−H to the C-unsubstituted imines, namely formaldimines, has not been developed, although this unique type of imine would feature even higher reactivity due to its strong electrophilicity and minimum steric hindrance (Scheme 1B). These potential aminomethylation processes are highly desirable as they would enable access to various α-substituted methylamines, including benzylamine derivatives, directly from hydrocarbons.

Scheme 1. Catalytic Addition of C−H to C-Substituted Imines and Formaldimines



Metal-catalyzed sp^2 C−H activation assisted by directing groups provides a general way to access metal aryl species, which would be aminomethylated by formaldimines. Among different directing groups, 2-pyridyl is particularly attractive as the resulting 2-(2-pyridyl)benzenemethanamine units are prevalent in biologically and pharmaceutically important molecules, such as potassium channel blockers[4] and MAPKAPK2 inhibitors,[5] as well as fluorescent chemosensors[6] (Scheme 1C). Moreover, N-heterotricyclic skeletons that have recently been revealed as key backbones in HIV replication inhibitors[7] and HMG-CoA reductase inhibitors[8] can also be readily accessed from the products of C−H amidomethylation. Therefore, development of an effective catalytic system for the C−H addition of arenes, especially 2-arylpyridines, to formaldimines is highly desirable.

During the past decade, several transition metal catalysts have been developed for the addition of C−H to various C-substituted imines (Scheme 2A). Pioneered by the groups of Ellman, Bergman, and Shi, Rh(III) catalysts have been shown to be highly effective and general.[3b,d−g,j−m,o,p] The method of using Co(III) species as capable catalysts has been developed by the group of Kanai and Matsunaga.[3h,i,n] Remarkably, the

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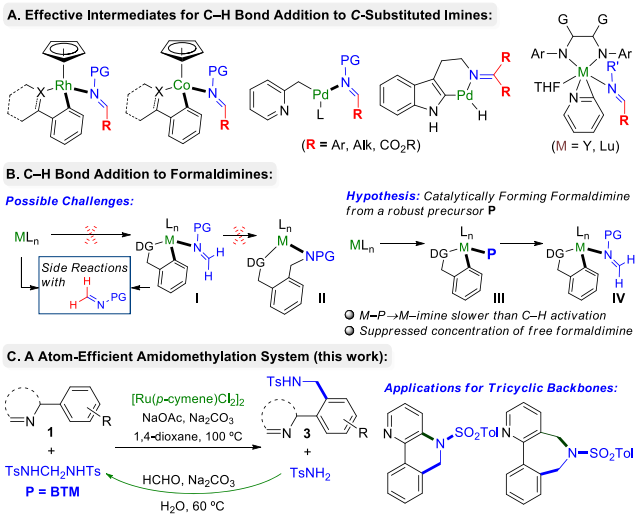
Scheme 2. Catalytic C−H Amidomethylation for the Synthesis of Benzylamine Derivatives

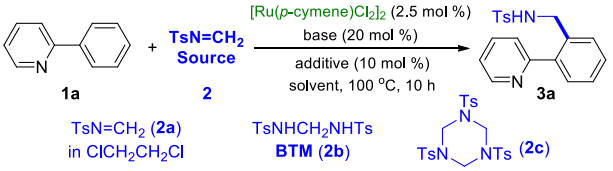


Huang group first demonstrated a palladium-catalyzed sp^3 addition of C−H to aldimines.[3q] Very recently, the group of Li and Zeng has developed an intramolecular addition of C−H to the trisubstituted imine moiety by palladium catalysts.[3a] Furthermore, early transition metals, ytterbium and lutetium, have just been disclosed as effective and stereoselective catalysts for the addition of pyridyl C−H to aldimines.[3c] Despite the rich development with C-substituted imines, formaldimines remain as a challenging class of π bond systems for catalytic C−H addition.[9]

Known for their challenging instability and excessive reactivity, formaldimines often require specific strategies for selective addition reactions.[10] The Lewis acidic and protic environment associated with the catalytic C−H activation process would cause quick decomposition and various homoadditions of formaldimines as side reactions (Scheme 2B).[10a,11] The fast consumption of formaldimine will disable the formation of the key intermediate **I**. Even when intermediate **I** is formed, its Lewis acid-activated formaldimine moiety would undergo faster side reactions with surrounding free imines than the desired insertion. To address these selectivity issues, identifying suitable precursors that could catalytically release the formaldimines at a proper rate appears to be crucial. We envision that a robust precursor that undergoes slower decomposition to formaldimines than the C−H activation step would promote the selective formation of intermediate **III**. The subsequently formed metal formaldimine complex **IV** would prefer the insertion reactions due to the suppressed concentration of free formaldimines in the system. Once the selectivity issues are addressed, the intrinsically reactive formaldimines would conduct productive C−H addition processes.

As a result, herein we wish to report the development of bis(tosylamido)methane (BTM) as a highly selective and sustainable formaldimine releaser for the catalytic arene C−H addition reactions (Scheme 2C). While Ru(II) species commonly tolerate imines as directing groups[12] and have barely been shown to catalyze addition of C−H to imines,[13] $[Ru(p\text{-cymene})Cl_2]_2$ has been proven to be highly effective for this amidomethylation system. Reagent BTM is synthesized in water with formaldehyde and tosylamide,[11] which is the only byproduct from the catalytic process. Considering the recyclable tosylamide, the overall production generates water as the sole stoichiometric byproduct. Moreover, the catalytic system employs only a catalytic amount of sodium salts, with

Table 1. Catalytic C−H Amidomethylation with Different Formaldimine Sources under Varied Conditions[a]



entry	imine source	base	additive	solvent	yield (%)[b]
1	$TsN{=}CH_2$ (sol) (**2a**)	–	NaOAc	$ClCH_2CH_2Cl$	<5
2	$TsNHCH_2NHTs$ (**2b**)	–	NaOAc	$ClCH_2CH_2Cl$	40
3	**2a**	Na_2CO_3	NaOAc	$ClCH_2CH_2Cl$	<5
4	**2b**	Na_2CO_3	NaOAc	$ClCH_2CH_2Cl$	81
5	**2b**	Na_2CO_3	NaOAc	toluene	57
6	**2b**	Na_2CO_3	NaOAc	1,4-dioxane	92 (86)[c]
7[d]	**2b**	Na_2CO_3	NaOAc	1,4-dioxane	nr
8	$(TsNCH_2)_3$ (**2c**)	Na_2CO_3	NaOAc	1,4-dioxane	68
9	**2b**	Li_2CO_3	NaOAc	1,4-dioxane	trace
10	**2b**	K_2CO_3	NaOAc	1,4-dioxane	87
11	**2b**	Cs_2CO_3	NaOAc	1,4-dioxane	64
12	**2b**	Na_2CO_3	KOAc	1,4-dioxane	86
13	**2b**	Na_2CO_3	–	1,4-dioxane	70
14	**2b**	Na_2CO_3	$MesCO_2H$	1,4-dioxane	47
15	**2b**	Na_2CO_3	Ph_2POH	1,4-dioxane	62
16	**2b**	Na_2CO_3	PPh_3	1,4-dioxane	49

[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol %), base (20 mol %), additive (10 mol %), solvent (0.5 mL), 100 °C, 10 h, under N_2. [b]The yield was determined by crude ^1H NMR with $PhNO_2$ as the internal standard. [c]Isolated yield in parentheses. [d]In the absence of the Ru catalyst.

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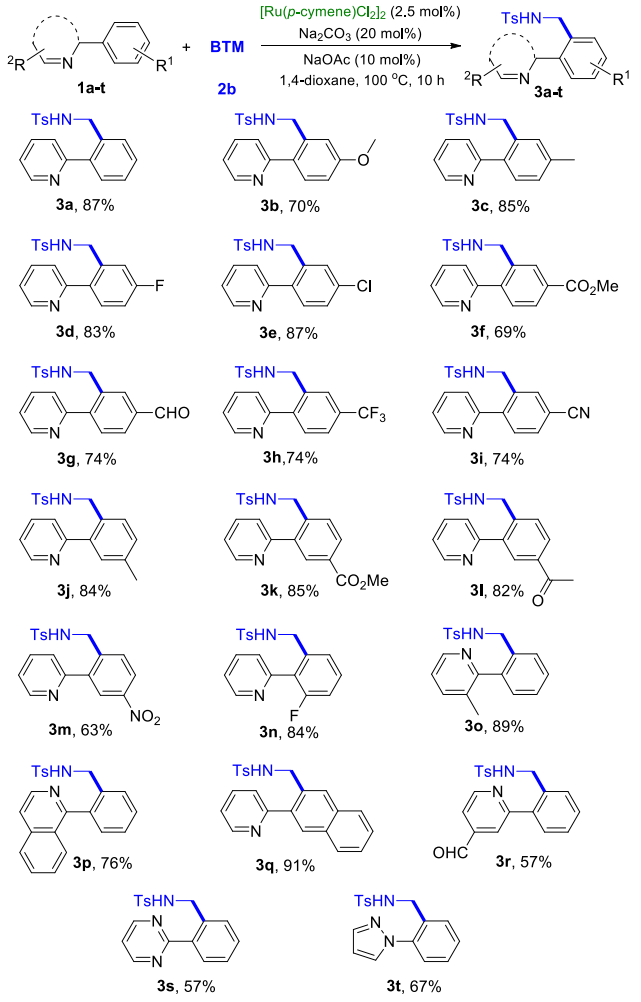
no need for silver salts that are commonly required in other systems, or other stoichiometric additives. As applications, new synthetic routes based on this catalytic system have been demonstrated for more atom-economic and step-efficient syntheses of two drug-related tricyclic skeletons.

Initial experiments were performed seeking an effective amidomethylative reagent for the proposed C−H addition (Table 1). Using 2-phenylpyridine (**1a**) as the model substrate and $[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst, formaldimine sources are investigated in the presence of 10 mol % NaOAc, which is commonly used to facilitate the metalation−deprotonation step.[14] Attempts started with a freshly prepared *N*-tosyl formaldimine (**2a**) solution, which was used successfully in our amidomethylative [2+2+2] reactions.[15] However, it was shown to be an ineffective reagent in this C−H addition system (Table 1, entry 1). Bis(tosylamido)methane (**2b**, BTM), which is readily synthesized under basic conditions,[13] would be a promising reagent as it could be activated by Lewis acids to form formaldimine **2a**. If the metal species can decompose it into **2a** at a matching rate, a productive reaction would be observed. As expected, the same conditions with BTM resulted in the desired *N*-[2-(pyridin-2-yl)benzyl]-sulfonamide **3a** in 40% yield (Table 1, entry 2). A slightly more basic condition with a catalytic amount of Na_2CO_3 led to a significantly increased yield of 81% with BTM, while hardly any reaction was observed again with a fresh **2a** solution (Table 1, entries 3 and 4, respectively). Solvent screening revealed better performance in dioxane, giving the product in 92% NMR yield (Table 1, entries 5 and 6). After confirming the necessity of the Ru(II) catalyst (Table 1, entry 7), we introduced 1,3,5-tritosyl-1,3,5-triazinane (**2c**) as another imine source, which ended up with a yield significantly lower than that under the optimal conditions (Table 1, entry 8). A possible reason may be that disassembly of this trimer was not able to cleanly generate the imine monomer. Subsequent experiments examined the cationic effects of the system with BTM (Table 1, entries 9−12). These indicated that Na and K salts are generally effective while Li_2CO_3 has slowed the reaction, presumably due to a stronger complexation of Li^+ with acetate anions. It is interesting to note that the reaction proceeded even without acetate as the additive, albeit with a lower yield (Table 1, entry 13). To improve our understanding of the additive effects, sterically hindered acid, secondary phosphine oxide, and triphenylphosphine were tested instead of the acetate (Table 1, entries 14−16, respectively). While they did not stifle the reactions, only moderate yields were observed. Notably, no silver salts are needed in these catalytic reactions.

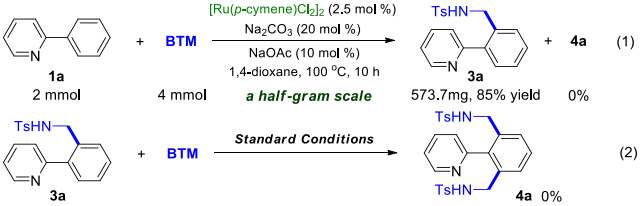
After BTM has been identified as a highly effective reagent that enables the C−H amidomethylation reaction with 2-phenylpyridine, continued efforts were focused on the substrate scope (Table 2). As expected, the amidomethylation exhibits high reactivity and tolerance to functional groups with different electronic properties, as exemplified by substrates **3b**−**3i** with varied electron-donating and -withdrawing *para* substituents. Generally good yields were also observed with substrates with methyl, ester, ketone, and nitro groups as *meta* substituents of the 2-phenylpyridines (**3j**−**3m**, respectively). Furthermore, *ortho* substituents on the phenyl and pyridyl rings have been shown to be effective, as demonstrated by products **3n** and **3o**. Moreover, sterically encumbered 1-phenylisoquinoline with a fused ring on the directing group side and 2-(naphthalen-2-yl)pyridine afforded 76% and 91%

Table 2. Bis(tosylamido)methane as an Effective Formaldimine Source for Ru(II)-Catalyzed Arene C−H Amidomethylation[a]



[a]Reaction conditions: **1** (0.1 mmol), **2b** (0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol %), Na_2CO_3 (20 mol %), NaOAc (10 mol %), 1,4-dioxane (0.5 mL), 100 °C, 10 h, under N_2. Isolated yields were recorded.

yields, respectively (**3p** and **3q**, respectively). Finally, electronically diverse directing groups, such as the 4-formyl pyridyl, pyrimidinyl, and pyrazolyl groups, have all been shown to smoothly afford the corresponding products (**3r**−**3t**, respectively).



To further test the practicality of the catalytic system, a half-gram-scale reaction was carried out under the standard conditions and afforded product **3a** in 85% isolated yield, indicating a good scalability of the process (eq 1). Notably, even in this larger-scale reaction, no bis-amidomethylated product **4a** was detected. The complete selectivity of monoamidomethylation was further confirmed by the negative

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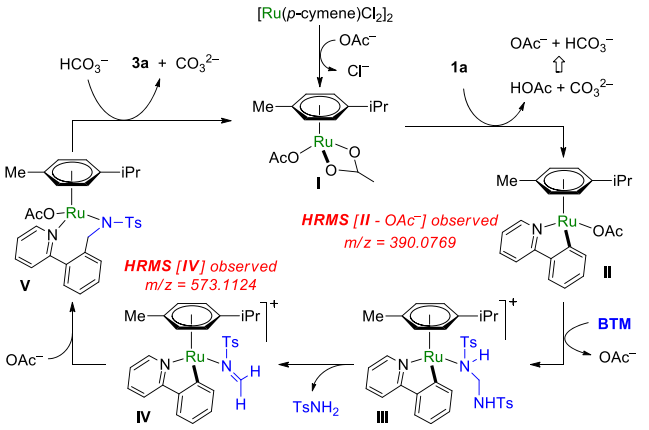
result from a reaction with **3a** as the reactant under the standard conditions (eq 2).

Previous mechanistic studies of the addition of C−H to C-substituted imines set a foundation for a plausible mechanism for this Ru(II)-catalyzed amidomethylation (Scheme 3).[1a−d,16]

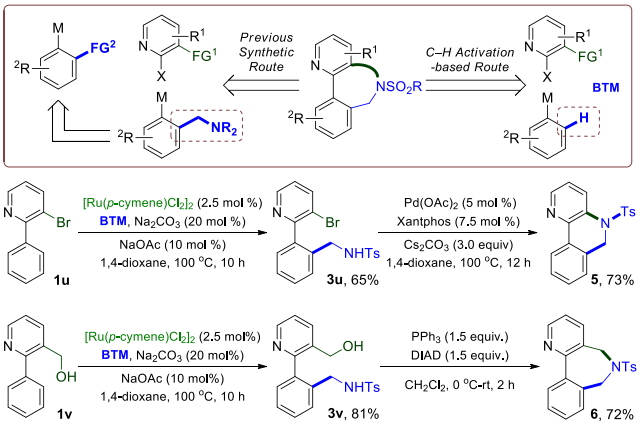
Scheme 3. A Plausible Mechanism for Ru(II)-Catalyzed C−H Amidomethylation with Bis(tosylamido)methane



Upon activation of the precatalyst $[Ru(p\text{-cymene})Cl_2]_2$, it is hypothesized that intermediate **I** would undergo a faster C−H activation to form a five-membered ruthenacycle **II** rather than to decompose BTM (for the H/D exchange reaction, see the Supporting Information). HRMS study of the reaction system indicated a major species matching cationic intermediate **II** without the acetate anion (see the Supporting Information for details). As a weak ligand, BTM would substitute the acetate in intermediate **II** to afford **III**, which might undergo a Lewis acid-facilitated decomposition to form Ru-imine intermediate **IV**. To our delight, cationic intermediate **IV** is also supported by the HRMS experiment. The catalytic formation of the imine units would largely suppress the concentration of the free formaldimine and thus promote the desired insertion reaction toward intermediate **V**. The major HRMS peak for Ru-formaldimine intermediate **IV** is consistent with the hypothesis that C−H activation is likely to have a rate faster than that of the decomposition of BTM. Finally, protonolysis of intermediate **V** occurred to produce **3a** and regenerate the catalyst.

The BTM-enabled catalytic system provides atom- and step-economic access to drug-relevant tricyclic structures, including 5-sulfonyl-5,6-dihydrobenzo[*c*][1,5]naphthyridine that is the backbone of a class of HIV replication inhibitors[7] and 6-sulfonyl-6,7-dihydro-5*H*-benzo[*c*]pyrido[2,3-*e*]azepine that is the core of a class of HMG-CoA reductase inhibitors (Schemes 1 and 4).[8] While the existing syntheses generally relied on the preinstallation of functional groups on both aryl and pyridyl sides for the closure of the central N-heterocycle,[7,8] we have designed new synthetic routes for both types of tricyclic backbones based on C−H amidomethylation. The access to **5** became promising when the catalytic process was proven to be successful with 2-phenylpyridine **1u** bearing a sterically hindered *o*-bromo atom. The resulting **3u** was smoothly transformed to tricyclic model compound **5** via Pd-catalyzed C−N coupling in satisfying yield. A new route to **6** was realized upon the successful tolerance of an *o*-hydroxymethyl group in the catalytic formation of **3v**, which was then readily cyclized to afford **6** via a Mitsunobu reaction. The new pathways to

Scheme 4. Synthetic Applications for Heterotricyclic Backbones



both core structures would provide general access, with increased step economy, to various functionalized targets.

In summary, catalytic addition of C−H to formaldimines has been developed as an effective and practical tool for the amidomethylation of arenes. Bis(tosylamido)methane has been revealed as a sustainable and readily available reagent that enabled the amidomethylation of 2-phenylpyridine derivatives. The hypothesized dual roles of the Ru(II) catalyst, including the catalytically controlled release of the formaldimine species, has led to the development of the working system. Furthermore, new synthetic routes based on this catalytic system have been developed for atom-economic and step-efficient syntheses of pharmaceutically relevant N-heterotricyclic structures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01183.

Experimental details and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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