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Rh(III)-Catalyzed C−H Bond Addition/Amine-Mediated Cyclization of Bis-Michael Acceptors

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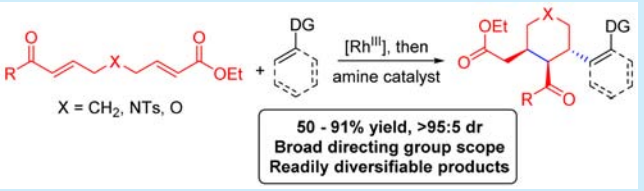
Supporting Information

ABSTRACT: A Rh(III)-catalyzed C−H bond addition/primary amine-promoted cyclization of bis-Michael acceptors is reported. The C−H bond addition step occurs with high chemoselectivity, and the subsequent intramolecular Michael addition, mediated by a primary amine catalyst, sets three contiguous stereocenters with high diastereoselectivity. A broad range of directing groups and both aromatic and alkenyl C−H bonds were shown to be effective in this transformation, affording functionalized piperidines, tetrahydropyrans, and cyclohexanes.



Transition-metal-catalyzed C−H functionalization has emerged as a powerful strategy for the synthesis of important medicinally relevant motifs.[1] In this regard, pentamethylcyclopentadienyl-ligated rhodium(III) (Cp^*Rh^{III}) catalysts have proven to be very effective for chelation-assisted C−H functionalization with high functional group compatibility.[2] Rh(III)-catalyzed additions to an alkene π-bond followed by cyclization upon the directing group have in particular been developed as a versatile approach for the rapid generation of various carbocyclic and heterocyclic products.[3]

In contrast, to our knowledge, there are only two examples of a Rh(III)-catalyzed C−H addition/cyclization sequence involving two tethered electrophiles. Tian, Lin, and co-workers reported the synthesis of substituted tetrahydrofurans by C−H bond addition to a terminal alkyne followed by cyclization upon a tethered enone (Scheme 1A).[4] As well, we have recently demonstrated a Rh(III)-catalyzed C−H addition/cyclization cascade using substrates containing an enone tethered to an aldehyde (Scheme 1B).[5,6] This reaction produces cyclic β-hydroxy ketones containing three contiguous stereocenters and proceeds in high yields and with high diastereoselectivity.

Herein, we have expanded the types of tethered electrophiles that can be employed by implementing a sequential catalysis approach with the initial Rh(III)-catalyzed C−H bond addition step followed by an organocatalytic transformation as demonstrated for C−H addition/primary amine-mediated cyclization of bis-Michael acceptors (Scheme 1C).[7] Piperidines, tetrahydropyrans, and cyclohexanes with three contiguous stereocenters were synthesized in good to excellent yields and with very high diastereoselectivities for a variety of directing groups and for both aromatic and alkenyl C−H bonds.

We began our investigation by employing amine tethered bis-Michael acceptor **1a** and pyridyl C−H functionalization substrate **2a** (Table 1). We reasoned that the enone and enoate functionality of **1a** would provide sufficient electronic differentiation to enable chemoselectivity in the initial Rh(III)-catalyzed C−H addition step. Using $[Cp^*RhCl_2]_2$ as a precatalyst and $AgSbF_6$ as the chloride abstractor with 20 mol % of AcOH in 1,4-dioxane as solvent, 89% of the conjugate addition product **3a** was observed (entry 1). Although desired product **4a** was not formed, we noted excellent chemoselectivity for the Rh(III) C−H addition across the alkene of the enone. In the absence of $[Cp^*RhCl_2]_2$ or $AgSbF_6$, no reaction was observed (entries 2 and 3). After significant screening of solvents, temperatures, and additives, **4a** was not observed,

Scheme 1. Rh(III)-Catalyzed C−H Addition/Cyclization Sequences Involving Tethered Electrophiles

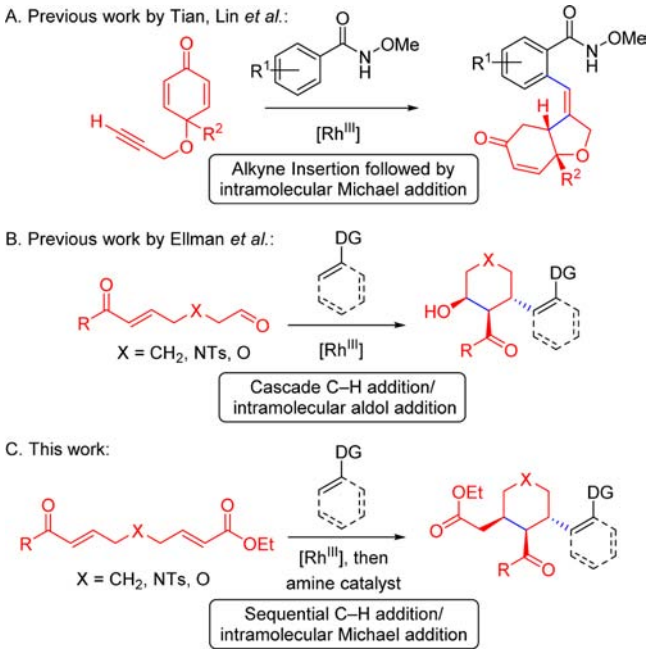


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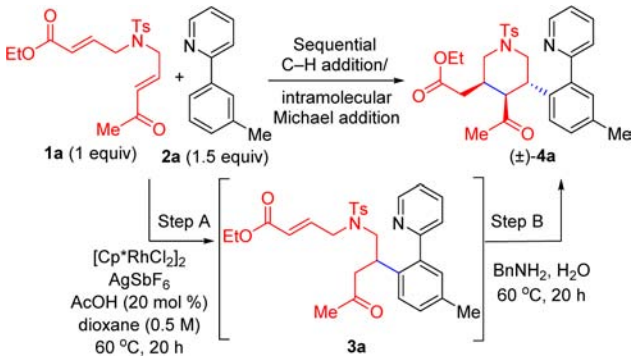
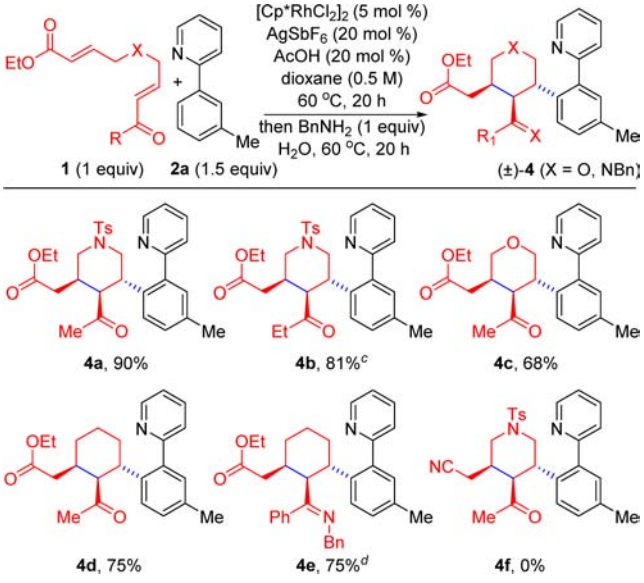
Table 1. Optimization of Reaction Conditions[a]



	step A		step B		yield (%)[b]	
entry[a]	Rh/Ag (mol %)	$BnNH_2$ (mol %)	H_2O (% vol)		**3a**	**4a**
1	5/20				89	0
2	0/20				0	0
3	5/0				0	0
4[c]	5/20	20	5		43	22
5[c]	5/20	100	5		0	0
6[d]	5/20	20	5		0	82(92)[e]
7[d]	5/20	100	5		0	70(90)[e]

[a]Conditions: 0.10 mmol of **1a** and 0.15 mmol of **2a** with $[Cp^*RhCl_2]_2$, $AgSbF_6$, 20 mol % of AcOH in dioxane (0.5 M) at 60 °C for 20 h. [b]Yields determined by ^1H NMR spectroscopic analysis relative to $SiMe_3Ph$ as an external standard. [c]$BnNH_2$ and H_2O added at t = 0. [d]After 20 h, $BnNH_2$ and H_2O were added, and the reaction mixture was heated at 60 °C for 20 h. [e]At 0.20 mmol scale with isolated yield in parentheses.

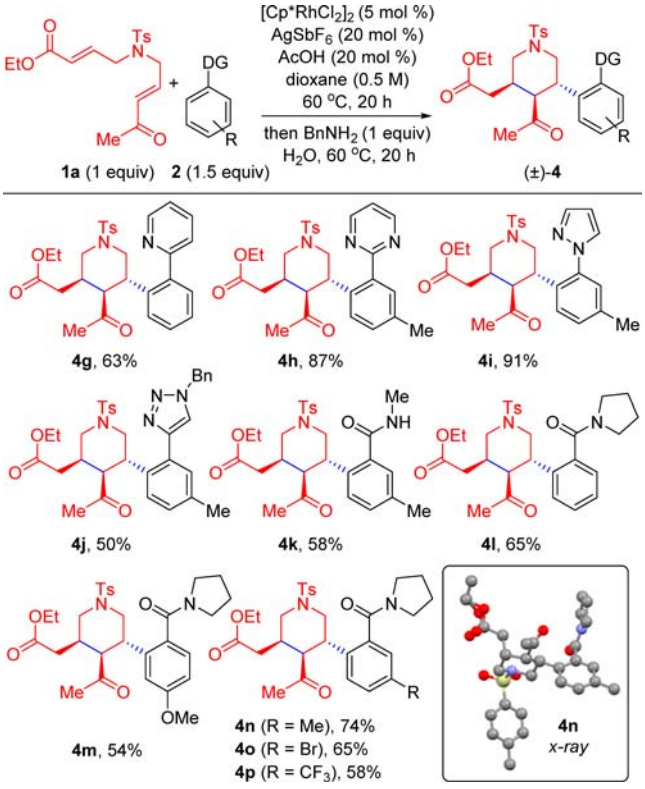
Scheme 2. Scope for Tethered Electrophile[a,b]



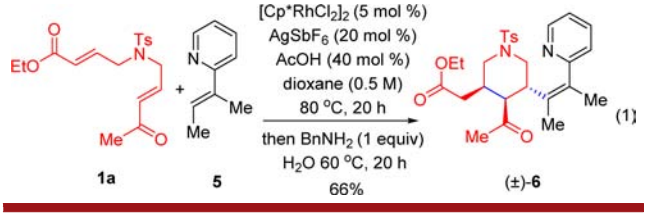
[a]Conditions: 0.20 mmol of **1** and 0.3 mmol of **2a** in dioxane (0.5 M). [b]Isolated yields after silica gel chromatography. [c]Reaction conducted using 40 mol % of AcOH and 40 μL of H_2O instead of 20 μL of H_2O. [d]Reaction conducted using 200 mol % of $BnNH_2$ and no water.

leading us to conclude that the Rh-enolate formed upon addition was unreactive toward the tethered enoate. At this point, we hypothesized that an amine catalyst could be used to promote the intramolecular cyclization through an enamine intermediate.[8] When 20 mol % of $BnNH_2$ and water were added to the reaction

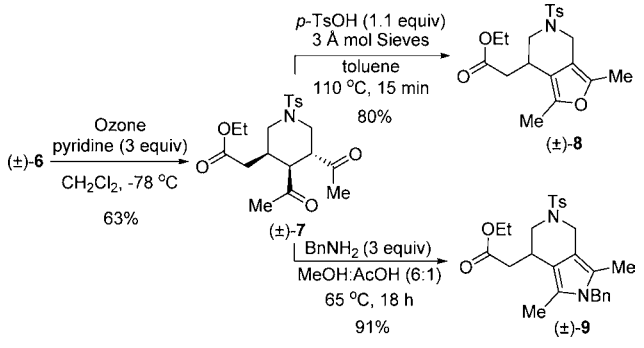
Scheme 3. C–H Functionalization Substrate Scope[a,b]



[a]Conditions: 0.20 mmol of **1** and 0.3 mmol of **2a** in dioxane (0.5 M). [b]Isolated yields after silica gel chromatography.



Scheme 4. Product Diversification



mixture simultaneously with the other reagents, 43% of **3a** was observed as well as 22% of the desired piperidine product **4a** with >95:5 diastereoselectivity (entry 4). Upon increasing the amount of $BnNH_2$ to 100 mol %, no conversion to **3a** or **4a** was observed due to inhibition of the Rh(III)-catalyzed C–H bond addition step (entry 5).[9] When 20 mol % of $BnNH_2$ and water were added to the reaction mixture after 20 h, full conversion to **4a** was observed, resulting in a 92% isolated yield (entry 6). Given the very low cost of $BnNH_2$, the addition of 100 mol % was also

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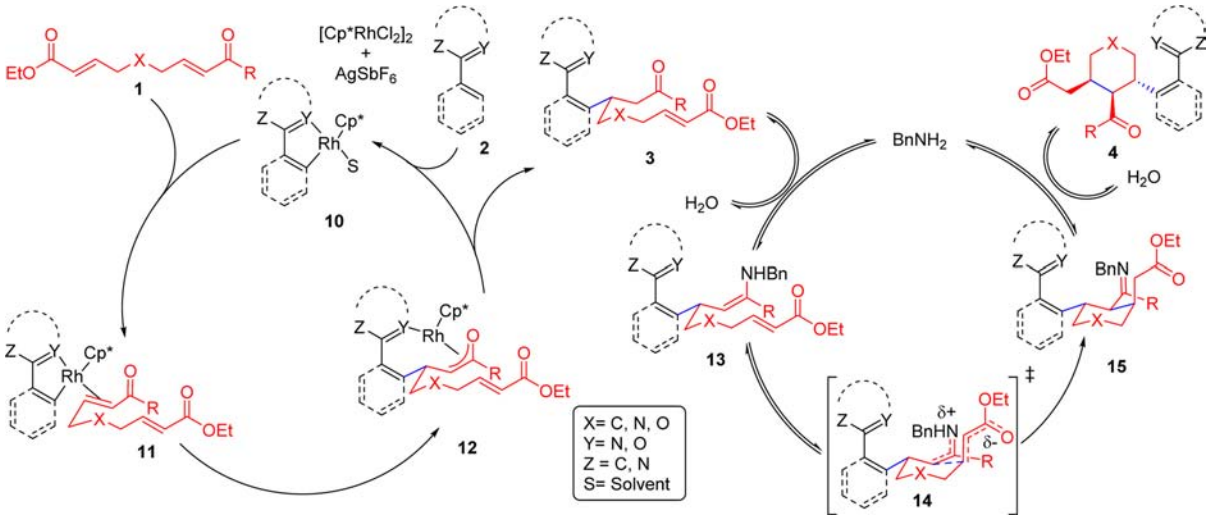
Scheme 5. Proposed Mechanism for the Transformation



evaluated, and after 20 h a similar yield was obtained (entry 7). These conditions ultimately proved to be more general across a broader range of electrophiles and C−H functionalization substrates (vide infra). It should be noted that for entries 6 and 7 the crude reaction mixtures contained some of the *N*-benzyl imine of **4a**, which readily hydrolyzed to **4a** on silica during purification and thus resulted in higher isolated yields relative to the corresponding NMR yields.

After identifying efficient conditions for the formation of piperidine **4a**, we next explored the scope of the bis-Michael acceptor (Scheme 2). The corresponding ethyl enone was an effective coupling partner affording piperidine **4b** in high yield. Tetrahydropyranyl (**4c**) and cyclohexanyl (**4d**) products could also be obtained in good yields and with high diastereoselectivities (>95:5) by substituting the nitrogen atom in the tether for an oxygen and carbon atom, respectively. An aryl enone underwent facile Rh(III)-catalyzed C−H addition, though enamine cyclization and hydrolysis proceeded much more slowly. By increasing the $BnNH_2$ loading to 200 mol % and excluding water, the cyclization product was isolated as imine **4e** in good yield. No conversion was observed when the ester was replaced with nitrile functionality (**4f**), which is consistent with previous reports that nitriles can coordinate to and deactivate Rh(III) C−H functionalization catalysts.[10]

We next explored the scope of the C−H functionalization coupling partner (Scheme 3). When using 2-phenylpyridine, **4g** could be isolated in pure form and in good yield, although minor byproducts arising from bis-C−H functionalization were observed by LC−MS analysis of the unpurified reaction product. To prevent over addition, the remainder of C−H functionalization substrates with nitrogen heterocycle directing groups incorporated *meta*-methyl blocking groups on the aromatic ring to prevent bis-C−H functionalization. The pyrimidine (**4h**) and pyrazole (**4i**) C−H bond partners were very effective in the transformation, while triazole (**4j**) provided a more modest yield. Synthetically useful benzamide substrates (**4k** and **4l**) were also effective. Electron rich (**4m**), electron neutral (**4n** and **4o**), and electron poor (**4p**) substituents performed well and provided moderate to good yields of the piperidine products.

Each of the products was obtained with >95:5 diastereoselectivity. Moreover, the relative stereochemistry of **4n** was rigorously confirmed by X-ray structural analysis.

In addition to aromatic C−H bond coupling partners, alkenyl substrate **5** was effective in this transformation, affording **6** in 66% yield with >95:5 dr (eq 1).

To showcase the utility of this C−H functionalization/cyclization sequence, piperidine **6** was efficiently transformed to useful, fused bicyclic heterocycle products (Scheme 4). Ozonolysis of **6** in the presence of pyridine yielded the 1,4-dicarbonyl **7** in good yield.[11] Paal−Knorr furan and pyrrole synthesis then afforded the piperidine-fused furan **8** and pyrrole **9** in 80% and 91% yield, respectively.

A mechanism for the sequential Rh(III)-catalyzed C−H addition/amine-catalyzed cyclization of bis-Michael acceptors is depicted in Scheme 5. First, concerted metalation/deprotonation of **2** generates rhodacycle **10**.[12] Coordination of the enone π-bond provides **11**, which upon insertion into the enone generates rhodium enolate **12**, with η^3-coordination depicted consistent with prior X-ray structural characterization of a Cp*Rh(III) enolate obtained by enone insertion.[5a] Protodemetalation of **12** releases the conjugate addition intermediate **3**, and cyclometalation with **2** regenerates rhodacycle **10**.[13] In the second step, condensation of $BnNH_2$ and **3** provides enamine **13**.[14] Intramolecular Michael addition must then proceed with the enoate in the pseudoaxial position as shown in **14** to provide the observed relative stereochemistry of the product as rigorously determined for **4n** by X-ray analysis. This enoate geometry presumably minimizes steric interactions with the R-substituent. Hydrolysis of **15** then liberates the cyclic product **4**.

In conclusion, we have developed a sequential Rh(III)-catalyzed C−H bond addition/primary amine-mediated intramolecular Michael reaction sequence for the efficient preparation of functionalized piperidines, tetrahydropyrans, and cyclohexanes. The C−H bond addition step occurred with high chemoselectivity, and the subsequent intramolecular enamine-Michael addition gave three contiguous stereocenters with high diastereoselectivity. Secondary and tertiary amides as well as various nitrogen heterocycles were effective directing groups. Moreover, alkenyl C−H functionalization followed by ozonolysis provided a 1,4-diketone that could readily be converted to piperidine-fused pyrrole and furan products in high yields. Future efforts will focus on further increasing electrophile scope through the implementation of sequential Rh(III)-catalyzed C−H bond addition followed by organocatalytic transformations.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01846.

Experimental details; characterization data (PDF)
crystallographic data for **4n** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) A competition experiment was conducted with an equimolar ratio of deuterio- and protio-2-phenylpyridine and **1a** under the standard reaction conditions. Consistent with the studies of Huang and co-workers (see ref 6b), extensive protio-deuterio scrambling of both 2-phenylpyridine and the addition product **3** was observed even at low conversion indicating highly reversible C−H activation (see Supporting Information).

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