

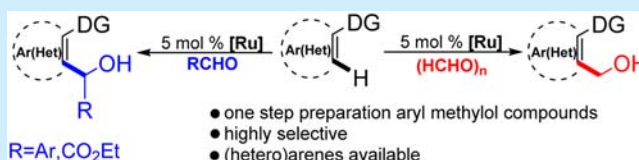
Ru-Catalyzed Regioselective Direct Hydroxymethylation of (Hetero)Arenes via C–H Activation

Guo-Fu Zhang, Yue Li, Xiao-Qiang Xie, and Cheng-Rong Ding*

College of Chemical Engineering, Zhejiang University of Technology, Hangzhou 310014, P. R. China

Supporting Information

ABSTRACT: An efficient and direct ruthenium-catalyzed regioselective hydroxymethylation of (hetero)arenes via C–H activation with paraformaldehyde as a hydroxymethylating reagent is described. The corresponding products can be obtained in good to excellent yield. A number of aryl aldehydes can also be used in place of paraformaldehyde giving the desired alcohol products with similarly good results.

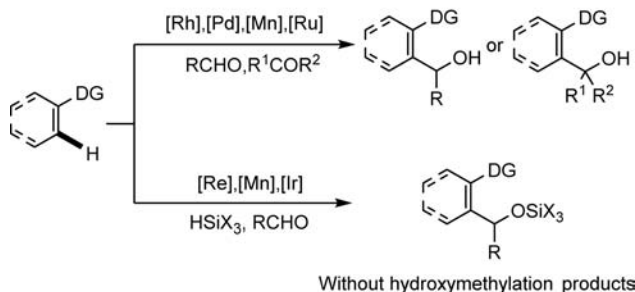


The methylol functional group (–CH₂OH) is present in a broad range of natural products and biologically active compounds. The physical properties of molecules, including lipophilicity, can be altered by the methylol functional group, greatly influencing the activity of the compound.¹ Furthermore, the CH₂OH group can be readily manipulated and converted into other functional groups allowing for the use of numerous synthetic protocols. Therefore, over the past few decades, hydroxymethylation has been a prominent research topic in drug discovery, material science, and the chemical industry.² Among the various hydroxymethylation reactions, a radical pathway has displayed encouraging versatility for the preparation of benzylalcohol and pyridylalcohol. Minisci³ and other groups^{4–6} have reported several significant developments in this area. Although a number of different approaches have been reported, the application of these reactions remains limited due to poor substrate scope and regioselectivity.

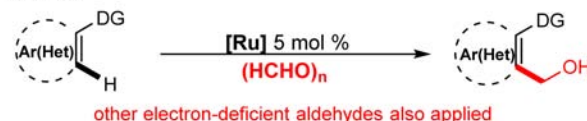
Recently, transition-metal-catalyzed C–H functionalization using a directing group has emerged as a very attractive strategy for structure elaboration because of its high efficiency and regioselective control. Among the many reported procedures,⁷ the directing group assisted metal-catalyzed C–H addition of arenes to aldehydes represents a unique strategy for accessing a variety of alcohol-containing structures. Significant progress has been made on this front. For example, the Li,⁸ Shi,⁹ and Chen groups¹⁰ have independently reported a Rh-catalyzed C–H addition to aldehydes. The Wang group¹¹ recently extended a Mn-catalyzed direct nucleophilic C(sp²)–H addition to aldehydes using a wide range of substrates. Kim¹² and co-workers reported addition reactions with indoles and indolines which use ethyl glyoxalate and ethyl trifluoropyruvate as raw materials. Murai,¹³ Takai,¹⁴ and Shi¹⁵ have independently developed alternative methodologies which utilize C–H addition to aldehydes and silyl capture, in which the aldehydes are activated by silicon and a catalyst. Although the aforementioned reactions provide separate routes for the preparation of various alcohol products, hydroxymethylation via directing C–H addition has not yet been reported (Scheme 1) and remains challenging. Herein we report a highly efficient Ru-catalyzed regioselective

Scheme 1. Previous Work and This Work

Previous Work:



This Work:

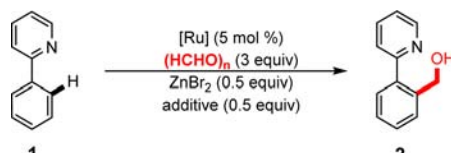


direct hydroxymethylation using paraformaldehyde as a hydroxymethylating reagent via C–H activation.¹⁶ The catalyst system is suitable for a broad range of substrates, and various electron-deficient aldehydes can be used in place of paraformaldehyde giving the desired alcohol products with similarly good results.

Initially, a Ru-catalyzed directed hydroxymethylation of 2-phenylpyridine **1** with paraformaldehyde was performed (Table 1). After catalyst screening, the hydroxymethyl product **2** was obtained in 35% yield by using [Ru(*p*-cymene)Cl₂]₂ and ZnBr₂ in CHCl₃ under an atmosphere of N₂ (entry 2). Encouraged by this result, a series of solvents were screened. DCE was found to be the most efficient solvent (entry 7). We next screened a number of Lewis acids as additives and found that FeF₃ exhibited the best effect (entry 9). A number of bases, which are helpful during the C–H bond cleavage, were also examined. The addition of AcONa (0.5 equiv) significantly improved the yield of the desired product

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Table 1. Optimization of Reaction Conditions^{a,b}


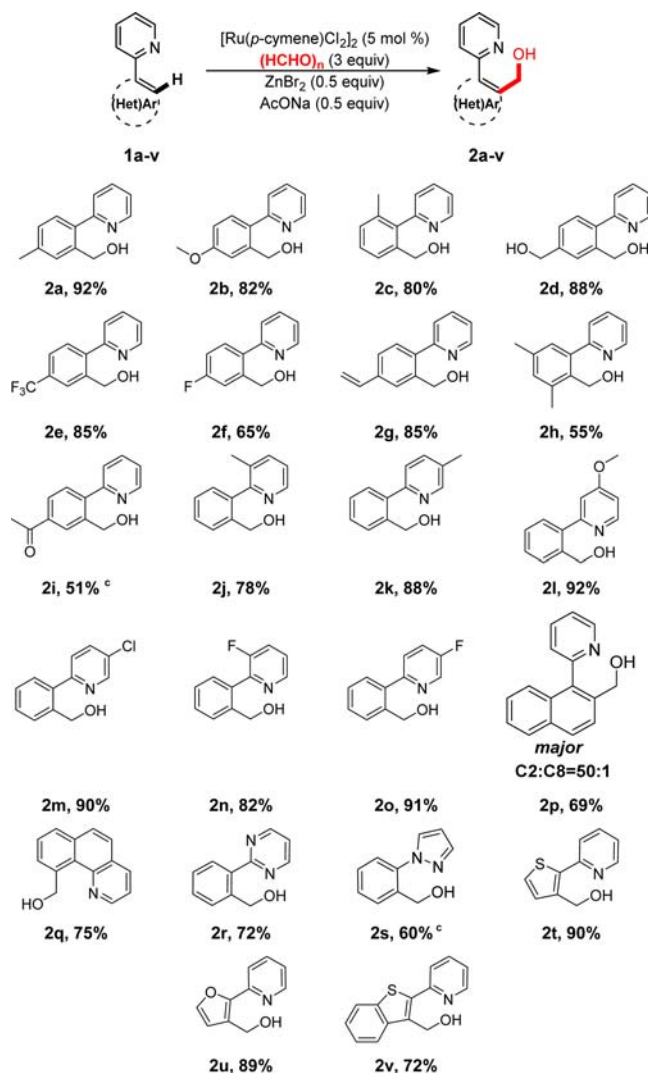
entry	[Ru]	additive	solvent	yield (%)
1	Ruthenocene		CH ₃ Cl	N.R.
2	[Ru(<i>p</i> -cymene)Cl ₂] ₂		CH ₃ Cl	35
3	[Ru(<i>p</i> -cymene)Cl ₂] ₂		<i>t</i> -BuOH	trace
4	[Ru(<i>p</i> -cymene)Cl ₂] ₂		THF	trace
5	[Ru(<i>p</i> -cymene)Cl ₂] ₂		MeOH	trace
6	[Ru(<i>p</i> -cymene)Cl ₂] ₂		DCM	53
7	[Ru(<i>p</i> -cymene)Cl ₂] ₂		DCE	61
8	[Ru(<i>p</i> -cymene)Cl ₂] ₂	AlBr ₃	DCE	trace
9	[Ru(<i>p</i> -cymene)Cl ₂] ₂	FeF ₃	DCE	75
10	[Ru(<i>p</i> -cymene)Cl ₂] ₂	FeCl ₃	DCE	33
11	[Ru(<i>p</i> -cymene)Cl ₂] ₂	AcOK	DCE	85
12	[Ru(<i>p</i> -cymene)Cl ₂] ₂	AcONa	DCE	96
13 ^c	[Ru(<i>p</i> -cymene)Cl ₂] ₂	AcONa	DCE	N.R.

^aReaction conditions: all reactions were performed with **1** (0.2 mmol), (HCHO)_n (3 equiv), [Ru] (5 mol %), ZnBr₂ (0.5 equiv), and additive (0.5 equiv) in solvent (2.0 mL) at 60 °C under N₂ for 24 h. ^bIsolated yield. ^cWithout ZnBr₂.

to 96% (entry 12). It is also worth noting that the reaction was highly monoselective, giving solely the monosubstituted product, most likely due to the intramolecular coordination of OH to N of the product.

With the optimized reaction conditions in hand, we proceeded to survey the scope of the reaction with substrates bearing substituted 2-phenylpyridine groups. As shown in Scheme 2, a wide variety of 2-phenylpyridine derivatives undergo hydroxymethylation efficiently, irrespective of the electronic character of the substituents. For example, electron-rich substituents bearing methyl-, methoxy-, trifluoromethyl-, and hydroxymethyl-substituted arenes all gave their corresponding products with good yields (**2a–e**). Additionally, halogen and vinyl substituents were well tolerated (**2f**, **2g**, **2m**, **2n**, **2o**). Of particular interest were the products of substrates bearing hydroxymethyl and chlorine or vinyl groups (**2d**, **2g**, **2m**), which allow for further derivatization. Electron-deficient arenes also underwent C–H activation smoothly, giving the desired hydroxymethylated products in moderate yield albeit requiring a prolonged reaction time (**2i**). A substrate bearing a disubstituted phenyl ring was also amenable to the reaction conditions providing the corresponding product in good yield (**2h**). The successful use of this method prompted us to examine the compatibility of hydroxymethylation with aromatic heterocycle substrates. We were pleased to discover that hydroxymethylation of furan (**2u**), thiophene (**2t**), and benzothiophene (**2v**) proceeded smoothly to give the corresponding hydroxymethyl heterocyclic products. Pyrimidine and pyrazole heterocycles could also be used as directing groups but were not as effective as pyridine (**2r**, **s**).

We subsequently investigated the use of other aldehydes in our reaction (Scheme 3). Addition of glyoxylate also proceeds in good yield (**3a**) as did the addition of terephthalaldehyde (**3b**). We discovered that the use of electron-deficient benzaldehydes bearing nitro, cyano, and methoxycarbonyl groups also provided the desired products in good yields. Both *para*- and *ortho*-substituted nitroaldehydes also underwent reaction with good yields (**3c**, **d**). The reaction was compatible with fluorine (**3e**),

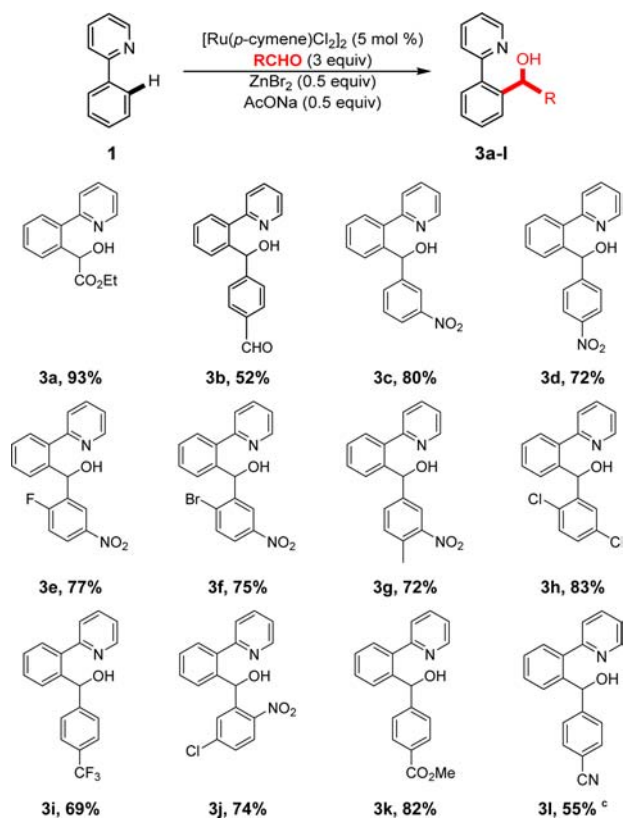
Scheme 2. Scope Hydroxymethylation of Substrates^{a,b}

^aReaction conditions: all reactions were performed with **1** (0.2 mmol), (HCHO)_n (3 equiv), [Ru(*p*-cymene)Cl₂]₂ (5 mol %), ZnBr₂ (0.5 equiv), and AcONa (0.5 equiv) in DCE (2.0 mL) at 60 °C under N₂ for 24 h. ^bIsolated yield. ^cFor 48 h.

bromine (**3f**), and chlorine (**3j**, **h**) groups on the aryl ring. A trifluoromethyl group at the *para*-position did not have a significant impact on product yield (**3i**). Gratifyingly, 2,5-dichlorobenzaldehyde also underwent addition giving the corresponding product in 83% yield (**3h**). C–H addition with methyl 4-formylbenzoate occurred with good yield under identical reaction conditions (**3k**). A nitrile group was also tolerable to the reaction conditions (**3l**).

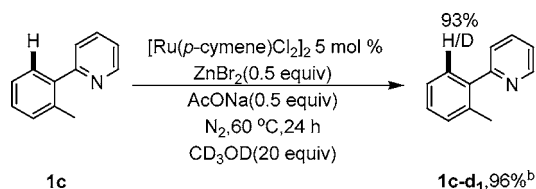
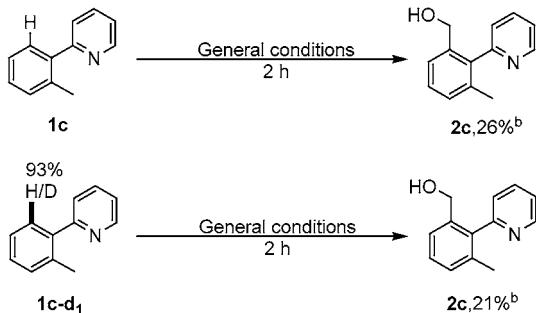
Studies were conducted to elucidate the mechanism of the reaction. A H/D exchange experiment of 2-phenylpyridine was carried out to investigate the reversibility of the C–H activation step (Scheme 4). As expected, 93% deuterium incorporation at the *ortho*-position was observed, supporting the hypothesis that the C–H activation step may be reversible. In addition, an intermolecular kinetic isotope effect value of 1.2 was observed, implying that cleavage of the C–H bond is not involved in the rate-determining step.

Based on the above results, the mechanism shown in Figure 1 has been proposed. Coordination of 2-phenylpyridine to the [Ru] catalyst is followed by *ortho* C–H activation to give a corresponding [Ru-substrate] intermediate. A hydrogen on the

Scheme 3. Scope of Aldehydes^{a,b}

^aReaction conditions: all reactions were performed with **1** (0.1 mmol), RCHO (3 equiv), $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ (5 mol %), ZnBr_2 (0.5 equiv), and AcONa (0.5 equiv) in DCE (1.0 mL) at 60 °C under N_2 for 24 h. ^bIsolated yield. ^cFor 48 h.

Scheme 4. Mechanism Studies

a) Reversibility in C-H activation^ab) Kinetic study^c

^aOn 0.2 mmol scale. ^bIsolated yield. ^cGeneral conditions: all reactions were performed with substrates (0.2 mmol), $(\text{HCHO})_n$ (3 equiv), $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ (5 mol %), ZnBr_2 (0.5 equiv), and AcONa (0.5 equiv) in DCE (2.0 mL) at 60 °C under N_2 for 2 h.

benzene ring is removed under the influence of $[\text{Ru}]$ and base.¹⁷ Activation of the aldehyde with ZnBr_2 and insertion give a

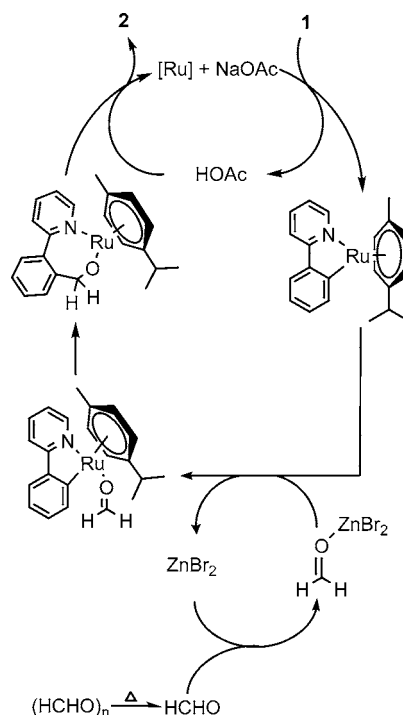


Figure 1. Proposed mechanism.

seven-membered metallocycle. After proton transfer, the catalyst $[\text{Ru}]$ is released for the next catalytic cycle.

In summary, we have developed an efficient, direct regioselective Ru-catalyzed hydroxyseven-metallocyclomethylation of (hetero)-arenes via C-H activation using paraformaldehyde as a hydroxymethylating reagent. The reaction shows good atom efficiency and is suitable for a broad range of substrates. Other electron-deficient aldehydes could also be used in place of paraformaldehyde to give the addition adducts in good to excellent yields.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00183.

Typical experimental procedure and characterization data for all products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dingcr@zjut.edu.cn.

ORCID

Cheng-Rong Ding: 0000-0001-6000-3965

Notes

The authors declare no competing financial interest.

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