JOC The Journal of Organic Chemistry

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Ruthenium-Catalyzed *N*-Alkylation of Amines with Alcohols under Mild Conditions Using the Borrowing Hydrogen Methodology

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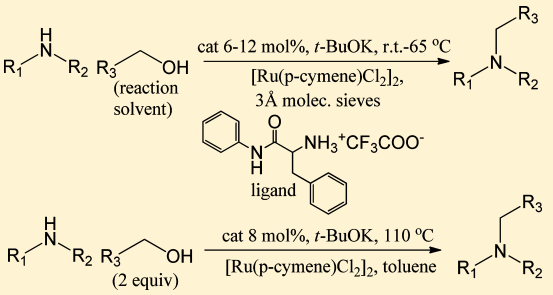
Supporting Information

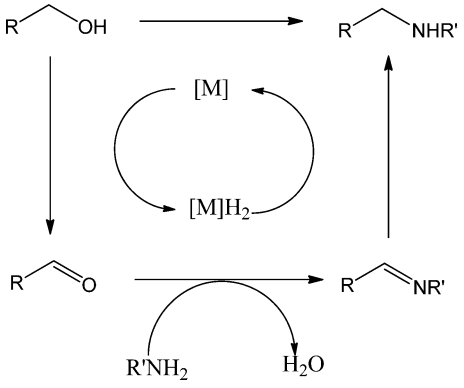
ABSTRACT: Using a simple amino amide ligand, ruthenium-catalyzed one-pot alkylation of primary and secondary amines with simple alcohols was carried out under a wide range of conditions. Using the alcohol as solvent, alkylation was achieved under mild conditions, even as low as room temperature. Reactions occurred with high conversion and selectivity in many cases. Reactions can also be carried out at high temperatures in organic solvent with high selectivity using stoichiometric amounts of the alcohol.



INTRODUCTION

N-Alkylamines are an important class of compounds found in natural products and pharmaceuticals. Thus, C−N bond-forming reactions are of considerable importance for the synthetic organic repertoire. Traditional synthetic routes to alkylamines involve substitution reactions employing environmentally harmful alkyl halides[1−4] or reductive aminations using stoichiometric reducing agents.[5,6] These reactions are wasteful and not atom economical. The use of alcohols through the borrowing hydrogen methodology[7−11] is an attractive alternative to the aforementioned reactions. The essential features of this catalysis are shown in Scheme 1.

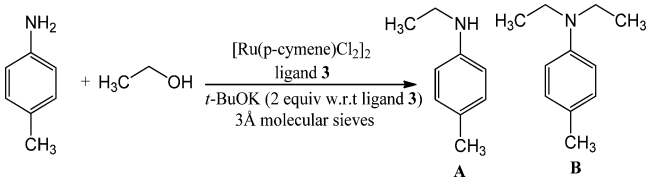
Scheme 1. Alkylation of Amines with Alcohols through the Borrowing Hydrogen Protocol



In this process, the alcohol is first activated toward nucleophilic attack by its ruthenium-mediated dehydrogenation to the corresponding carbonyl. Following the condensation of the carbonyl with the amine, the intermediate imine is hydrogenated, with the equivalent of H_2 that was "borrowed" by ruthenium, to form the *N*-substituted amine. This is a one-pot, atom-economical, and operationally simple reaction. Linking the carbonyl condensation of an amine to the catalytic transfer hydrogenative transformation of an alcohol to an imine produces water as the only reaction byproduct, making this a more environmentally desirable amine alkylation process than conventional methods.[12]

The first examples of homogeneous amine alkylation with alcohols were developed by Grigg[13] and Watanabe[14−17] in 1981 using rhodium- and ruthenium-based catalysts, respectively. Temperatures as high as 180 °C were required for these transformations. More recent developments have led to more active catalysts and relatively milder reaction conditions. Fujita,

Table 1. Optimization of Reaction Conditions[a]



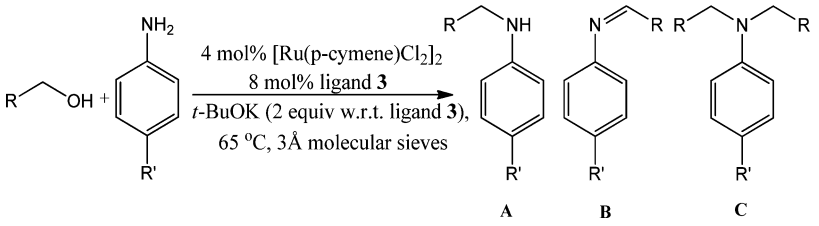
				product selectivity	
entry	cat. (mol %)	temp (°C)	% conv	% A	% B
1	10	65	100	94	6
2	10	60	78	100	0
3	8	65	92	98	2
4	8	60	73	100	0
5	6	60	69	100	0
6	no ligand	60	13	0	0

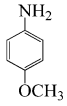
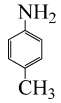
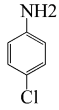
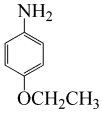
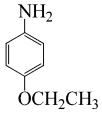
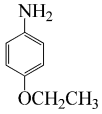
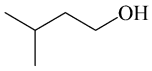
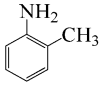
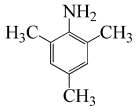
[a]Reaction conditions: amine (1 mmol), alcohol (solvent), ligand **3** (*x* mol %), $[Ru(p\text{-cymene})Cl_2]_2$ (*x*/2 mol %), *t*-BuOK (2 equiv wrt **3**), 60−65 °C, and 3 Å molecular sieves.

Received: June 10, 2014
Published: July 9, 2014

   dx.doi.org/10.1021/jo501273t | J. Org. Chem. 2014, 79, 7553−7563

Table 2. Alkylation of Primary Aromatic Amines[a]



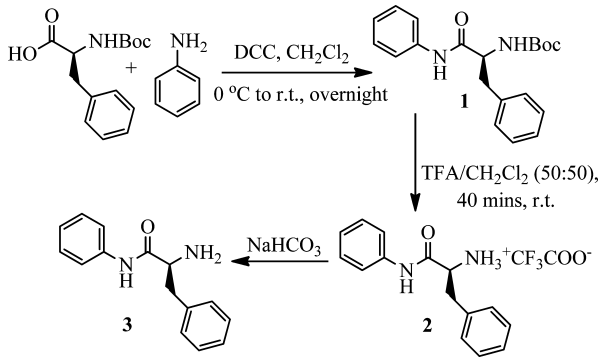
Entry	Amine	Alcohol	Time (h)	%Conversion	Product Selectivity			% Yield[b] (A) (isolated yield)
					%A	%B	%C	
1			25	99	94	0	6	93
2			48	85	100	0	0	85
3			48	92	98	0	2	90 (89)
4			48	60	100	0	0	60
5			24	>99	96	0	4	95 (79)
6			48	>99	98	0	2	97 (73)
7			48	>99	90	10	0	89 (82)
8			48	13	100	0	0	13
9			48	1	0	100	0	0

[a]Reaction conditions: amine (1 mmol), alcohol (solvent), ligand **3** (8 mol %), [Ru(*p*-cymene)Cl_2]$_2$ (4 mol %), *t*-BuOK (0.16 mmol) 65 °C, 3 Å molecular sieves. [b]Yield calculated by GCMS using *N*,*N*-dimethylbenzylamine as the internal standard.

Yamaguchi,[18−28] and co-workers successfully used Cp*Ir complexes for the alkylation of amines and sulfonamides. The Williams[29−38] group has also been very successful in using ruthenium- and iridium-based catalysts for such alkylation reactions. Also noteworthy is the Yus group,[39−41] who have been successful in using simple palladium and copper salts for the alkylation of amines, amides, and sulfonamides. Using $Ru_3(CO)_{12}$ combined with various ligands, the Beller group[29,42−47] has been able to carry out alkylation reactions with great success. Other iridium catalysts have also been used by the Kempe[48−51] group and have shown good results. Significantly, they were the first to report reaction temperatures as low as 70 °C.[49,51] Martin-Matute and co-workers also reported an iridium catalyst capable of amine alkylation with alcohols at 50 °C.[52] Recently, alkylation at 50 °C and room temperature was reported by the Andersson group[53] using an iridium catalyst. This is the first time amine alkylation using alcohols has been performed at room temperature, though it was limited only to alkylation of anilines. To the best of our knowledge, no ruthenium catalyst has been reported under mild conditions or at room temperature. Other iridium,[52,54−64] ruthenium,[65−70] osmium,[71] copper,[72−76] gold,[77] iron,[78] silver,[79−82] and palladium[83] catalysts have recently been reported for the alkylation of amines.

dx.doi.org/10.1021/jo501273t | J. Org. Chem. 2014, 79, 7553−7563

Scheme 2. Aminoamide Ligand Synthesis

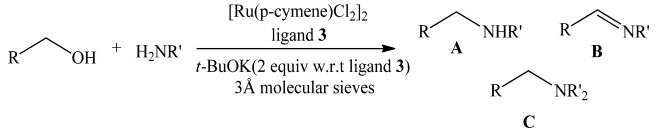


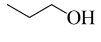
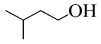
RESULTS AND DISCUSSION

Most alcohol alkylations of amines through borrowing hydrogen are carried out at high temperatures with only one example of room temperature alkylation of anilines. There is, therefore, the need for more active catalysts that span a wider range of amines. Here, we report the first ruthenium-catalyzed alkylation of primary and secondary amines under mild conditions using the alcohol as the solvent or cosolvent of the reaction. We also present, to the best of our knowledge, the first examples of this chemistry at room temperature using a ruthenium catalyst. Catalysis can also be carried out at higher temperatures with near-stoichiometric amounts of alcohol.

All catalytic reactions were performed using the inexpensive and readily accessible amino amide ligand **3** or its TFA salt (**2**), whose synthesis is shown in Scheme 2. Boc-Phe-OH was coupled to aniline using DCC and subsequently deprotected with trifluoroacetic acid in methylene chloride. Ligand **3** is unstable under ambient conditions and has to be stored at −20 °C. On the other hand, the TFA salt of the ligand, **2**, is indefinitely stable on the benchtop and was thus a more convenient alternative to **3**. Use of either **2** or **3** in combination with the ruthenium precursor, Ru[(p-cymene)Cl_2]$_2$, resulted in identical catalytic performance.

Table 3. Alkylation of Primary Aliphatic Amines[a]

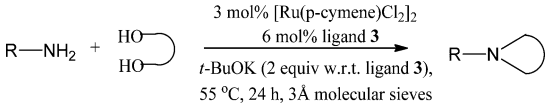


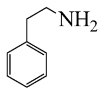
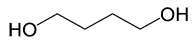
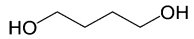
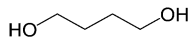
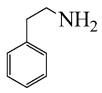
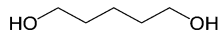
Entry	Amine	Alcohol	Cat mol%	T, °C	Time (h)	%Conv	Product Selectivity			Yield[b] (A)
							%A	%B	%C	
1			6	55	12	100	67	0	33	67
2			6	40	22	100	91	0	9	91
3			7	65	21	>99	76	23	<1	75
4			7	65	29	>99	74	18	8	73
5			7	65	48	>99	61	13	25	60
6			6	45	24	>99	84	9	7	83
7			6	45	24	>99	88	12	0	87
8			7	65	48	>99	75	19	6	74
9			7	65	48	>99	64	26	10	63

[a]Reaction conditions: amine (1 mmol), alcohol (solvent), ligand **3** (x mol %), [Ru(p-cymeneCl_2]$_2$ (x/2 mol %), t-BuOK (2 equiv wrt **3**), 45−65 °C, 3 Å molecular sieves. [b]Yield calculated by GCMS using *N,N*-dimethylbenzylamine as the internal standard.

dx.doi.org/10.1021/jo501273t | J. Org. Chem. 2014, 79, 7553−7563

Table 4. Alkylation of Primary Amines with Diols[a]



Entry	Amine	Alcohol	%Conversion	%Yield[b]
1			>99	99
2			>99	99
3			>99	99
4			>99	99

[a]Reaction conditions: amine (1 mmol), alcohol (solvent), ligand **3** (6 mol %), [Ru(*p*-cymeneCl$_2$]$_2$ (3 mol %), *t*-BuOK (0.12 mmol), 55 °C, 3 Å molecular sieves. [b]Yield calculated by GCMS using *N*,*N*-dimethylbenzylamine as the internal standard.

In preliminary screening experiments, we discovered that when the alcohol was used as the solvent for the reaction, catalytic alkylation reactions proceeded with high conversion and selectivities. This was a deviation from the stoichiometric reactions that are usually performed in toluene. We proceeded with the optimization of temperature and catalyst loading, using as a model reaction the alkylation of *p*-toluidine in ethanol, and the results are shown in Table 1. We were pleased to find that monoalkylation occurred at 65 °C and 8 mol % catalyst loading after 48 h with high selectivity. This is the first time to the best of our knowledge that ruthenium-catalyzed alkylation of amines has been achieved below 70 °C. Increasing the catalyst loading to 10 mol % led to complete conversion but with more of the dialkylated product. At lower temperatures, we observed a decreased conversion. No amine product was observed when the ligand was absent, indicating the ligand is crucial for catalytic activity.

We were pleased to find that alkylation of many substituted anilines was achieved, although small amounts of dialkylation were also observed (entries 1, 3, 5, and 6, Table 2). We observed a correlation between the amine nucleophilicity and the overall reactivity. Electron-donating groups on the ring resulted in shorter reaction times (entries 1 and 5, Table 2), while electron-withdrawing groups resulted in lower conversions after 48 h (entry 4, Table 2). Also, apparent reaction rates (judging from the longer reaction time and reduced fraction of dialkylated product) decreased as the chain length of the alcohol was increased (entries 5−7, Table 2). We also observed significant rate retardation for sterically hindered anilines (entries 8 and 9, Table 2). Conversion was significantly diminished with *ortho* substitution, and disubstitution at both *ortho* positions resulted in even lower conversion.

We then looked at the alkylation of primary aliphatic amines with aliphatic alcohols and found that they required lower catalyst loadings and lower temperatures. At 6 mol % catalyst loading and only 45 °C, complete conversion was achieved, although a greater amount of dialkylated product was observed compared to the anilines (entries 6 and 7, Table 3). Alkylations using benzyl alcohol required higher catalyst loading and temperatures (entries 3−5, 8 and 9, Table 3) and resulted in significant dialkylation. The longer reaction times could be as a result of steric hindrance of the aromatic ring and also due to decreased reactivity of the intermediate benzaldehyde (oxidation product) compared to aliphatic aldehydes. It is unclear why we observe such poor selectivity with primary aliphatic amines, but it may be a result of their higher nucleophilic reactivity and lower steric demand compared to anilines. Further investigation is needed to better understand these trends.

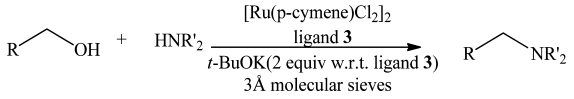
We investigated the use of diols as alkylating agents for the synthesis of *N*-heterocycles. With butanediol and pentanediol as alkylating agents, complete conversion to substituted pyrrolidines and piperidines was observed at low temperature and low catalyst loading with no detectable impurities (Table 4).

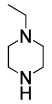
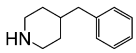
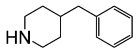
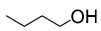
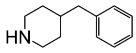
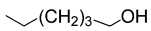
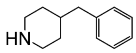
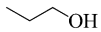
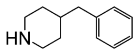
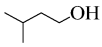
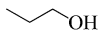
Encouraged by the results in Table 4, we explored the alkylation of secondary aliphatic amines. We found that these alkylations occurred at low temperatures for simple aliphatic alcohols (entries 1−3, Table 5). For example, the alkylation of morpholine with ethanol occurred at 55 °C and 6 mol % catalyst loading with complete conversion in 13 h. This is the first example of secondary amine alkylation using ruthenium catalysis at this temperature. As with anilines, total conversion time increased with increasing alcohol chain length (entries 3−5, Table 5). This could be attributed to increase in steric bulk at the electrophilic carbon of corresponding aldehyde. When using benzyl alcohol as alkylating agent, a higher catalyst loading and higher temperatures were required (entries 6 and 7, Table 5). Again, steric interference by the ring could be the cause of the lower reaction rate.

We were curious to discover the lower temperature limits under which the catalysis would operate at reasonable rates. To our surprise, amine alkylation proceeded at room temperature, albeit with higher catalyst loadings. To the best of our knowledge, this is the first time room-temperature alkylation of

dx.doi.org/10.1021/jo501273t | J. Org. Chem. 2014, 79, 7553−7563

Table 5. Alkylation of Secondary Amines[a]



Entry	Amine	Alcohol	Cat mol%	T, °C	Time, (h)	%Conv	%Yield[b] (isolated yield)
1			6	55	13	>99	>99
2			6	55	13	>99	>99
3			6	55	13	>99	>99 (85)
4			6	55	24	>99	>99 (97)
5			6	55	24	>99	>99 (90)
6			8	65	48	>99	>99
7			8	65	48	>99	>99
8			6	55	26	>99	>99
9			6	55	26	>99	>99
10			6	55	24	>99	>99

[a]Reaction conditions: amine (1 mmol), alcohol (solvent), ligand **3** (*x* mol %), [Ru(p-cymeneCl$_2$]$_2$ (*x*/2 mol %), *t*-BuOK (2 equiv wrt**3**), 55−65 °C, 3 Å molecular sieves. [b]Yield calculated by GCMS using *N*,*N*-dimethylbenzylamine as the internal standard.

amines with alcohols has been performed at room temperature using a ruthenium catalyst (Table 6). The ability to carry out this catalysis at room temperature is especially important for amine alkylations of substrates that may occur in late stages of a multistep synthesis and possibly contain sensitive functional groups or be unstable toward thermal carbon skeletal rearrangements. The high catalyst loading notwithstanding, we believe this is a good first step with plenty of room for improvement.

Employing alcohols as the solvent *and* the alkylating agent is convenient with simple and readily available alcohols. However, this may not be possible when the alcohol is prohibitively expensive or is itself a high value intermediate in a convergent synthetic strategy. To this end, we studied the catalysis under stoichiometric alcohol conditions in toluene, dichloroethane, and dimethylacetamide solvents. The reaction proceeded, although it required higher temperatures. Interestingly, increasing the polarity of the solvent decreased the overall conversion of the reaction (entries 4−6, Table 7). This is a bit counterintuitive because the reaction had been previously run in polar alcohols as the solvent. We also noticed 110 °C was the best temperature for the reaction. Two equivalents of alcohol gave the best results, while the reaction was almost completely shut down in the absence of ligand (entry 7, Table 7).

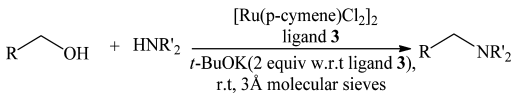
Having optimized the conditions for stoichiometric reaction, we turned our attention to the alkylation of primary and secondary amines. We were very pleased to find that alkylation of primary aliphatic amines occurred with high selectivity (entries 1−6, Table 8), whereas anilines did not show good conversion (entries 7−9, Table 8). This is the reverse of the trend we observed previously when the alcohols were used as solvent.

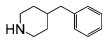
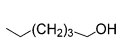
Phenethylamine, for example, was alkylated using 1-hexanol to yield *N*-hexylphenethylamine as the only product. The reaction of *p*-toluidine, on the other hand, gave only 53% conversion using 1-hexanol as the alkylating agent; however, the selectivity was still very good. Steric effects were not significant under these conditions as complete conversion was achieved with alcohols of various sizes. This is also contrary to the reactions in which the alcohol was used as solvent.

Catalytic alkylation of secondary aliphatic amines was equally high yielding and selective as seen in Table 9. For example, 4-Benzylpiperidine was alkylated using 1-hexanol, to give *N*-hexyl-4-benzylpiperidine as the only product. Altering the size

dx.doi.org/10.1021/jo501273t | J. Org. Chem. 2014, 79, 7553−7563

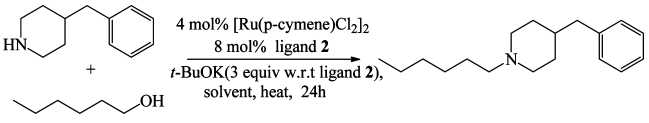
Table 6. Alkylation of Secondary Aliphatic Amines at Room Temperature[a]



	Amine	Alcohol	Cat (mol%)	Time (h)	Conv %
1			6	13	36
2			6	22	54
3			6	36	65
4			6	46	74
5			6	61	81
6			10	48	45
7			12	48	>99
8			12	48	>99
9			12	48	>99
10			12	48	>99

[a]Reaction conditions: amine (1 mmol), alcohol (solvent), ligand **3** (x mol %), [Ru(p-cymeneCl$_2$]$_2$ (x/2 mol %), t-BuOK (2 equiv wrt **3**), room temperature, 3 Å molecular sieves. [b]Conversion determined by GCMS with *N,N*-dimethylbenxylamine as the internal standard.

Table 7. Optimization of the Stoichiometric Reaction[a]



entry	anine (mmol)	alcohol (mmol)	temp (°C)	solvent	% conversion
1	1	1	100	toluene	42
2	1	1	110	toluene	70
3	1	1.5	110	toluene	80
4	1	2.0	110	toluene	>99
5	1	2.0	110	dichloroethane	68
6	1	2.0	110	dimethylacetamide	25
7	1	2.0	110	toluene	16 (no ligand)

[a]Reaction conditions: amine (x mmol), alcohol (x mmol), ligand **2** (8 mol %), [Ru(p-cymeneCl$_2$]$_2$ (4 mol %), t-BuOK (3 equiv wrt **2**), 110 °C, solvent.

of the alkylating alcohol did not alter the results, thus the steric disposition of the alcohol did not influence the outcome of the reaction

We were puzzled by the improved selectivity of the alkylation reaction of the primary aliphatic amines in toluene relative to alcohols as the solvent. Thus, we decided to explore the effect of the toluene/alcohol cosolvent systems on the reaction selectivity. The alkylation of phenethylamine with 90:10 ethanol−toluene solvent resulted in complete dialkylation (Table 10, entry 1). As we reduced the amount of ethanol, the selectivity toward the monoalkylated product increased. At about 30:70 ethanol−toluene we observed the exclusive formation of the monoalkylated product (Table 10, entry 4). The 30:70 alcohol−toluene cosolvent ratio gave consistently high yields and selectivity with other alcohols (Table 11). The optimum conditions for cosolvent reactions required raising the catalyst loading and temperatures slightly, but these conditions are still very mild compared to other ruthenium catalysts.

■ CONCLUSION

In summary, we have shown the successful application of an aminoamide ligand for the ruthenium-catalyzed alkylation of amines. Alkylation proceeded with high conversions and selectivities at 45−65 °C when simple alcohols were used as the solvent of the reaction. These are the mildest conditions for ruthenium-based catalysis of amine alkylations by the borrowing hydrogen methodology. We have also shown the first examples of this chemistry at room temperature with a ruthenium catalyst. Higher temperatures (110 °C) were required when alcohols were used stoichiometrically. Work is in progress to improve reactivity and selectivity of some of the reactions and also to reduce the loading of ruthenium in the room temperature reactions.

We have demonstrated a catalytic system that is efficient, selective, mild, and versatile. The reaction and its workup are simple, making the entire process scalable. This is a flexible reaction, having several variations in reaction conditions to accommodate diverse substrates. The catalytic alkylation of amines with alcohols avoids the use of environmentally unfriendly reagents and produces water as its sole by product,

■ EXPERIMENTAL SECTION

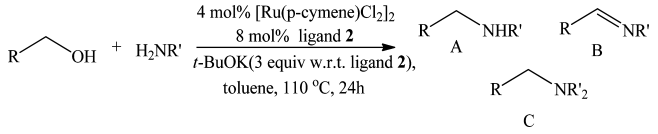
All reactions were carried out under inert atmosphere in sealed reaction vials or high-pressure tubes. All solvents used were purchased from commercial sources, dried, and degassed on a Schlenk line before use. All the alcohols used either as solvent or stoichiometric reagents were dried and degassed on the Schlenk line. For the reactions in which molecular sieves were used, the sieves were suspended over the reaction solution. Purification was done by flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz machine (at 400 and 100 MHz, respectively.) ESI MS data was obtained using purified product samples on an instrument with an ion trap mass analyzer. Direct GCMS analysis of reaction mixtures was used to obtain GCMS data. The reaction yields and selectivities were determined by GCMS using *N,N*-dimethylbenzylamine as the internal standard.

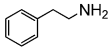
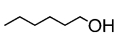
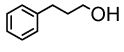
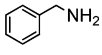
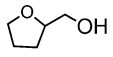
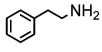
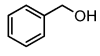
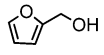
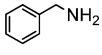
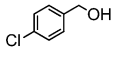
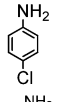
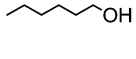
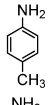
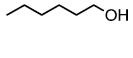
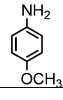
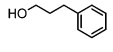
Synthesis of Amino Amide Ligands. The Boc-Phe-OH (3.18 g, 12.0 mmol) was dissolved in dry dichloromethane (60 mL) and cooled in an ice bath. To the solution was added 1,3-dicyclohexylcarbodiimide (DCC) (2.47 g, 12.0 mmol) in small portions followed by stirring in an ice bath for 15 min. Aniline (1.09 mL, 12.0 mmol) was then added to the solution, and the reaction was allowed to warm to room temperature and stir for 24 h. The reaction was filtered, and the filtrate was washed twice with deionized water. The organic fractions were combined and dried over anhydrous magnesium sulfate. The solution was filtered, and the filtrate was recovered and concentrated under vacuum. Hexane was added, and a white solid was filtered.

The Boc-amino amide was quantitatively transferred to a flask, and a 50:50 (v/v) solution of trifluoroacetic acid (10 equiv) in dichloromethane

dx.doi.org/10.1021/jo501273t | J. Org. Chem. 2014, 79, 7553−7563

Table 8. Stoichiometric Alkylation of Primary Aliphatic and Aromatic Amines[a]



Entry	Amine	Alcohol	Conversion (%)	Selectivity %A	%B	%C	Yield[b] A (isolated yield,)
1			>99	100	0	0	>99 (81)
2			>99	100	0	0	>99
3			>99	100	0	0	>99
4			>99	93	7	0	92 (70)
5			>99	94	6	0	93
6			>99	100	0	0	>99
7			50	100	0	0	50
8			53	100	0	0	53 (50)
9			56	100	0	0	56

[a]Reaction conditions: amine (1 mmol), alcohol (2 mmol), ligand **2** (8 mol %), [Ru(*p*-cymeneCl$_2$]$_2$ (4 mol %), *t*-BuOK (3 equiv wrt **2**), 110 °C, toluene solvent. [b]Yield calculated by GCMS using *N,N*-dimethylbenzylamine as the internal standard.

was added. The reaction was stirred at room temperature for 40 min, and then solvent was removed under vacuum.

For the synthesis of ligand **2**,[84] diethyl ether was added to the residue to precipitate a white solid. The solid was filtered and washed several times with ether and allowed to dry (2.52 g, 60%). This compound was stable under ambient conditions: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.33 (s, 3H), 7.50−7.43 (m, 2H), 7.34−7.17 (m, 7H), 7.11−7.02 (m, 1H), 4.14 (t, J = 7.0 Hz, 1H), 3.09 (m, J = 13.8, 7.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO) δ 167.1, 138.2, 135.2, 129.9, 129.3, 128.9, 127.7, 124.6 120.1, 54.7, 37.5.

For the synthesis of ligand **3**,[84] the residue was dissolved in dichloromethane and washed three times with a saturated sodium bicarbonate solution. The organic fractions were combined and washed three times with brine. The organic layer was recovered and dried over anhydrous magnesium sulfate. The solution was filtered off, filtrate was recovered, and solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel using 4% MeOH/CH_2Cl_2 solution giving a white solid (1.20 g, 68%). Product was stored in the freezer: ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.41 (s, 1H), 7.63−7.55 (m, 2H), 7.38−7.22 (m, 7H), 7.11 (m, 1H), 3.73 (dd, J = 9.5, 3.9 Hz, 1H), 3.37 (dd, J = 13.8, 3.9 Hz, 1H), 2.79 (dd, J = 13.8, 9.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.4, 137.7, 137.7, 129.3, 128.9, 128.8, 126.9, 124.1, 119.5, 56.8, 40.7.

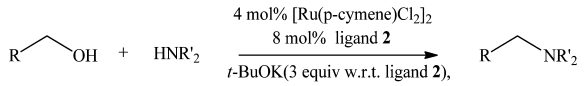
Typical Procedure for Alkylation Reaction (Example of *p*-Toluidine Alkylation in Ethanol). The aminoamide ligand **3** (19.2 mg, 0.08 mmol), *t*-BuOK (9.0 mg, 0.08 mmol), and [Ru(*p*-cymene)Cl$_2$]$_2$ (24.5 mg, 0.04 mmol) were dissolved in dry degassed dichloromethane (10 mL) and stirred at room temperature under nitrogen for 1 h. The solvent was then removed completely using a stream of nitrogen. *p*-Toluidine (107.0 mg, 1.0 mmol) was dissolved under nitrogen in dry degassed ethanol (5 mL), and the solution was transferred to the reaction. *t*-BuOK (9.0 mg, 0.08 mmol) was dissolved under nitrogen in dry degassed ethanol (6 mL) and transferred to the reaction. The reaction was stirred at 65 °C under nitrogen and monitored by GCMS.

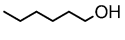
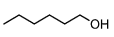
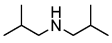
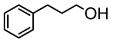
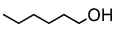
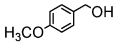
N-Ethyl-4-methylaniline[85] *(Table 2, Entry 3).* Purified using 4% MeOH/CH_2Cl_2 (light yellow oil 120.0 mg, 89%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 6.98 (d, J = 8.4 Hz, 2H), δ 6.54 (d, J = 8.4 Hz, 2H), δ 3.13 (q, J = 7.2 Hz, 2H), δ 2.23 (s, 3H), δ 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 129.7, 129.7, 126.4, 112.9, 38.8, 20.4, 16.9; MS(EI) [M$^+$] 135.1.

Typical Procedure for Stoichiometric Alkylation Reaction (Example of 4-Benzylpiperidine Alkylation with 1-Hexanol). The aminoamide ligand **3** (28.3 mg, 0.08 mmol), *t*-BuOK (27.0 mg, 0.24 mmol), and [Ru(p-cymene)Cl$_2$]$_2$ (24.5 mg, 0.04 mmol) were dissolved in dry degassed dichloromethane (5 mL) and stirred at room temperature under nitrogen for 1 h. The solvent was the removed completely using a stream of nitrogen. 4-Benzylpiperidine (175.5 μL,

dx.doi.org/10.1021/jo501273t | J. Org. Chem. 2014, 79, 7553−7563

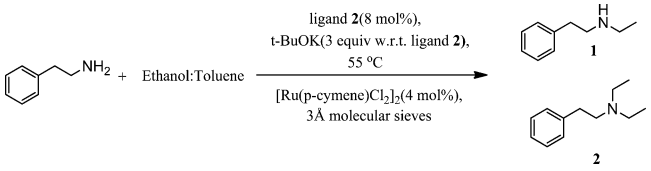
Table 9. Stoichiometric Alkylation of Secondary Amines[a]



Entry	Amine	Alcohol	Conv (%)	Yield[b] (isolated yield)
1			>99	>99 (93)
2			>99	>99
3			>99	>99
4			>99	>99 (85)
5			>99	>99
6			>99	>99 (94)
7			>99	>99 (80)
8			>99	>99
9			>99	>99 (78)

[a]Reaction conditions: amine (1 mmol), alcohol (2 mmol), ligand **2** (8 mol %), [Ru(*p*-cymeneCl$_2$]$_2$ (4 mol %), *t*-BuOK (3 equiv wrt **2**), 110 °C, toluene solvent. [b]Yield calculated by GCMS using *N,N*-dimethylbenzylamine as the internal standard.

Table 10. Optimization of Primary Amine Alkylation with Toluene as Co-solvent[a]



		selectivity[b] (%)	
entry	ethanol/toluene (%)	**1**	**2**
1	90:10	0	100
2	70:30	52	48
3	50:50	97	3
4	30:70	>99	<1

[a]Reaction conditions: amine (1 mmol), 30% alcohol/toluene (solvent), ligand **2** (*x* mol %), [Ru(*p*-cymeneCl$_2$]$_2$ (*x*/2 mol %), *t*-BuOK (3 equiv wrt **2**), 55 °C, 3 Å molecular sieves. [b]Selectivity calculated by GCMS using *N,N*-dimethylbenzylamine as the internal standard.

1.0 mmol) and 1-hexanol (250.6 μL, 2.0 mmol) were dissolved under nitrogen in dry degassed toluene (5 mL), and the solution was transferred to the reaction. The reaction tube was sealed, and the reaction was stirred at 110 °C under nitrogen and monitored by GCMS.

4-Benzyl-N-hexylpiperidine[86] *(Table 9, Entry 1, and Table 5, Entry 5).* Purified using 60% EtOAc/35% hexane/5% Et$_2$N (light yellow oil, 242.0 mg, 93% and 233.0 mg, 90%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.28−7.24 (m, 2H), 7.19−7.12 (m, 3H), 2.89 (m, 2H), 2.52 (d, *J* = 8 Hz, 2H), 2.26 (m, 2H), 1.82 (m, 2H), 1.62 (m, 2H), 1.57−1.43 (m, 3H), 1.36−1.26 (m, 8H) 0.86 (t, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 140.8, 129.1, 128.1, 125.7, 59.3, 54.0, 43.3, 38.0, 32.3, 31.8, 27.5, 27.1, 22.6, 14.1; MS(ESI) [M + H]$^+$ 260.4500.

4-Ethoxy-N-ethylaniline[87] *(Table 2, Entry 5).* Purified using 4% MeOH/CH$_2$Cl$_2$ (light brown oil, 130.0 mg, 79%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 6.78 (d, *J* = 8 Hz, 2H), 6.57 (d, *J* = 8 Hz, 2H), 3.96 (q, *J* = 7.0 Hz, 2H), 3.11 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.0 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.3, 142.7, 115.8, 114.1, 64.1, 39.5, 15.03, 15.01; MS(EI) [M$^+$] 165.1.

4-Ethoxy-N-propylaniline[88] *(Table 2, Entry 6).* Purified using 4% MeOH/CH$_2$Cl$_2$ (brown oil, 130.0 mg, 73%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 6.77 (d, *J* = 8 Hz, 2H), 6.57 (d, *J* = 8 Hz, 2H), 3.96 (q, *J* = 7.0 Hz, 2H), 3.03 (t, *J* = 7.1 Hz, 2H), 1.64 (m, 2H), 1.37 (t, *J* = 7.0 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.3, 142.8, 115.8, 114.0, 64.2, 46.9, 22.8, 15.0, 11.7; MS(EI) [M$^+$] 179.2.

4-Ethoxy-N-isopentylaniline[88] *(Table 2, Entry 7).* Purified using 4%MeOH/CH$_2$Cl$_2$ (brown oil, 170.0 mg, 82%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 6.78 (d, *J* = 8 Hz, 2H), 6.57 (d, *J* = 8 Hz, 2H), 3.95 (q, *J* = 7.0 Hz, 2H), 3.07 (t, *J* = 7.0 Hz, 2H), 1.71 (m, 1H), 1.49 (m, 2H), 1.36 (t, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.2, 142.8, 115.8, 113.9, 64.1, 43.2, 38.7, 26.0, 22.6, 15.0; MS(EI) [M$^+$] 207.3.

4-Benzyl-N-ethylpiperidine[89] *(Table 5, Entry 3).* Purified using 60% EtOAc/35% Hexane/5% Et$_2$N (pale yellow oil, 175.6 mg, 85%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.28−7.24 (m, 2H), 7.19−7.13 (m, 3H), 2.91 (m, 2H), 2.53 (d, *J* = 8 Hz, 2H), 2.36 (q, *J* = 8 Hz, 2H), 1.82 (m, 2H), 1.64 (m, 2H), 1.50 (m, 1H), 1.31 (m, 2H), 1.06 (t, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 140.8, 129.1, 128.1, 125.7, 53.6, 52.6, 43.3, 38.0, 32.2, 12.2; MS(CI) [M + H]$^+$ 204.1.

4-Benzyl-N-butylpiperidine[89] *(Table 5, Entry 4).* Purified using 60% EtOAc/35% hexane/5% Et$_2$N (pale brown oil, 227.0 mg, 97%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.28−7.24 (m, 2H), 7.19−7.12 (m, 3H), 2.89 (m, 2H), 2.52 (d, *J* = 8 Hz, 2H), 2.27 (m, 2H), 1.82 (m, 2H), 1.62 (m, 2H), 1.57−1.42 (m, 3H), 1.36−1.26 (m, 4H) 0.90 (t, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 140.7, 129.1, 128.1, 125.7, 58.9, 53.9, 43.2, 37.9, 32.2, 29.2, 20.9, 14.0; MS(ESI) [M + H]$^+$ 232.4100.

N-Hexylphenethylamine[90] *(Table 8, Entry 1).* Purified using 5% MeOH/CH$_2$Cl$_2$ (pale yellow oil, 166.0 mg, 81%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.31−7.25 (m, 2H), 7.21−7.15 (m, 3H), 2.91−2.76 (m, 4H), 2.60 (t, *J* = 7.6 Hz, 2H), 1.45 (m, 2H), 1.27 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 140.4, 128.9, 128.6, 126.2, 51.4, 50.1, 36.6, 31.9, 30.3, 27.2, 22.8, 14.2; MS(CI) [M + H]$^+$ 206.3.

N-Benzylphenethylamine[91] *(Table 8, Entry 4).* Purified using 4% MeOH/CH$_2$Cl$_2$ (colorless oil, 138.0 mg, 70%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32−7.17 (m, 10H), 3.79 (s, 2H), 2.92−2.81 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 140.3, 140.0, 128.7, 128.4, 128.4, 128.0, 126.9, 126.1, 53.9, 50.6, 36.4; MS(CI) [M + H]$^+$ 212.2.

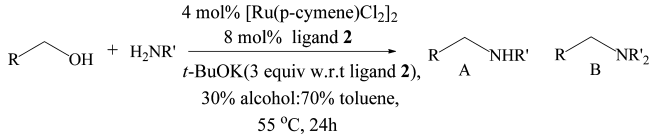
N-Hexyl-4-methylaniline[92] *(Table 8, Entry 8).* Purified using 60% EtOAc/35% hexane/5% Et$_2$N (yellow oil, 95.0 mg, 50%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 6.96 (d, *J* = 8.0 Hz, 2H), δ 6.60 (d, *J* = 8.4 Hz, 2H), δ 3.63 (t, *J* = 6.8 Hz, 2H), δ 2.23 (s, 3H), δ 1.56 (m, 2H), 1.39−1.26 (m, 6H), 0.89 (t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 143.8, 129.8, 127.8, 115.3, 63.1, 32.8, 31.7, 25.5, 22.6, 20.4, 14.0; MS(CI) [M + H] $^+$ 191.2.

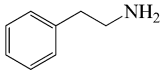
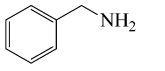
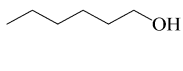
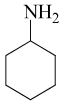
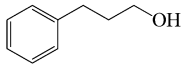
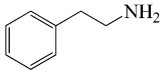
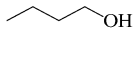
N-(3-Phenylpropyl)diisobutylamine[93] *(Table 9, Entry 4).* Purified using 4% MeOH/CH$_2$Cl$_2$(pale brown oil, 208.8 mg, 85%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.29−7.14 (m, 5H), 2.62 (t, *J* = 8.0 Hz, 2H), 2.36 (t, *J* = 6.8 Hz, 2H), 2.05 (d, *J* = 7.6 Hz, 4H), 1.70 (m, 2H), 0.88(d, *J* = 6.4 Hz, 12H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 142.9, 128.3, 128.2, 125.5, 64.1, 54.9, 33.9, 29.4, 26.6, 20.9; MS(ESI) [M + H]$^+$ 248.4500.

N-Benzyldibutylamine[91] *(Table 9, Entry 6).* Purified using 60% EtOAc/hexanes (pale brown oil, 205 mg, 94%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.35−7.19 (m, 5H), 2.54 (s, 2H), 2.39 (t, *J* = 7.2 Hz, 4H), 1.48−1.40 (m,4H), 1.33−1.24 (m, 4H), 0.87(t, *J* = 7.2 Hz, 6H);

dx.doi.org/10.1021/jo501273t | J. Org. Chem. 2014, 79, 7553−7563

Table 11. Alkylation of Primary Aliphatic Amines with Toluene Co-solvent



Entry	Amine	Alcohol	Conv (%)	Selectivity(%) A	Selectivity(%) B	Yield[b] (isolated) (A)
1			>99	>99	<1	>99
2			>99	93	0	92
3			>99	91	0	90
4			>99	91	0	90 (83)

[a]Reaction conditions: amine (1 mmol), 30% alcohol/toluene (solvent), ligand 2 (x mol %), [Ru(p-cymeneCl_2]$_2$ (x/2 mol %), t-BuOK (3 equiv wrt 2), 55 °C, 3 Å molecular sieves. [b]Yield calculated by GCMS using N,N-dimethylbenzylamine as the internal standard.

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 128.7, 127.9, 126.5, 58.6, 53.5, 29.2, 20.6, 14.0; MS(CI) [M + H] $^+$ 220.3.

N-Benzyl-4-benzylpiperidine[94] *(Table 9, Entry 7).* Purified using 60% EtOAc/35% hexane/5% Et_2N (white solid, 212.3 mg, 80%): ^{1}H NMR (400 MHz, chloroform-d) δ 7.29−7.10 (m, 10H), 3.46(s, 2H), 2.84 (m, 2H), 2.51(d, J = 7.2 Hz, 2H) 1.88(m,2H), 1.61−1.45 (m, 3H), 1.31(m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 138.6, 129.2, 129.1, 128.12, 128.10, 126.8, 125.7, 63.5, 53.8, 43.3, 37.9, 32.2; MS(CI) [M + H] $^+$ 266.4.

N-(4-Methoxybenzyl)dibutylamine[95] *(Table 9, Entry 9).* Purified using 60% EtOAc/35% hexane/5% Et_2N (pale yellow oil, 195.0 mg, 78%): ^{1}H NMR (400 MHz, chloroform-d) δ 7.23 (d, J = 8.4 Hz, 2H), δ 6.83 (d, J = 8.8 Hz, 2H), δ 3.79 (s, 3H), 3.48(s, 2H), 2.38 (t, J = 7.6 Hz, 4H), 1.47−1.34 (m,4H), 1.33−1.24 (m, 4H), 0.87(t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 132.2, 129.8, 113.4, 57.8, 55.2, 53.3, 29.2, 20.6, 14.1; MS(CI) [M + H] $^+$ 250.4.

N-Butylphenethylamine[96] *(Table 11, Entry 4).* Purified using 55% EtOAc/35% hexane/5% Et_2N/5% MeOH (pale yellow oil, 146.9 mg, 83%): ^{1}H NMR (400 MHz, chloroform-d) δ 7.30−7.27 (m, 2H), 7.21−7.18 (m, 3H), 2.90−2.78 (m, 4H), 2.61 (t, J = 7.2 Hz, 2H), 1.49−1.41 (m, 2H), 1.36−1.26 (m, 6H), 0.87(t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 128.7, 128.4, 126.0, 51.3, 49.6, 36.4, 32.2, 20.5, 13.9; MS(CI) [M + H] $^+$ 177.9.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR and ESI-MS data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Department of Chemistry at Georgetown University

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