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Catalytic N-Alkylation of Amines Using Carboxylic Acids and Molecular Hydrogen

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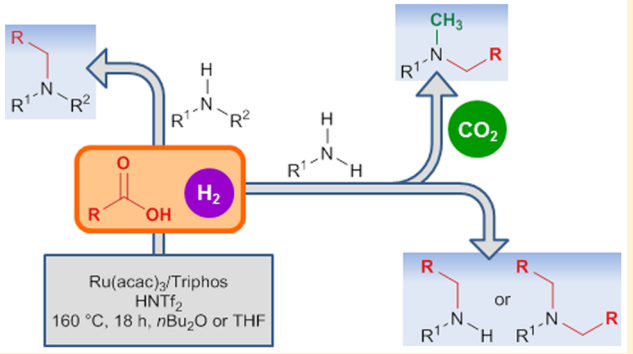
Supporting Information

ABSTRACT: A convenient, practical and green N-alkylation of amines has been accomplished by applying readily available carboxylic acids in the presence of molecular hydrogen. Applying an in situ formed ruthenium/triphos complex and an organic acid as cocatalyst, a broad range of alkylated secondary and tertiary amines are obtained in good to excellent yields. This novel method is also successfully applied for the synthesis of unsymmetrically substituted N-methyl/alkyl anilines through a direct three-component coupling reaction of the corresponding amines, carboxylic acids, and CO_2 as a C_1 source.



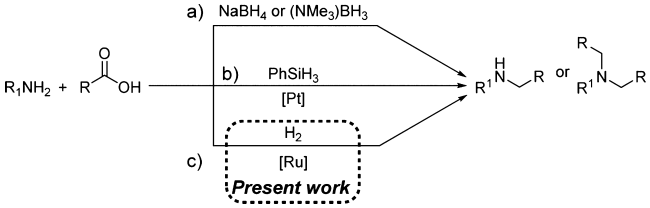
INTRODUCTION

N-Alkylated amines constitute highly valuable organic compounds in many research areas because of their use in the preparation of natural products, pharmaceuticals, dyes, agrochemicals, and other fine chemicals.[1] Therefore, it is not surprising that in spite of the existing methods,[2,3] the development of new versatile and efficient protocols for their synthesis is of continuing interest.

Well established methods to produce secondary and tertiary amines involve reductive domino processes of carbonyl compounds. Among them, the direct reductive alkylation using aldehydes or ketones are the most popular.[4,5] Compared to the conventional reduction of imines[6,7] or amides,[8,9] these tandem processes constitute a more benign and practical strategy since they avoid additional reaction steps for the synthesis and isolation of the corresponding substrates.[10] However, in some cases the necessary aldehydes or ketones are not easily available or undergo unwanted side-reactions, e.g., aldol condensations. In addition to sensitive carbonyl compounds, readily available and more stable carboxylic acids can also be employed for the reductive alkylation of amines. Surprisingly, until now these latter transformations have been scarcely investigated.

Known synthetic routes for the alkylation of amines with alkyl and aryl carboxylic acids involve the use of stoichiometric amounts of metal borohydride reagents (Scheme 1a).[11] More recently, we reported the first platinum-catalyzed N-alkylation of amines with different carboxylic acids under mild conditions using silanes as reducing agents (Scheme 1b).[12] However, both protocols suffer from the low atom-efficiency and the laborious workup procedures. In this respect, the use of molecular hydrogen, the least expensive and most "green" reductant, would be advantageous. Therefore, the development of a reductive alkylation using all kinds of carboxylic acids in the presence of hydrogen is highly desired. To the best of our knowledge, there is only one known example. More specifically, Cole-Hamilton and co-workers reported the synthesis of a mixture of *N*-nonylamine and *N*,*N*-dinonylamine in low yield (15% and 47%, respectively) and selectivity by hydrogenation of nonanoic acid under an ammonia atmosphere.[9a] Herein, we disclose a general Ru-catalyzed N-alkylation of amines with carboxylic acids using benign molecular hydrogen as the reducing agent and trifluoromethanesulfonimide ($HNTf_2$) as the cocatalyst (Scheme 1c).

Scheme 1. N-Alkylation of Amines with Carboxylic Acids: (A) Borohydride Reduction, (B) Catalytic Hydrosilylation, and (C) Catalytic Hydrogenation



RESULTS AND DISCUSSION

To identify critical reaction parameters, the alkylation of aniline (**1a**) with acetic acid in the presence of molecular hydrogen was investigated as a benchmark system. On the basis of the recent

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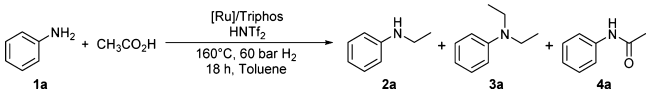
catalytic methylations using formic acid[13] or CO_2,[14] as well as the hydrogenation of carboxylic acid derivatives,[8,9,15] initially several ruthenium complexes in the presence of the so-called triphos ligand (1,1,1-tris(diphenylphosphinomethyl)ethane) were evaluated in the model reaction (Table 1). The most

Table 1. Ruthenium-Catalyzed N-Alkylation of Aniline (1a) with Acetic Acid and H_2[a]



entry	[Ru] precursor	conversion (%)[b]	yield (%)[b] 2a	3a	4a
1	–	63	–	–	59
2	$Ru(acac)_3$	>99	16	78	–
3	$Ru(2\text{-methylallyl})_2(cod)$	>99	50	50	–
4	$RuCl_2(bipy)_2{\cdot}xH_2O$	59	–	–	57
5	$RuCl_3{\cdot}xH_2O$	67	–	–	55
6	$RuCl_2[CH_3S(O)CH_3]_4$	67	–	–	49
7	$RuCl_2(PPh_3)_3$	65	–	–	59
8[c]	$[RuCl_2(C_{10}H_{14})]_2$	>99	–	–	–
9	$Ru_3(CO)_{12}$	56	–	–	49
10[d]	$Ru(acac)_3$	>99	31	61	–
11[d,e]	$Ru(acac)_3$	77	59	2	–
12[d,f,g]	$Ru(acac)_3$	>99	43	49	–
13[d,g]	$Ru(acac)_3$	>99	19	75	–
14[g,h]	$Ru(acac)_3$	>99	2	91	–
15[i]	$Ru(acac)_3$	98	84	13	–

[a]Reaction conditions: substrate (0.5 mmol), [Ru] precursor (4 mol %), Triphos (6 mol %), $HNTf_2$ (10 mol %), CH_3CO_2H (2.5 equiv), toluene (2 mL). [b]Determined by GC using *n*-hexadecane as an internal standard. [c]*N*-Cyclohexylacetamide was formed as product. [d]$HNTf_2$ (5 mol %). [e]140 °C. [f]15 bar H_2. [g]nBu_2O used as a solvent. [h]Ru catalyst (5 mol %), Triphos (7.5 mol %), $HNTf_2$ (7.5 mol %), CH_3CO_2H (4 equiv). [i]Ru catalyst (2 mol %), Triphos (3 mol %), $HNTf_2$ (2 mol %), CH_3CO_2H (1.7 equiv), THF (2 mL).

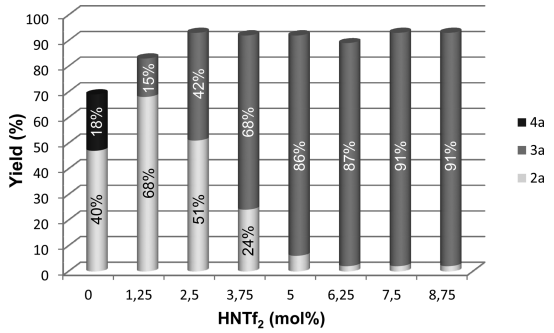
active catalyst was generated by using ruthenium acetylacetonate [$Ru(acac)_3$] (4 mol %; metal/triphos ratio 1:1.5) as metal precursor in combination with a catalytic amount of trifluoromethanesulfonimide ($HNTf_2$; 10 mol %) achieving full conversion of **1a** with 16 and 78% yield of *N*-ethylaniline (**2a**) and *N*,*N*-diethylaniline (**3a**), respectively (Table 1, entry 2). Among the other tested ruthenium precursors, only [$Ru(2\text{-methylallyl})_2(cod)$] (cod = cyclooctadiene) showed a similar reactivity (Table 1, entry 3). The other tested ones did not afford any desired alkylated products, and in all cases small amounts of *N*-phenylacetamide were detected.

Notably, in the absence of any ligand *N*-cyclohexylacetamide was formed as a main product, and the use of other phosphane ligands with different structure revealed almost no reactivity in the alkylation reaction (Table SI1 in the Supporting Information). Temperature and pressure proved to be also critical for the efficiency of the alkylation reaction. Indeed, a decrease in conversion and yield of alkylated products was observed at 140 °C or by dropping the pressure to 15 bar (Table 1, entries 11 and 12, respectively).

Next, the influence of different Lewis and Bronsted acids on the model reaction in toluene was investigated (Table SI2 in the Supporting Information). Without cocatalyst or in the presence of methanesulfonic acid or LiCl, significantly lower reactivity was observed. Among the various triflate salts, the best result for the dialkylated product are obtained using $HNTf_2$. Remarkably, using catalytic amounts of aluminum triflate or lithium triflimide high selectivity toward the monoalkylated product are observed. Next, the influence of the solvent was investigated. Gratefully, using nBu_2O a slight improvement of the degree of alkylation is observed (Table 1, entry 13; see also Supporting Information, Table SI3).

Finally, *N*,*N*-diethylaniline (**3a**) is afforded in 91% yield after increasing the amount of acetic acid (4 equiv) and adjusting the co- and catalyst loading to 7.5 and 5 mol %, respectively (Table 1, entry 14).

Interestingly, as shown in Figure 1 the degree of alkylation (di- versus monoalkylation) largely depends on the amount of



Reaction conditions: **1a** (0.5 mmol), $Ru(acac)_3$ (5 mol%), Triphos (7.5 mol%), CH_3CO_2H (4 equiv), 160 °C, 60 bar H_2, 18 h, nBu_2O (2 mL)

Figure 1. Influence of $HNTf_2$ on the N-alkylation of **1a** with acetic acid.

$HNTf_2$ present in the reaction mixture. This prompted us to investigate the possibility to get selectively the monoalkylated product **2a** too. To our delight, by tuning the stoichiometry of the reagents and using THF as solvent, *N*-ethylaniline (**2a**) is obtained in 84% yield with a 10:1.5 mono/dialkylation ratio (Table 1, entry 15).

Encouraged by this result, the monoalkylation of a variety of anilines bearing electron-withdrawing or electron-donating substituents with acetic acid was examined in more detail (Table 2). Under optimized conditions, the desired substituted monoalkylated products are obtained in high yields and selectivity. It is noteworthy that both electronic and steric properties of the substituents affect the efficiency of the monoalkylation reaction. For example, para-substituted anilines with electron-donating substituents, such as methyl or ether groups, showed higher reactivity than electron-withdrawing groups in the same ring position. Consequently, a lower amount of acetic acid was required in order to avoid over alkylation. Moreover, monoalkylation of a sterically hindered aliphatic amine, such as 1-adamantylamine, proceeded smoothly with high selectivity affording *N*-ethyladamantan-1-amine in 91% yield (Table 2, entry 8).

Next, the potential of this catalytic protocol for the preparation of alkyl-substituted tertiary amines was further explored. As shown in Table 3, a variety of primary and secondary amines were reacted with acetic acid. Gratifyingly, both anilines bearing electron-withdrawing and electron-donating groups are efficiently alkylated affording the corresponding tertiary anilines in good to excellent yields. Again, the alkylation activity is highly dependent on the electronic and steric properties of the substituent. When the amino group is sterically hindered, an increased catalyst loading

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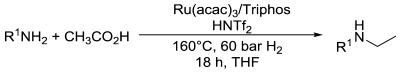
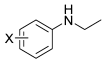
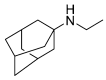
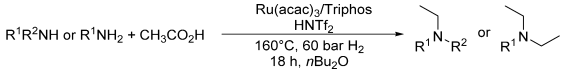
Table 2. N-Monoalkylation of Primary Amines with Acetic Acid and H_2[a]

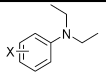
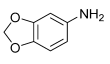
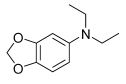
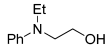


entry	substrate	product	conv. (%)[b]	yield (%)[b]
				
1[c,d]	X = 4-Me	X = 4-Me	95	85 (71)
2[c]	X = 4-Cl	X = 4-Cl	96	83 (76)
3[c]	X = 3-Cl	X = 3-Cl	90	80 (73)
4[c,e]	X = 4-F	X = 4-F	94	85 (71)
5[c,d]	X = 4-OMe	X = 4-OMe	93	86 (75)
6[c]	X = 3-OMe	X = 3-OMe	98	77 (71)
7[c,d]	X = 4-OPh	X = 4-OPh	91	86 (72)
8[f,g,h]			>99	91

[a]Reaction conditions: substrate (0.5 mmol), $Ru(acac)_3$ (2 mol %), Triphos (3 mol %), $HNTf_2$ (2 mol %) CH_3CO_2H (1.7 equiv), THF (2 mL). [b]Determined by GC using *n*-hexadecane as an internal standard; isolated yield in parentheses. [c]Dialkylated product was detected as a byproduct. [d]CH_3CO_2H (1.3 equiv). [e]$Ru(acac)_3$ (1.5 mol %), Triphos (2.25 mol %), $HNTf_2$ (1.5 mol %). [f]$Ru(acac)_3$ (10 mol %), Triphos (15 mol %), $HNTf_2$ (20 mol %), CH_3CO_2H (8 equiv), nBu_2O (2 mL). [g]*N*-(adamantan-1-yl)acetamide was detected as a byproduct. [h]Yield <10% upon isolation by column chromatography.

Table 3. Preparation of Tertiary Amines Through to N-Alkylation with Acetic Acid and H_2[a]



entry	substrate	product	conv. (%)[b]	yield (%)[b]
				
1[c]	X = 4-Me	X = 4-Me	>99	83 (76)
2[c,d,e]	X = 4-Cl	X = 4-Cl	>99	(72)
3	X = 4-F	X = 4-F	>99	(80)
4[d]	X = 4-SMe	X = 4-SMe	>99	(82)
5[c]	X = 3-OMe	X = 3-OMe	>99	92 (83)
6[c]	X = 4-OPh	X = 4-OPh	>99	(77)
7[c,f]	X = 2,6-Me	X = 2,6-Me	94	(69)
8[c,g]	X = 2-Ph	X = 2-Ph	>99	(65)
9			>99	(63)
10[h]			>99	>99 (94)
11[h]			>99	(70)
12[g,i,j]	$BnNH_2$	$BnNEt_2$	>99	62 (50)
13[h,j,k]	Bn_2NH	Bn_2NEt	>99	83 (68)
14[d,e,j,l,m]			82	68

[a]Reaction conditions: substrate (0.5 mmol), $Ru(acac)_3$ (5 mol %), Triphos (7.5 mol %), $HNTf_2$ (7.5 mol %), CH_3CO_2H (4 equiv), nBu_2O (2 mL). [b]Determined by GC using *n*-hexadecane as an internal standard; isolated yield in parentheses. [c]Monoalkylated product was detected as a byproduct. [d]$Ru(acac)_3$ (6 mol %), Triphos (9 mol %), $HNTf_2$ (9 mol %). [e]CH_3CO_2H (5 equiv). [f]$Ru(acac)_3$ (8 mol %), Triphos (12 mol %), $HNTf_2$ (12 mol %), CH_3CO_2H (7 equiv). [g]$Ru(acac)_3$ (10 mol %), Triphos (15 mol %), $HNTf_2$ (15 mol %), CH_3CO_2H (8 equiv). [h]$Ru(acac)_3$ (3 mol %), Triphos (4.5 mol %), $HNTf_2$ (4.5 mol %), CH_3CO_2H (2.5 equiv). [i]Acetamide derivatives were detected as byproducts. [j]THF used as a solvent. [k]Tribenzylamine and *N*,*N*-dibenzylacetamide were detected as byproducts. [l]*N*-cyclohexyl-*N*-ethylacetamide was detected as a byproduct. [m]Yield <10% upon isolation by column chromatography.

and amount of acetic acid are required to afford the desired amines in moderated yields (Table 3, entries 7–8). Notably, the selective *N*-alkylation of amino alcohols can be achieved, thus avoiding additional protection/deprotection steps for their preparation (Table 3, entry 11). Moreover, our catalytic protocol also allowed for the alkylation of benzylic and aliphatic amines. Although less effective than the alkylation of aromatic amines, good yields of the corresponding alkylated products are achieved by increasing the stoichiometry of the reactants and using THF as solvent (Table 3, entries 12–14).

With good reactivity for acetic acid in hand, the generality of this hydrogenative alkylation was explored by reaction of aniline with different carboxylic acids (Table 4). Carboxylic acids with both electron-donating and electron-withdrawing substituents can be successfully used as alkylating reagents. For example, carboxylic acids with longer alkyl chain length including linear, branched, as well as cyclic moieties gave the corresponding secondary N-alkylated anilines in 76–94% yield (Table 4, entries 1–9). Interestingly, fluoroalkyl-substituted anilines with potential applications in the pharmaceutical industry,[16] are efficiently synthesized from easy available fluorinated carboxylic acids (Table 4, entries 3 and 9). Moreover, heterocyclic and carboxylic acids containing aromatic ethers were used as alkylating reagents (Table 4, entries 10–11). Benzylation of aniline with benzoic acid in THF achieved full conversion with 70% yield of *N*-benzylaniline and *N*-phenylpyrrolidine as byproduct, which is presumably formed from the acid catalyzed reaction of aniline with THF (Table 4, entry 12; X = OH).[9c] Unfortunately, the use of different solvents in order to avoid the formation of this byproduct led to a much lower conversion and yield. However, when phenylglyoxylic acid was used as an alkylating reagent, *N*-benzylaniline is afforded in 92% yield (Table 4, entry 12; X = CO_2H). A plausible route for the formation of this product involves a conventional reductive amination of the ketone first, followed by a C–C bond cleavage.[17] Interestingly, excellent reactivity was observed with different arylacetic acids furnishing the expected products in good to excellent yields (Table 4, entries 13–18). Noteworthy, ibuprofen, which is an important nonsteroidal anti-inflammatory drug widely used for the treatment of pain, inflammation, and fever,[18] afforded the corresponding derivative in 88% yield (Table 4, entry 18). As expected, under the present reaction conditions the use of the enantiomerically pure (S)-(+)-ibuprofen led to a racemic

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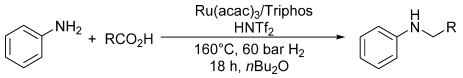
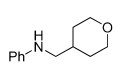
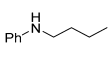
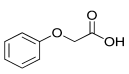
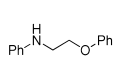
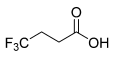
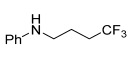
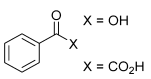
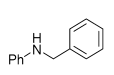
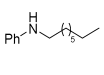
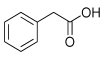
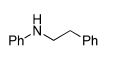
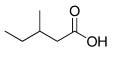
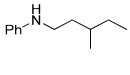
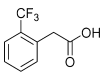
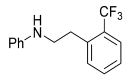
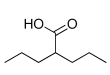
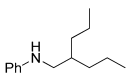
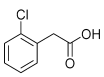
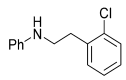
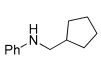
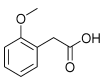
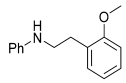
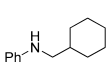
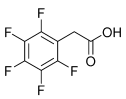
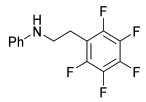
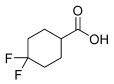
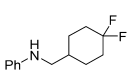
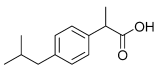
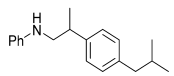
Table 4. N-Alkylation of Aniline (1a) with Various Carboxylic Acids and H_2[a]



entry	RCO_2H	product	conv. (%)[b]	yield (%)[b]	entry	RCO_2H	product	conv. (%)[b]	yield (%)[b]
1[c,d]			96	94 (84)	10			94	(79)
2[c,d]			97	93 (82)	11[c]			86	40 (32)
3[c,e]			>99	(80)	12[j]			>99 99	70 (65) 92 (85)
4[c,f]			96	85 (76)	13[c]			95	69 (61)
5[e,g]			90	(81)	14[e]			97	(77)
6[h]			89	(76)	15[c]			>99	(82)
7[i,g]			>99	(93)	16[c,k]			>99	(78)
8[i,g]			>99	93 (87)	17[e]			98	(86)
9[i,g]			>99	(91)	18[e]			>99	(88)

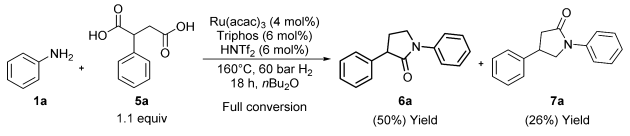
[a]Reaction conditions: substrate (0.5 mmol), $Ru(acac)_3$ (2 mol %), Triphos (3 mol %), $HNTf_2$ (3 mol %), RCO_2H (1.7 equiv), nBu_2O (2 mL). [b]Determined by GC using *n*-hexadecane as an internal standard; isolated yield in parentheses. [c]Dialkylated product as a byproduct. [d]$HNTf_2$ (2 mol %), THF (2 mL). [e]$Ru(acac)_3$ (4 mol %), Triphos (6 mol %), $HNTf_2$ (6 mol %). [f]$Ru(acac)_3$ (2.5 mol %), Triphos (3.75 mol %), $HNTf_2$ (3.75 mol %). [g]RCO_2H (2 equiv). [h]$Ru(acac)_3$ (5 mol %), Triphos (7.5 mol %), $HNTf_2$ (7.5 mol %), RCO_2H (2.5 equiv). [i]$Ru(acac)_3$ (3 mol %), Triphos (4.5 mol %), $HNTf_2$ (4.5 mol %). [j]X = OH: $Ru(acac)_3$ (6 mol %), Triphos (9 mol %), $HNTf_2$ (10 mol %), RCO_2H (3 equiv), THF (2 mL). [k]RCO_2H (1.1 equiv).

product. Finally, the reaction of 2-phenylsuccinic acid (**5a**) with aniline gave a 2:1 mixture of the corresponding pyrrolidones (Scheme 2).

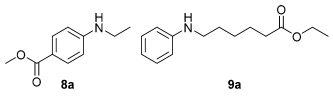
Typically, under catalytic hydrogenation conditions carboxylic esters are considered to be more reactive than carboxylic acids and carboxamides.[8b,19] Therefore, a selective carboxylic acid-mediated reductive N-alkylation method in the presence of carboxylic esters would be interesting.[20] Surprisingly, monoalkylation reactions of methyl 4-aminobenzoate with acetic acid and aniline (**1a**) with monoethyl adipate gave in both cases the desired products (Scheme 3).

With respect to organic synthesis, the intramolecular cyclization of amino carboxylic acids, a structural motif largely found in numerous bioactive compounds,[21] would constitute a useful tool for the preparation of cyclic amines. As shown in

Scheme 2. N-Alkylation of Aniline (1a) with 2-Phenylsuccinic Acid (5a)



Scheme 3. N-Alkylations of Anilines in the Presence of Esters



	RCO_2H (equiv)	$Ru(acac)_3$ (mol%)	Triphos/$HNTf_2$ (mol%)	Conv. (%)	Yield (%)
8a	2.5	3	4.5	96	(73)
9a	2	2	3	93	(65)

substrate (0.5 mmol), 160 °C, 60 bar H_2, 18 h, nBu_2O (2 mL)

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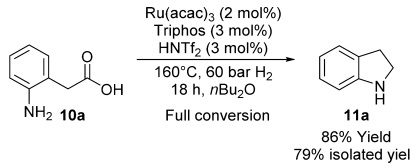
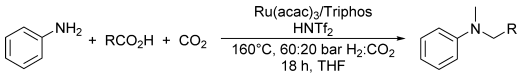
Scheme 4, indoline (**11a**) is accessed in a straightforward manner from 2-aminophenylacetic acid (**10a**) in 86% yield.

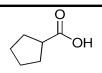
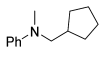
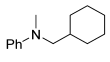
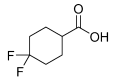
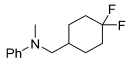
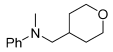
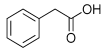
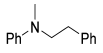
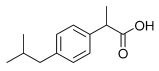
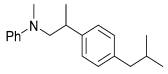
Scheme 4. Intramolecular N-Alkylation of Amino Carboxylic Acids



Next, we envisioned the possibility for a direct three-component coupling reaction of primary amines, carboxylic acids, and CO_2 as a renewable C_1 building block to yield unsymmetrical tertiary amines.[22] As shown in Table 5, cyclic

Table 5. Synthesis of Tertiary *N*-Methyl/Alkyl Anilines from Carboxylic Acids, CO_2 and H_2[a]



entry	RCO_2H	product	conv. (%)[b]	yield (%)[b]
1[c]			>99	(77)
2[c]			>99	(82)
3[c]			>99	(59)
4[c,d]			>99	(62)
5[c,e,f]			>99	(58)
6[c,d]			>99	(65)

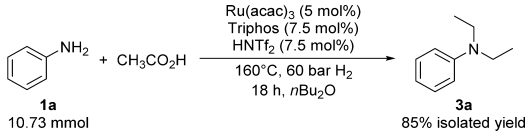
[a]Reaction conditions: substrate (0.5 mmol), $Ru(acac)_3$ (6 mol %), Triphos (9 mol %), $HNTf_2$ (15 mol %), RCO_2H (2 equiv), THF (2 mL). [b]Yield of isolated products in parentheses. [c]*N*,*N*-Dimethylaniline was detected as a byproduct. [d]1.7 equiv RCO_2H. [e]Dialkylated product was detected as a byproduct. [f]1.3 equiv of RCO_2H

and heterocyclic aliphatic as well as arylacetic carboxylic acids were successfully applied in this new one-pot domino transformation affording the corresponding unsymmetrically substituted N-methyl/alkyl anilines in good yields.

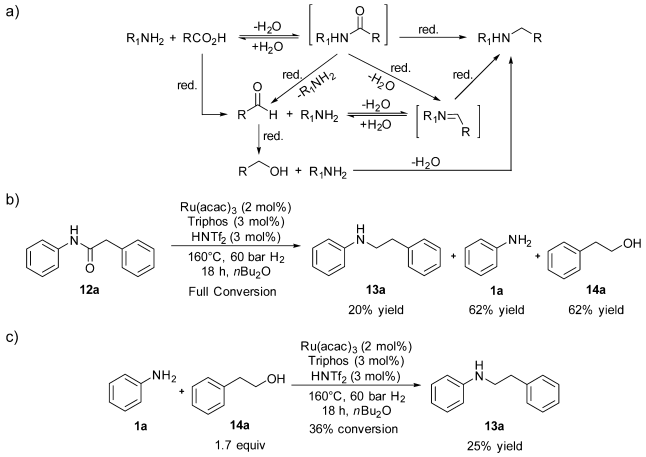
It should be noted that in all cases the catalytic experiments were performed on 0.5 mmol scale; however, it is no problem to run similar experiments on the gram-scale (Scheme 5). In fact, upscaling by a factor of 20 did not change the yield compared to the standard 0.5 millimole-scale reaction.

Regarding the mechanism of the hydrogenative alkylation process, several reaction pathways exist (Scheme 6a): (1) formation of the carboxamide followed by reduction[23] and (2) reduction of the carboxylic acid to the alcohol (via aldehyde) and subsequent alkylation.[14b,24] Indeed, the observation of carboxamide intermediates and alcohols (vide supra) suggests that both pathways might be feasible. To further understand the

Scheme 5. Synthesis of *N*,*N*-Diethylaniline (3a) on the Gram-Scale



Scheme 6. Control Experiments and Proposed Pathways for the Ru-Catalyzed N-Alkylation of Amines with Carboxylic Acids and H_2



reaction mechanism, the reduction of *N*,2-diphenylacetamide (**12a**) was performed under standard reaction conditions. Here, three major products are obtained: the desired *N*-phenethylaniline (**13a**) in 20% yield and the products generated from the reductive C−N bond cleavage, aniline (**1a**), and phenethyl alcohol (**14a**) in 62% yield (Scheme 6b). Furthermore, the alkylation of aniline (**1a**) with **14a** was investigated under otherwise the same reaction conditions. As shown in Scheme 6c, this reaction also affords the expected alkylated product **13a** in 25% yield.

Apparently, both reaction pathways involving either the direct reduction of the amide or the alkylation from aldehydes or alcohols, generated in situ by reduction of carboxylic acids[15a,b,25] or by reductive C−N cleavage of the initially formed carboxamide,[8c,26] are possible under our reaction conditions.

Finally, we addressed the identification and basic reactivity of Ru-containing species involved in this hydrogenative alkylation protocol. When a mixture of $Ru(acac)_3$/Triphos/CH_3CO_2H/$HNTf_2$/aniline was submitted to catalytic conditions, the ESI-MS and ^{31}P NMR data of the crude solid obtained by cooling the reaction mixture were consistent with the formation of the previously reported cationic $[(Triphos)Ru(OAc)(solvent)]^+$ (**15**$^+$) complex (Figure SI1 in the Supporting Information).[22n,27] Minor amounts of dimeric Ru-containing species, mainly the $[Ru_2(\mu\text{-}H)_2(Triphos)_2]$ (**16**) and $[Ru_2(\mu\text{-}OH)_2(Triphos)_2]$ (**17**) compounds were also detected. It is noteworthy that no additional intermediates containing aniline (**1a**) were observed on the basis of ESI-MS, and virtually identical spectroscopic data were obtained in the absence of **1a** (Figure SI2 in the Supporting Information).

In order to probe whether the cationic acetate complex **15**$^+$ is an active intermediate, the alkylation of **1a** with acetic acid was carried out by using the isolated $[\mathbf{15}(NTf_2)]$[22n] complex (7.5 mol %) as a precatalyst in the absence of any additional

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cocatalyst. Notably, the dialkylated product **3a** was achieved in 92% yield, thus revealing that the cationic acetate complex $\mathbf{15}^+$ is the resting state, which is converted to the presumed ruthenium-hydride intermediate species upon hydrogenative removal of the acetate ligand.[15a] In addition, this result also suggests that the major role of the required acid cocatalyst in the combined in situ $Ru(acac)_3$/Triphos system is the generation of cationic ruthenium species as the catalytically active complex (presumably $[(Triphos)Ru(H)(H_2)(solvent)]^+$). Such species have also been proposed in the Ru/Triphos-catalyzed hydrogenation of carbon dioxide to methanol.[22n] Noticeably, by using the $Ru(acac)_3$/Triphos system, no obvious incubation period is observed from a reaction profile of the alkylation of **1a** with acetic acid under standard reaction conditions (Scheme SI1 in the Supporting Information).

When a mixture of $Ru(acac)_3$/Triphos/$HNTf_2$ was heated under catalytic conditions, the formation of dimer **16** is evidenced as a dominant product as shown by ESI-MS and $^{31}P\{^1H\}$ NMR (Figure SI3 in the Supporting Information).[9c] Notably, with the reaction mixture containing dimer **16**, a marginal degree of alkylation of **1a** with acetic acid (36% yield of **2a**; 3% yield of **3a**) is achieved even using $HNTf_2$ as the cocatalyst. This makes it likely that formation of dimer **16** constitutes a noncatalytically relevant pathway. In fact, the observed low catalytic activity can be explained by the presence of traces of the cationic complex $\mathbf{15}^+$ in the reaction mixture (Figure SI4 in the Supporting Information).

Inspired by the recyclability of a related formate complex by Klankermayer and Leitner et al.,[22n] we decided to perform recycling experiments of the catalyst. As shown in Figure 2, the

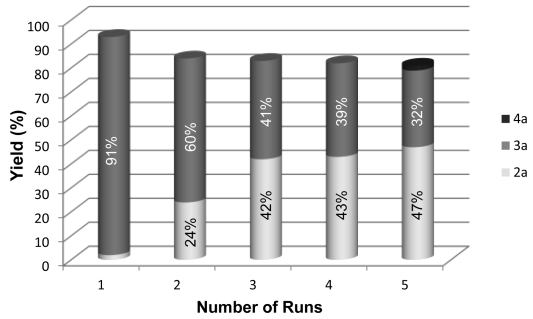

Figure 2. Recycling experiments of the N-alkylation of **1a** with acetic acid.

catalyst was reused up to five times in the model reaction. Interestingly, the catalyst could be recovered after each run by simple decantation of the colorless solution obtained by cooling the reaction mixture to room temperature. After the first recycling, a moderate decrease of reactivity of the catalyst is observed, which is explained by the dimerization process to give **16**.

SUMMARY

In conclusion, we have developed the first general catalytic *N*-alkylation of amines with a variety of carboxylic acids using molecular hydrogen as reducing agent. The use of an in situ formed ruthenium/Triphos-based catalyst in combination with $HNTf_2$ as cocatalyst allows for successful alkylation of aromatic and aliphatic amines with different kinds of carboxylic acids affording selectively secondary or tertiary amines depending on the reaction conditions. In addition, unsymmetrically substituted *N*-methyl/alkyl anilines are accessible in a most efficient manner through a new three-component coupling reaction of the corresponding amines, carboxylic acids and CO_2. It should be noted that such compounds typically have been prepared by using additional protection/deprotection steps.

Compared to the previously known reductive alkylations of carboxylic acids (in the presence of stoichiometric amounts of metal hydrides or hydrosilanes) the use of hydrogen makes this protocol a cleaner and more atom-efficient methodology. Moreover, the reaction is easily scaled up and the catalyst can be recycled. We believe this method provides a convenient alternative to traditional reductive aminations and will find increasing applications including renewable feedstocks.

EXPERIMENTAL SECTION

General Procedure for the Dialkylation Reaction of Aniline with Acetic Acid. An 8 mL glass vial containing a stirring bar was sequentially charged with $[Ru(acac)_3]$ (10 mg, 0.025 mmol), Triphos (23.3 mg, 0.038 mmol), **1a** (46.6 mg, 0.5 mmol), *n*-hexadecane (50 μL) as an internal standard, nBu_2O (2 mL), CH_3CO_2H (115 μL, 2 mmol), and a freshly prepared 0.2 M in nBu_2O solution of cocatalyst $HNTf_2$ (188 μL, 0.038 mmol). Afterward, the reaction vial was capped with a septum equipped with a syringe and set in the alloy plate, which was then placed into a 300 mL autoclave. Once sealed, the autoclave was purged 3 times with hydrogen, then pressurized to 60 bar and placed into an aluminum block, which was preheated at 160 °C. After 18 h, the autoclave was cooled in an ice bath, and the remaining gas was carefully released. Finally, the reaction mixture was diluted with ethyl acetate and analyzed by GC. To determine the isolated yield of the alkylated amines, no internal standard was added and the reaction mixture was purified by silica gel column chromatography (*n*-heptane/ethyl acetate mixtures) to give the corresponding alkylated amines.

General Procedure for the One-Pot Synthesis of Unsymmetrically Substituted *N*-Methyl/Alkyl Anilines through the Direct Three-Component Coupling Reaction. The general procedure described above for the alkylation of amines with carboxylic acids was applied with a minor modification. After the autoclave was sealed and purged 3 times with CO_2, it was pressurized with CO_2 (20 bar) and H_2 (60 bar).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07994.

Extended data about optimization of reaction conditions, scaled up, and catalyst recycling experiments, alkylation/time profile, ESI and NMR data of the chemical speciation, and spectroscopic data of isolated products (PDF)

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Notes

The authors declare no competing financial interest.

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