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Ruthenium-Catalyzed Urea Synthesis Using Methanol as the C1 Source

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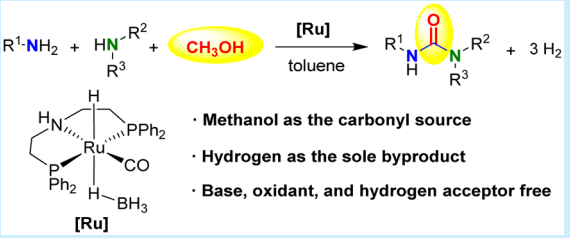
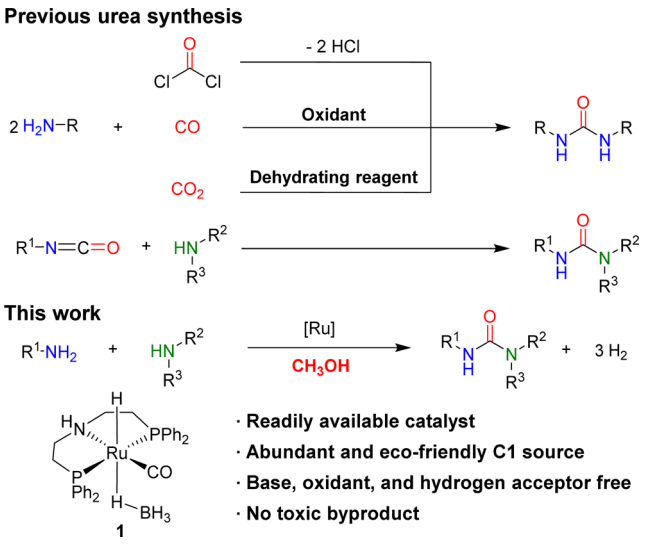
Supporting Information

ABSTRACT: An unprecedented protocol for urea synthesis directly from methanol and amine was accomplished. The reaction is highly atom-economical, producing hydrogen as the sole byproduct. Commercially available ruthenium pincer complexes were used as catalysts. In addition, no additive, such as a base, oxidant, or hydrogen acceptor, was required. Furthermore, unsymmetrical urea derivatives were successfully obtained via a one-pot, two-step reaction.



Urea derivatives are commonly found in widespread applications, such as biologically active compounds, pharmaceuticals, agricultural pesticides, dyes for cellulose fibers, and antioxidants in gasoline.[1] Many classical protocols and catalytic transformations have been developed for urea synthesis. Traditional syntheses of urea derivatives use phosgene and isocyanates, which cause tremendous toxicological and environmental problems (Scheme 1).[2] Alternative routes using carbon monoxide (CO) as the source of the carbonyl moiety have been developed;[3] these carbonylation reactions are generally carried out at high temperatures under high CO pressure with oxidants. In recent years, the utilization of CO_2 has attracted significant attention because it is a renewable carbon resource.[4] However, the required stoichiometric use of expensive and waste-producing dehydrating reagents, such as di-*tert*-butyl azodicarboxylate (DBAD), to generate the isocyanate intermediates still limits the utility of the reaction.[4] Therefore, versatile urea synthesis under mild conditions that avoids environmentally harmful reagents remains a major challenge.

Scheme 1. Synthesis of Urea Derivatives



Recently, environmentally benign and atom-economical C−N and C−C bond formation reactions utilizing alcohols, generating water[5] or hydrogen[6,7] as the byproduct, have attracted much attention. By applying the concept of acceptorless dehydrogenative activation of alcohols,[7] and based on the thermodynamic feasibility for the formation of 1,3-dimethyl urea from methylamine and methanol (ΔH°_{298} = −66.2 kJ/mol, ΔG°_{298} = −268.8 kJ/mol),[8] we envisioned an unprecedented strategy to synthesize urea derivatives directly from amines utilizing methanol as the C1 source.

Utilization of methanol as the C1 feedstock could be an ideal solution to reduce the predominant dependence on conventional toxic C1 sources, such as phosgene and isocyanates, for urea synthesis.[9] For intermolecular coupling of alcohols and amines, three pathways, i.e., imination,[10] alkylation,[7e] and amidation,[11] have been well reported. Recently, formylation of amines using methanol as the C1 source has been developed.[12] Inspired by previous works, we devised a possible strategy to synthesize urea utilizing methanol as follows: (1) Generation of formamide in situ and (2) coupling of the formamide with amine using an active catalyst that can mediate activation of formamide followed by dehydrogenation of the resultant hemiaminal intermediate.

To identify an active catalyst for the proposed urea synthesis, we investigated complex **4**, which was recently used for the

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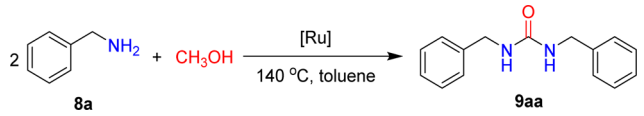
formylation of amine and nitrile with excess methanol.[12a] The reaction of benzylamine (**8a**) and methanol under modified conditions with less methanol (1.0 equiv vs amine) generated a trace amount of 1,3-dibenzyl urea (**9aa**, 5%) (Table 1, entry 5).

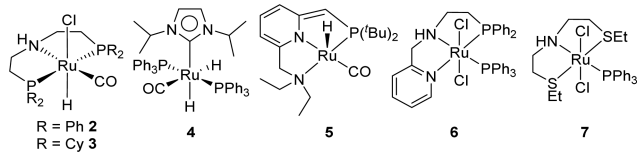
Table 1. Urea Synthesis from Methanol and Benzylamine Using Various Catalysts[a]



8a **9aa**

entry	Ru complex (0.5 mol %)	solvent	yield (%)
1	**1**	toluene	97
2[b]	**2**	toluene	93
3[b]	**3**	toluene	88
4[c]	[Ru(cod)(2-methylallyl)$_2$]	toluene	0
5	**4**	toluene	5
6	**5**	toluene	0
7[b]	**6**	toluene	0
8[b]	**7**	toluene	0
9	**1**	hexane	81
10	**1**	THF	80
11	**1**	dioxane	60
12	**1**	*p*-xylene	87

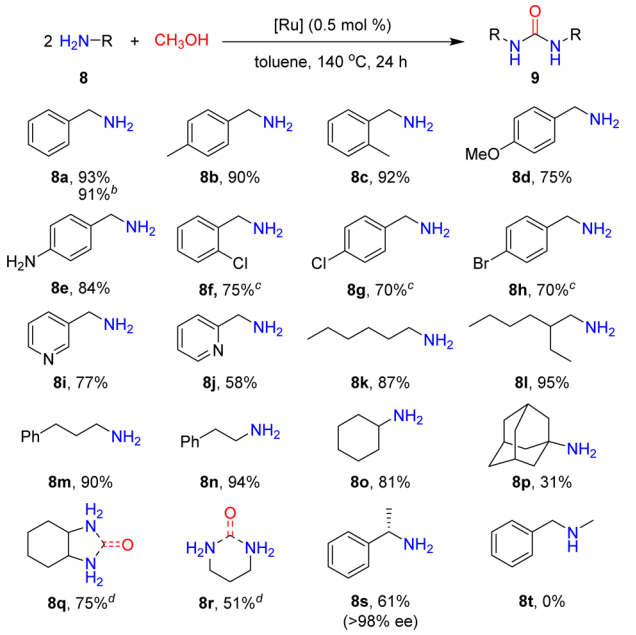
[a]Reaction conditions: benzylamine (2 mmol, 1.0 equiv), [Ru] (0.5 mol %), methanol (2 mmol), toluene (1.5 mL), 140 °C, 24 h in a closed vessel; NMR yield; *p*-xylene was used as a standard. [b]K_2CO_3 (0.5 mol %). [c][Ru(cod)(2-methylallyl)$_2$] (0.5 mol %), KO*t*Bu (1.5 mol %), and dicyclohexylimidazolium chloride (ICy-HCl, 1 mol %).



Inspired by this result, other Ru-based complexes that had been reported to catalyze acceptorless dehydrogenative coupling reactions were screened to improve the reaction efficiency. The N-formylation catalytic system developed by the Glorius group was not active for urea synthesis (entry 4).[12b] Milstein's catalyst (**5**)[11d] also did not produce any urea under the reaction conditions (entry 6). Complexes **6** and **7**, which showed excellent performance for hydrogenation of esters,[13] were not active for this reaction (entries 7 and 8). To our delight, Ru complex **2**, which is known as the Ru-MACHO catalyst,[6b,14] afforded desired product **9aa** in an excellent yield (93%) in the presence of a catalytic amount of K_2CO_3 (entry 2). Analogous complex **3** containing cyclohexyl groups on the phosphine moiety gave a slightly lower yield (88%, entry 3). Finally, when complex **1** (Ru-MACHO-BH) was used as a precatalyst, a quantitative amount of **9aa** was obtained under base-free conditions (entry 1). The reaction was optimized in a closed reaction vessel due to the low boiling point of methanol. Toluene was the best solvent among those tested (entries 9–12). Notably, the developed reaction is highly atom-economical, produces hydrogen gas as the sole byproduct, and is catalyzed by a low loading of the Ru catalyst (0.1 mol %, TONs ≈ 295, Table S2) without any additive such as a base, oxidant, or hydrogen acceptor.

Using the optimized conditions, the scope of the reaction was examined (Scheme 2). Various amines smoothly provided the corresponding symmetrical urea products in good to

Scheme 2. Symmetrical Urea Synthesis from Methanol and Amine[a]



[a]Reaction conditions: amine (2 mmol, 1.0 equiv), **1** (0.5 mol %), methanol (2 mmol), toluene (1.5 mL), 140 °C, 24 h in a closed vessel; isolated yield. [b]Amine (10 mmol, 1.0 equiv), **1** (0.5 mol %), [c]**1** (2 mol %), methanol (4 mmol), KOH (15 mol %). [d]Amine (1 mmol, 1.0 equiv), **1** (1 mol %), methanol (2 mmol).

excellent yields. Electron-rich benzylamines (**8a–e**) produced the corresponding ureas smoothly. The reaction worked efficiently even in a gram-scale reaction (1.07 g of **8a**, 91%). The use of chloride- and bromide-substituted benzylamines (**8f–8h**) required a higher catalyst loading (**1**, 2 mol %) and a base additive (KOH, 15 mol %) to obtain the products in good yields. Pyridine functional groups (**8i** and **8j**) were tolerated under the reaction conditions. Various kinds of aliphatic amines afforded the desired urea products in very good to excellent yields (**8k–8o**). In the case of 2-adamantyl amine (**8p**), a poor yield of **9pp** (31%) was observed and most of the **8p** remained; this was presumably due to high steric hindrance. Furthermore, the use of diamines **8q** and **8r** in the reaction resulted in the production of cyclic ureas. The yield of the product was relatively decreased probably due to the coordination effect of diamine. To our delight, subjection of chiral amine **8s** to the reaction generated urea product **9ss** with no epimerization. However, secondary amines, such as **8t**, and electron-deficient aryl amines, such as aniline, were not applicable under the developed reaction conditions. In the case of **8t**, the corresponding formamide was formed as the major product, which implies that the second nucleophilic addition of the secondary amine to formamide could be the limiting step for the urea synthesis. Aniline did not react at all under the reaction conditions. Therefore, in the case of 4-aminobenzyl amine (**8e**), selective urea formation on the aliphatic amine group was achieved in an 84% yield.

Next, we turned our attention to the synthesis of unsymmetrical urea derivatives. Traditionally, unsymmetrical ureas are synthesized via nucleophilic attack of amines on isocyanates. Recently, Buchwald and co-workers reported an unsymmetrical urea synthesis using an arylisocyanate intermediate synthesized by Pd-catalyzed cross-coupling of aryl

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chlorides and triflates with sodium cyanate.[15] Other efforts have been devoted to achieve in situ generation of isocyanates from different precursors, such as carboxylic acids, carbamic acids,[4c] carbamates,[16] acyl azides,[17] hydroxamic acids,[18] or acetoacetanilide.[19] They have also been prepared by functionalization of mother ureas via N-alkylation[20] or N-arylation.[21] Despite the significant advances in this field, many procedures still suffer from a limited availability of starting materials and a restricted substrate scope.

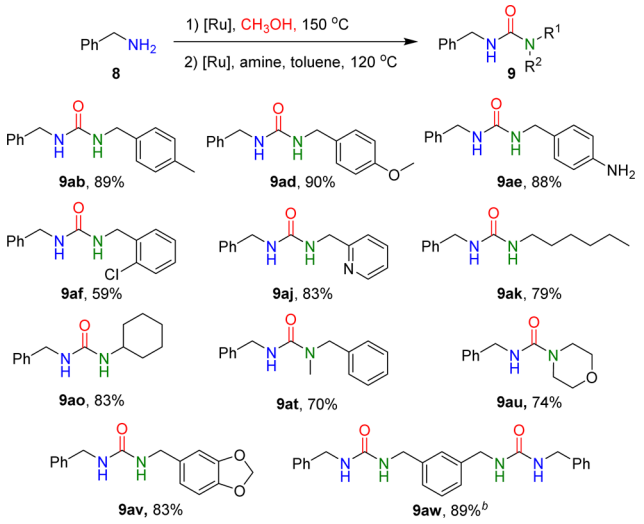
To elucidate the viability of the optimized reaction conditions for the synthesis of unsymmetrical urea, two different aliphatic amines, i.e., **8a** and **8k**, were reacted in a reaction vessel (Scheme S1). This reaction produced three of the corresponding urea derivatives with a statistical distribution: Symmetrical **9aa** (21%) and **9kk** (25%), and unsymmetrical **9ak** (48%). The reaction of 4-aminobenzyl amine (**8e**) with benzylamine resulted in a similar distribution of products. To improve the selectivity toward the unsymmetrical ureas, we devised a strategy comprising a sequential two-step reaction in one pot by first generating formamide from an amine and methanol, and then reacting the formamide with the second amine. This reaction strategy was proven to be viable by the reaction of **10** and **8k** to produce **9ak** in an excellent yield (94%) under the catalytic conditions of **1**. Recently, Reddy and co-workers reported Cu-catalyzed unsymmetrical urea synthesis from formamide and amines using *tert*-butylhydroperoxide (TBHP) as a stoichiometric oxidant at a relatively low efficiency (mostly <50% yields).[22] Here, an unsymmetrical urea synthesis from formamide and amine was achieved under oxidant-free conditions with high efficiency.

Combining the current strategy and the previous report of formamide synthesis using methanol,[12] we attempted selective unsymmetrical urea synthesis in one pot. After first generating benzyl formamide from **8** using methanol as the solvent, the methanol was removed in vacuum. Then, *n*-hexyl amine and toluene were added to the reaction tube with an additional loading of Ru complex **1** under inert conditions. After further reaction for 16 h at 120 °C, desired 1-benzyl-3-hexyl urea **9ak** was obtained in a good yield (79%).

The scope of the reaction was expanded to include a variety of coupling partners, and various unsymmetrical ureas were synthesized in good to excellent yields (Scheme 3). Reactions with amines containing heterocycles provided the corresponding ureas, i.e., **9aj** and **9av**, in very good yields. Notably, using secondary amines as the second cross partners was successful (**9at** and **9au**) although symmetrical urea synthesis of secondary amines was not possible; this implies that tertiary formamides are not reactive for further urea functionalization because of steric congestion. Unfortunately, the use of aniline in the reaction did not generate a urea derivative, as in the case of symmetrical urea synthesis. It is worthwhile to note that a diamine reacted with in situ generated formamide to afford a diurea compound (**9aw**).

An independent reaction with paraformaldehyde and benzylamine under our reaction conditions gave 1,3-dibenzylurea (Scheme S3a). To investigate the possibility of an isocyanate mediated mechanism, *N*-benzyl formamide was treated with aniline utilizing complex **1**, but no reaction occurred (Scheme S3b). Since benzyl isocyanate is easily reacted with aniline to form the corresponding urea,[23] the isocyanate mediated urea formation pathway was ruled out. In addition, isocyanate was not observed from *N*-benzyl formamide under our reaction conditions (Scheme S3b). Involvement of amidine was also

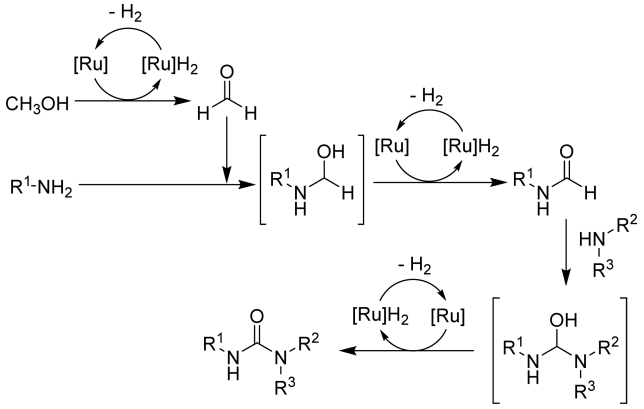
Scheme 3. Unsymmetrical Urea Synthesis from Methanol and Amine[a]



[a]Reaction conditions: (1) amine (0.5 mmol, 1.2 equiv), **1** (2 mol %), methanol (2 mL), 150 °C, 12 h in a closed vessel; (2) amine (0.42 mmol, 1 equiv), toluene (1.5 mL), **1** (4 mol %), 120 °C, 16 h in a closed vessel; isolated yield. [b]*m*-Xylylenediamine (0.21 mmol) in the second step.

excluded, as we could not observe the formation of amidine under our reaction conditions even in the presence of molecular sieves to remove water. Based on the results, the formation of urea is proposed to follow the pathway shown in Scheme 4. The primary amine is oxidatively coupled with

Scheme 4. Proposed Mechanism



formaldehyde, which is formed from dehydrogenation of methanol, to generate the formamide. Subsequent nucleophilic attack of an amine on the formamide generates the hemiaminal analogue, which is further dehydrogenated to the urea.

In conclusion, we reported a novel urea synthetic method directly from methanol and amines catalyzed by a readily available ruthenium PNP catalyst with hydrogen as the sole byproduct. No additive, such as a base, oxidant, or hydrogen acceptor, was required. Symmetrical and unsymmetrical urea derivatives were successfully obtained using methanol as the C1 feedstock by applying a dehydrogenative condensation strategy.

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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.5b03328.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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