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Efficient Ruthenium-Catalyzed N-Methylation of Amines Using Methanol

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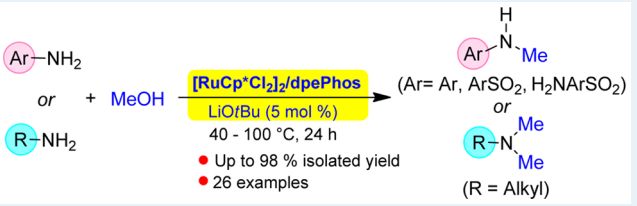
Supporting Information

ABSTRACT: An in situ-generated complex from $[RuCp^*Cl_2]_2$ and dpePhos ligand is reported as an efficient catalyst in the presence of 5 mol % of LiOtBu for the N-methylation of amines using methanol as the methylating agent at moderate conditions, following hydrogen borrowing strategy. This simple catalyst system provides selective N-monomethylation of substituted primary anilines and sulfonamides as well as N,N-dimethylation of primary aliphatic amines in excellent yields at 40−100 °C with good tolerance to reducible functional groups. The catalytic intermediate Cp*Ru(dpePhos)H was isolated and was shown to be active for methylation in the absence of base.



KEYWORDS: *methylation, methanol activation, hydrogen borrowing, ruthenium catalyst, amine synthesis*

INTRODUCTION

The direct N-methylation of amines is one of the most important transformations in the synthesis of fine chemicals and pharmaceuticals as well as natural products.[1] The conventional N-methylation methods using reactive and toxic methyl halides as methylating agents[2] have serious selectivity issues, forming overalkylated products that not only reduce the overall yield of the desired product but also render the separation of the products tedious. In addition to the use of excess base, the generation of toxic halogenated byproducts makes the downstream processing challenging and expensive. Other common electrophilic methylating agents such as dimethyl sulfate and diazomethane also have similar drawbacks.[3] Industrial production of methyl amines still depends on the reductive amination using toxic formaldehyde in the presence of suitable reducing agents (Eschweiler−Clarke methylation).[4] Hence, the need to develop efficient methylation protocols using safer methylating agents is obvious and is of prime importance.[5]

N-Methylarenes could potentially be prepared catalytically by Buchwald−Hartwig[6] C−N coupling reaction of methyl amines with aryl halides employing palladium[6,7] or nickel[6,8] catalysts, often in the presence of overstoichiometric amounts of base. Copper powder[9] in the presence of air (Ullmann type) or homogeneous copper catalysts in the presence of a base (Buchwald−Taillefer)[10] are other promising C−N coupling catalyst systems. Recently, utilization of CO_2[11] as a C-1 source in the presence of silanes[12] or boranes[13] was reported as a promising alternative methylation strategy. A requirement of excess reducing agents, separation of the silyl and borane byproducts and their regeneration, as well as tolerance to reducible functional groups[14] could be, in general, a potential concern in creating multifunctional scaffolds and for large-scale applications. Accordingly, a new protocol was developed to use hydrogen as a reducing agent.[15] In this case, the initially formed *N*-formyl intermediate is reduced to the N-methylated product, releasing only water as the byproduct. However, higher pressure (30−100 bar) and temperature (140−170 °C) as well as the expensive inventory requirements could be potential hurdles for laboratory scale as well as low volume-high value applications.

Dimethyl carbonate (DMC)[16] obtained from CO_2 and methanol is another alternative N-methylation agent.[17] Generally, higher temperatures (>150 °C) are required to improve the selectivity toward methylation vs carbamoylation. Recently, a low-temperature (100 °C) protocol was developed using iron-[18] or nickel-based[19] catalysts; however, this requires excess hydrosilane (5 equiv) as a reducing agent. Formic acid (HCOOH)[20] is also an interesting renewable C-1 feedstock for methylation; however, a higher temperature (150 °C) is required with ruthenium as the catalyst,[21] or excess silanes (3−5 equiv) are required as the reducing agent in the presence of a platinum catalyst (Karstedt's catalyst)[22] at room temperature. Although excellent yields for the tertiary amines (R_2NMe and $RNMe_2$) were achieved using CO_2 or DMC or HCOOH as the C-1 source for methylation, the selective formation of secondary amines (RNHMe) by monomethylation of primary amines still remains as a challenge.

When DMC is used, CO_2 and methanol are produced as byproducts that need to be potentially recycled when used in large scale. Hence, an attractive methylation strategy could be utilizing the readily available and inexpensive methanol[23] as the methylating agent following the recently developed transition metal-catalyzed hydrogen borrowing strategy.[24] In this method,

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the transition metal catalyst activates methanol in situ by dehydrogenation, forming formaldehyde, which condenses with the amine to give another transient imine intermediate that upon catalytic (transfer) hydrogenation forms the N-methylated amine. Water is the only byproduct in this reaction and, hence, could be considered as a promising green and sustainable alternative N-methylation protocol, if methanol is available through sustainable technologies.[23]

N-Methyl amines are present in many important drug molecules[25] and bioactive natural products (Figure 1). In many

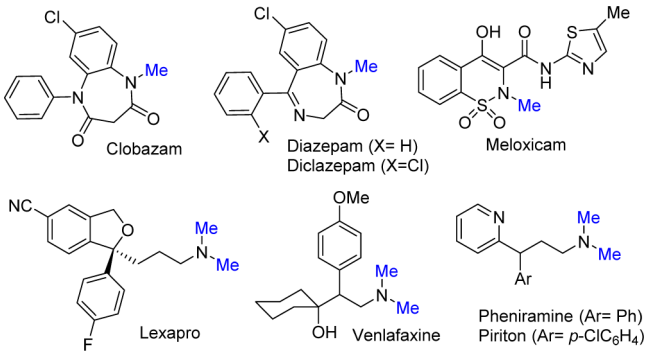

Figure 1. Representative examples from pharmaceuticals containing *N*-methylamines.

cases, the synthesis of selective N-monomethylated arylamine intermediates is either challenging or requires many synthetic manipulations.[26] A direct and selective N-monomethylation using methanol could offer an alternative and attractive pathway to access these intermediates in an efficient way.

Selective double N-methylation of aliphatic amines using methanol could also be promising toward the synthesis of important drugs such as Lexapro,[27] Venlafaxine,[28] Pheniramine,[29] Piritone, etc. However, a major problem with activation by dehydrogenation of methanol is that it requires higher activation energy compared with other higher alcohols (e.g. ethanol (ΔH = +84 vs +68 kJ mol^{-1})),[30] thus posing challenges for its activation under relatively mild conditions.

In the past, N-methylation of amines with methanol was mainly carried out using Lewis acid catalysts under harsh reaction conditions.[31] Supercritical methanol was also used in the presence of solid acid−base bifunctional catalysts that give a mixture of mono- and dimethylated amine products at 300 °C and 80 atm pressure in a continuous flow reactor.[31d,e] In contrast, room temperature N-methylation was reported to be possible using photocatalysts based on Pd/TiO_2[32] or Ag/TiO_2[33] that selectively give the dimethylated product from the respective primary amine under suitable UV irradiation. Palladium on carbon (Pd/C or $Pd(OH)_2$/C) in the presence of molecular hydrogen was reported to give the corresponding tertiary methyl amine from primary or secondary amino acids at room temperature.[34]

So far, only a few studies on transition metal-catalyzed N-methylation of amines using methanol following hydrogen borrowing strategy have been reported.[35−39] Watanabe et al. reported the first Ru-catalyzed N-methylation of various anilines at 180 °C.[35] A high catalyst loading (20 mol % of Ru) was employed to afford moderate yield (30−80%) of the N-methylated amine products. Naskar and Bhattacharjee described a cationic Ru−PPh_3 complex for N-methylation of aminoarenes to give the corresponding *N*-methyl arylamines in moderate yields (30−76%) with limited substrate scope.[36] A cyclopentadienyl Ru−PPh_3 complex was reported by Zotto et al.[37] for the N,N-dimethylation of aliphatic amines at 100 °C; however, the catalyst was shown to be inactive for the methylation of anilines. Recently, Li and co-workers have reported the first Ir-catalyzed methylation of aryl sulfonamides providing N-monomethylated products in 71−97% isolated yields;[38] however, the reaction requires higher temperatures of 150 °C and stoichiometric amounts of a strong base. Crabtree and co-workers[39] reported selective N-monomethylation of various anilines under microwave irradiation conditions at 120 °C using an iridium carbene complex catalyst in the presence of 1−5 equiv of KOH to achieve up to 95% yield. In general, these reported catalyst systems require either harsh reaction conditions or more than stoichiometric amounts of base to achieve high yields when methanol is used as the methylating agent following hydrogen borrowing strategy. Moreover, a catalyst that works for both aromatic and aliphatic amines is rare.

In our continued efforts to develope efficient methods for N-alkylation using alcohols,[40] we became interested in developing efficient and selective N-methylation protocols for both aromatic and aliphatic amines that work under relatively mild operating conditions, preferably using readily available catalysts. Herein, we report a highly efficient homogeneous ruthenium catalyst for the selective N-monomethylation of aryl amines as well as N,N-dimethylation of aliphatic amines using methanol under mild operating conditions in the presence of 5 mol % of LiO*t*Bu.

RESULTS AND DISCUSSION

Initial optimization studies using methanol for the N-methylation of aniline showed that homogeneous ruthenium catalysts obtained in situ from $[RuCl_2(p\text{-cymene})]_2$ and a bidentate phosphine ligand such as dpePhos could catalyze the formation of *N*-methylaniline in 52% yield in the presence of 0.5 equiv of KO*t*Bu as a base at 120 °C for 18 h (Table 1, entry 1). The yield was improved to 72% when $[RuCp^*Cl_2]_2$ (**Ru-2**) was used as the catalyst precursor (entry 2). Other common ruthenium catalyst precursors (**Ru-3**−**Ru-6** and $RuCl_3{\cdot}xH_2O$; entries 3−7) gave inferior results compared with that of $[RuCp^*Cl_2]_2$ (**Ru-2**); hence, **Ru-2** was selected as the catalyst precursor for further investigations.

A quick screening of different bases (entries 8−10) revealed LiOH to be a better choice compared with KO*t*Bu, resulting in up to 89% yield. Several bidentate phosphine ligands (XantPhos, NiXantPhos, dppf, dppe, BINAP) were examined in the presence of 0.5 equiv of LiOH because the base at 120 °C gave inferior results (entries 11−18) compared with dpePhos. Interestingly, quantitative yield was achieved when 0.5 equiv of LiO*t*Bu (entry 19) was used as a base instead of LiOH, even at a lower temperature of 100 °C after 24 h (entry 20). Interestingly, the amount of base could be further reduced to 0.05 equiv without a significant decrease in the product yield (entry 21). Reducing the temperature under this condition decreased the yield to 82%; however, the yield was improved to 96% upon increasing the reaction time to 36 h (entry 22). The amount of methanol can be reduced to 0.5 mL without significant change in the product yield. Control experiments in the presence of either 0.5 equiv of LiO*t*Bu with no Ru catalyst (entry 23) or the Ru catalyst in the absence of LiO*t*Bu (entry 24) gave no product, indicating the requirement of both the Ru catalyst and a suitable base for this N-methylation reaction. Any

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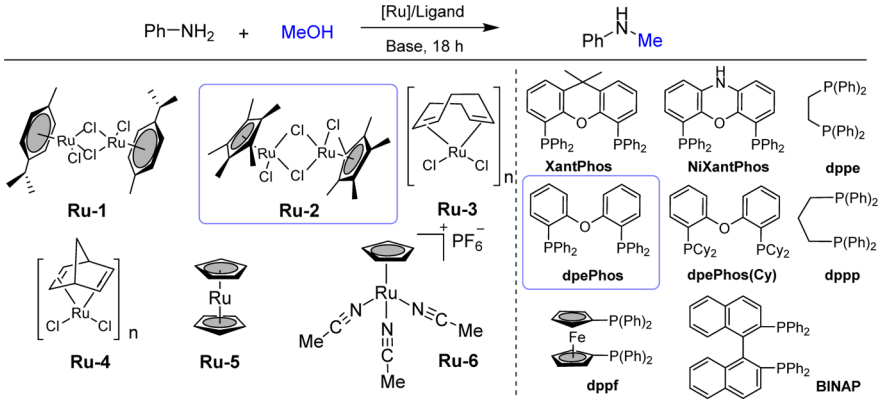
Table 1. Optimization of Catalyst and Conditions for N-Alkylation of Aniline Using Benzyl Alcohol[a]



entry	cat. (mol %)	base (equiv)	ligand	temp (°C)	conversion (%)[b]	product (%)[b]
1	Ru-1 (0.5)	KO*t*Bu (0.5)	dpePhos	120	53	52
2	Ru-2 (0.5)	KO*t*Bu (0.5)	dpePhos	120	76	72
3	Ru-3 (1)	KO*t*Bu (0.5)	dpePhos	120	63	62
4	Ru-4 (1)	KO*t*Bu (0.5)	dpePhos	120	64	64
5	Ru-5 (1)	KO*t*Bu (0.5)	dpePhos	120	n.d.[c]	4
6	Ru-6 (1)	KO*t*Bu (0.5)	dpePhos	120	35	32
7	$RuCl_3 \cdot xH_2O$ (1)	KO*t*Bu (0.5)	dpePhos	120	36	36
8	Ru-2 (0.5)	LiOH (0.5)	dpePhos	120	92	89
9	Ru-2 (0.5)	KOH (0.5)	dpePhos	120	79	74
10	Ru-2 (0.5)	K_2CO_3 (0.5)	dpePhos	120	67	66
11	Ru-2 (0.5)	LiOH (0.5)	dpePhos(Cy)	120	n.d.[c]	15
12	Ru-2 (0.5)	LiOH (0.5)	XantPhos	120	53	49
13	Ru-2 (0.5)	LiOH (0.5)	NiXantPhos	120	41	40
14	Ru-2 (0.5)	LiOH (0.5)	dppe	120	54	53
15	Ru-2 (0.5)	LiOH (0.5)	dppp	120	29	25
16	Ru-2 (0.5)	LiOH (0.5)	dppf	120	n.d.[c]	15
17	Ru-2 (0.5)	LiOH (0.5)	BINAP	120	26	24
18	Ru-2 (0.5)	LiOH (0.5)	PPh_3	120	n.d.[c]	5
19	Ru-2 (0.5)	LiO*t*Bu (0.5)	dpePhos	120	>99	>99
20	Ru-2 (0.5)	LiO*t*Bu (0.5)	dpePhos	100	>99	91 (>99)[d]
21	Ru-2 (0.5)	LiO*t*Bu (0.05)	dpePhos	100	>99	98[d], (96)[e]
22	Ru-2 (0.5)	LiO*t*Bu (0.05)	dpePhos	80	98	82[d] (96)[f]
23		LiO*t*Bu (0.5)	dpePhos	100	n.d.[c]	n.d.
24	Ru-2 (0.5)		dpePhos	100	n.d.[c]	n.d.

[a]Aniline (1 mmol), methanol (2 mL), [Ru] (1 mol %), ligand (1.2 mol %); yields were determined by ^{1}H NMR using mesitylene as the internal standard. [b]Reaction was carried out for 24 h. [c]Not determined because the quantity is insignificant. [d]24 h. [e]0.5 mL of methanol, [f]36 h.

possibility of enhanced reactivity from other trace metals[41] in this reaction is ruled out because LiO*t*Bu does not contain a significant amount (<20 ppb) of any other potential metal impurities (see Supporting Information). With the optimized conditions (entry 21) in hand, we further explored the scope of this simple methodology for the N-methylation of various aromatic and aliphatic amines.

Good to excellent yields of the corresponding N-monomethylated products were obtained with various aryl primary amines as the substrates at 100 °C in the presence of 5 mol % LiO*t*Bu, as shown in Table 2. Aniline and *para*-methyl aniline gave isolated yields of 95% (**1**) and 88% (**2**) respectively, whereas sterically hindered *ortho*-methyl aniline gave a promising yield of 73% (**3**). Several common functional groups, such as methoxy (**4**), fluoro- (**5**), iodo- (**6**), bromo- (**7**, **9**), and chloro- (**8**, **9**), were well tolerated, and the corresponding N-monomethylated products were obtained in 84−97% yields. Interestingly, less nucleophilic anilines having electron-withdrawing and potentially reducible functional groups, such as ester (**10**), ketone (**11**), primary amide (**12**), nitrile (**13**), and nitro (**14**), were tolerated under the reaction conditions, providing the respective N-monomethylated secondary amine products in excellent yields (76−96%) at 100 °C for 48 h. This unprecedented chemoselectivity is noteworthy because to the best of our knowledge, the substrates containing these potentially reducible functional groups have not been successfully reported with other transition-metal catalyst systems that follow hydrogen-borrowing strategy. Aromatic heterocyclic amines also required a longer reaction time of 48 h to achieve excellent yields. Accordingly, N-monomethylation of pyridyl (**15**) and pyrimidyl (**16**) amines provided the corresponding products in up to 95% yields. Sulfonamides (**17**, **18**) were also found to be excellent substrates and were efficiently N-monomethylated at a lower temperature of 60 °C for 24 h, giving quantitative yields. Notably, only monomethylated products were observed in all the cases of aromatic primary amines[42] and sulfonamides investigated under the present optimized conditions giving the

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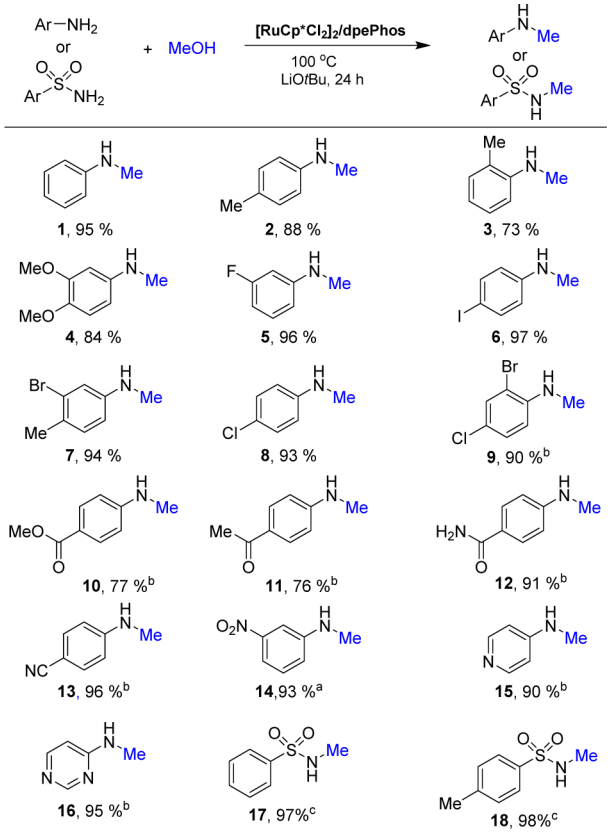
Table 2. N-Monomethylation of Aromatic Amines and Sulfonamides Using Methanol[a]

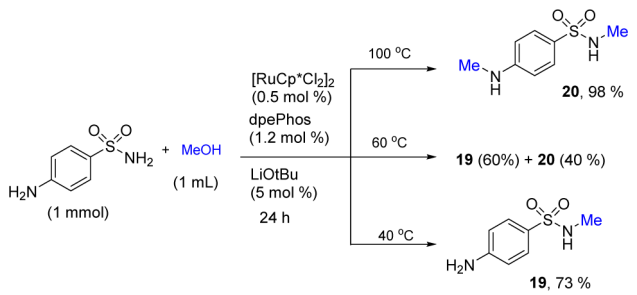


[a]$ArNH_2$ or $ArSO_2NH_2$ (1 mmol), methanol (1 mL), $[RuCp^*Cl_2]_2$ (0.5 mol %), dpePhos (1.2 mol %), LiO*t*Bu (5 mol %); isolated yields are given. [b]48 h. [c]60 °C for 24 h.

corresponding *N*-methyl secondary amine or sulfonamide products.

On the basis of the interesting observation that sulfonamide requires only 60 °C to achieve quantitative yields for N-methylation, we have further investigated the N-methylation selectivity between primary amine and sulfonamide functional groups, as in the case of sulfanilamide. At 60 °C, no particular selectivity was observed (Scheme 1) giving a mixture of methylated products that are formed from N-monomethylation only at the sulfonamide nitrogen (**19**) and N-monomethylation at both the nitrogens (**20**). Decreasing the temperature to control the reactivity resulted in the preferential methylation of sulfonamide, and surprisingly, up to 73% isolated yield was achieved for **19** at a lower temperature of 40 °C for 24 h. With

Scheme 1. Temperature-Controlled Selectivity in N-Methylation of Sulfanilamide Using Methanol

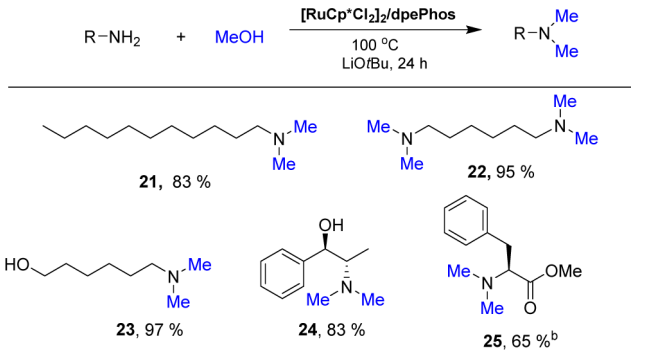


an increase in temperature, methylation of the amino group also increased, thus driving the selectivity toward **20**, providing up to 98% yield at 100 °C. This selective methylation of sulfonamide vs amino groups in sulfanilamide leading to the observed temperature-dependent chemoselectivity may be due to the enhanced nucleophilicity of sulfonamide in the presence of the electron-donating amino group and the decreased nucleophilicity of the amino group in the presence of an electron-withdrawing sulfonamide group.

We then turned our attention to aliphatic amines that are generally more nucleophilic than aromatic amines. It was observed that the N-methylation occurred even at a lower temperature of 60 °C; however, as the reaction progressed, double N-methylation occurred, leading to a mixture of mono- and dimethylated amines. Complete selectivity to N,N-dimethylation can be achieved by increasing the reaction temperature. The N,N-dimethylated aliphatic amines are important in pharmaceuticals (Scheme 1) and also as alkyl dimethyl amines (ADMA), which is an important class of specialty products for the production of surfactants, germicides, softeners, etc.

Good isolated yield (83%) of N,N-dimethylated amine product (**21**) was achieved in the case of a long-chain alkylamine such as undecylamine as the representative aliphatic amine at 100 °C for 24 h (Table 3). A typical diamine such as

Table 3. N,N-Dimethylation of Aliphatic Amines Using Methanol[a]



[a]RNH_2(1 mmol), methanol (1 mL), $[RuCp^*Cl_2]_2$ (0.5 mol %), dpePhos (1.2 mol %), LiOtBu (5 mol %); yields given are isolated yields. [b]120 °C.

1,6-diaminohexane provided the tetramethylated product **22** in excellent isolated yield of 95%. Interestingly, primary and secondary hydroxyl groups were well tolerated, and the corresponding N,N-dimethylated amino alcohols **23** and **24** were achieved in 97% and 83% yield, respectively, when 1-aminohexanol and ephedrine were used.

(−)-*N*-methylephedrine (**24**) is a natural product isolated from *Ephedra distachya* and is important in organic synthesis as a resolving agent and as a precursor for chiral supporting electrolytes, phase-transfer catalysts, and reducing agents. Its tolerance to hydroxyl groups prompted us to investigate if higher alcohols are active under the present catalyst system. Surprisingly, ethanol gave poor reactivity, and in an equal mixture of ethanol and methanol, preferential N-methylation occurred (83%), compared with N-ethylation (12%) under the optimized conditions,[43] showing the advantage of this catalyst system for the preferential N-methylation reaction. Amino acids did not yield any product, which may be due to the quenching

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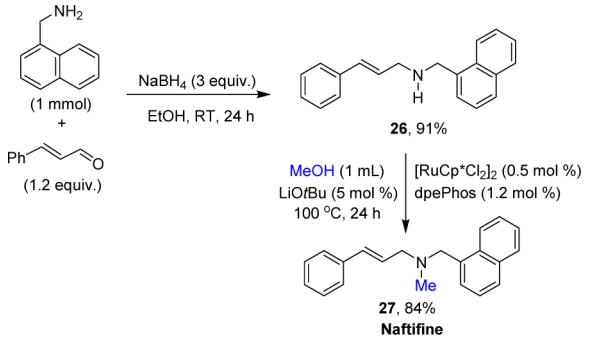
of the small amount of LiO*t*Bu that is needed for initiating the catalytic cycle (vide infra); however, the corresponding amino acid ester provided the dimethylated product **25** in up to 65% isolated yield at 120 °C.

A practical application of this simple N-methylation protocol using methanol was demonstrated for the synthesis of Naftifine (**27**),[44] an antifungal agent for the topical treatment of fungal infections. As shown in Scheme 2, the intermediate **26**[45] was

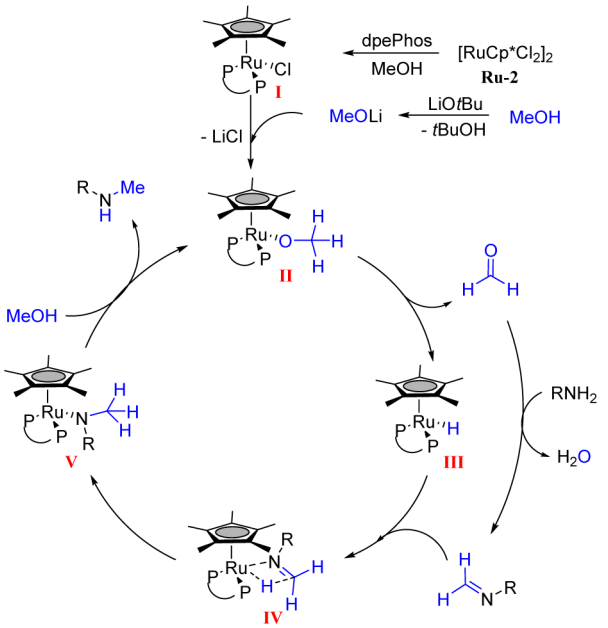
Scheme 2. Synthesis of Naftifine



readily prepared by condensation of 1-naphthylmethylamine with cinnamaldehyde, followed by reduction. The potentially reducible double bond in **26** is well-tolerated, and Naftifine was isolated in 84% yield after the standard N-methylation reaction at 100 °C.

On the basis of our results, the known mechanism of alcohol activation following hydrogen borrowing,[46] and the transfer hydrogenation,[47] a simple mechanism that proceeds through the formation of a ruthenium hydride intermediate could be easily proposed (Scheme 3). The catalytic cycle is believed to be initiated by the formation of an active Ru−methoxy complex (**II**) from the in situ-formed Ru phosphine complex **I** and the methoxide. Complex **II** on β-hydride abstraction generates the Ru−H species (**III**), releasing the transient formaldehyde

Scheme 3. Proposed Mechanism for Ru-Catalyzed N-Methylation of Amines Using Methanol



intermediate. In an attempt to detect the formation of any Ru−H species formed under the reaction conditions, an intermediate sample of a standard N-methylation of aniline using 5 mol % of **Ru-2** and 12 mol % of dpePhos at 100 °C for 2 h was analyzed by ^{1}H NMR. The crude mixture showed a broad peak at −2.5 ppm, presumably that of a Ru−H species and a singlet at 9.6 ppm corresponding to the in situ-formed formaldehyde.

To gain more insights into the active catalytic intermediates, Cp*Ru(dpePhos)Cl (**I**) was synthesized from $[RuCp^*Cl_2]_2$ (**Ru-2**) and dpePhos using a similar protocol reported by Nozaki et al.[48] for the preparation of Cp*Ru(XantPhos)Cl complex. The formation of Cp*Ru(dpePhos)Cl was confirmed by NMR spectroscopy and HRMS analysis (cf. Supporting Information). Formation of the proposed complex III, Cp*Ru(dpePhos)H, from Cp*Ru(dpePhos)Cl was investigated by reacting with NaOMe in methanol at 50 °C for 4 h. The isolated yellow powder showed a distinct triplet at −12.1 ppm (J_{PH} = 37.6 Hz) in the ^{1}H NMR spectrum, a relatively broad signal in the ^{31}P NMR spectrum at 57.1 ppm confirming the formation of complex III. HRMS analysis was also in agreement with the formation of the Cp*Ru(dpePhos)H complex. The formation of similar Ru−H complexes has been identified as intermediates in ruthenium-catalyzed dehydrogenation reactions.[49] Both the complexes were found to be active and gave a similar performance for the methylation of aniline under the optimized reaction conditions (Table 1, entry 21). In principle, the Ru hydride complex III may not require base to continue the catalytic cycle; however, it does need the presence of an imine. Accordingly, when the reaction was carried out using complex **III** as the catalyst in the presence of a catalytic amount of an imine (2 mol % of *N*-phenylbenzylimine) and in the absence of LiO*t*Bu, N-methylation of aniline smoothly proceeded, providing up to 65% yield in 18 h at 100 °C together with a small amount of *N*-benzylaniline. In this case, the small amount of added imine initiates the catalytic cycle by forming the intermediate **IV** and gets transfer-hydrogenated, releasing the *N*-benzylaniline and generating the active complex **II** in the presence of methanol for further methylation reaction of the aniline substrate, as shown in Scheme 3.

In conclusion, we have reported a simple, practical, and highly efficient homogeneous ruthenium catalyst system in the presence of 5 mol % of LiO*t*Bu for the N-methylation of amines using methanol. The selective N-monomethylation of aromatic primary amines and sulfonamides as well as selective N,N-dimethylation of aliphatic primary amines were achieved at temperatures of 60−100 °C. Selective N-monomethylation of the sulfonamide functional group vs amino group was achieved under the mild condition of 40 °C. Importantly, several reducible functional groups were well tolerated, and an application is demonstrated for the synthesis of Naftifine. The key catalytic intermediate species, the ruthenium hydride complex, was isolated and was shown to be active even in the absence of base. Because this simple catalyst system offers selective N-methylation under mild conditions, it would be useful for further applications in the synthesis of complex amines having various other functional groups. Further investigation is currently in progress at our laboratory.

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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/acscatal.5b00606.

Experimental procedures, characterization data of the products and Ru complexes, NMR spectra of products and Ru complexes (PDF)

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Notes

The authors declare no competing financial interest.

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