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Discovery and Mechanistic Studies of a General Air-Promoted Metal-Catalyzed Aerobic *N*-Alkylation Reaction of Amides and Amines with Alcohols

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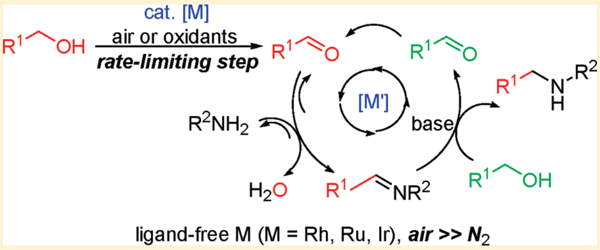
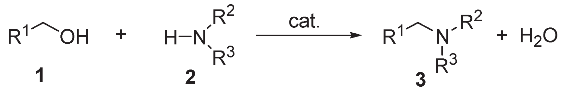
Supporting Information



ABSTRACT: The thermodynamically unfavorable anaerobic dehydrogenative alcohol activation to aldehydes and hydridometal species is found to be the bottleneck in metal-catalyzed *N*-alkylations due to a general and unnoticed catalyst deactivation by amines/amides. Thus, different from the anaerobic dehydrogenation process in borrowing hydrogen or hydrogen autotransfer reactions that require noble metal complexes or addition of capricious ligands for catalyst activation, the water-producing, exothermic, metal-catalyzed aerobic alcohol oxidation is thermodynamically more favorable and the most effective and advantageous aldehyde generation protocol. This leads to a general and advantageous air-promoted metal-catalyzed aerobic *N*-alkylation methodology that effectively uses many simpler, less expensive, more available, and ligand-free metal catalysts that were inactive under typical anaerobic borrowing hydrogen conditions, avoiding the use of preformed metal complexes and activating ligands and the exclusive requirement of inert atmosphere protection. This aerobic method is quite general in substrate scope and tolerates various amides, amines, and alcohols, revealing its potentially broad utilities and interests in academy and industry. In contrast to the commonly accepted borrowing hydrogen mechanism, based on a thorough mechanistic study and supported by the related literature background, a new mechanism analogous to the relay race game that has never been proposed in metal-catalyzed *N*-alkylation reactions is presented.

■ INTRODUCTION

The catalytic construction of carbon−nitrogen bonds[1−5] is a topic of great interest since nitrogen functionalities occur in numerous compounds of synthetic and pharmaceutical significance as well as in important biologically active molecules.[6] Formation of C−N bonds not only is of concern for chemical and pharmaceutical syntheses[1−5] but also is applicable to explorations of the role of prebiotic synthesis in the origins of life.[7] In comparison with other transition-metal-catalyzed methodologies, e.g., amination of organohalides (Buchwald−Hartwig amination),[1] reductive amination of carbonyl compounds or reductive alkylation of amines,[2] hydroamination,[3] and hydroaminomethylation[4] of carbon−carbon unsaturated compounds, etc.,[5] the *N*-alkylation of amines/amides **2** with alcohols **1** (eq 1), with only water produced as the byproduct, may serve as a relatively green and environmentally benign alternative.[8,9] The use of alcohols as the alkylating agent is direct and simple as the alcohols are readily available, highly stable, low in toxicity, easily stored and handled, low in cost, and relatively high in atom efficiency.



$$R^1CH_2OH + HNR^2R^3 \xrightarrow{cat.} R^1CH_2NR^2R^3 + H_2O \qquad (1)$$

However, alcohols are inactive in nature and require demanding procedures to activate the hydroxyl group.[8,9] Although the dehydrative *N*-alkylation of amines with alcohols was discovered more than 100 years ago,[10] the early methods were usually performed under harsh conditions of high temperature and/or high pressure.[9f] After the pioneering work on the homogeneous transition-metal-catalyzed reactions reported by Grigg and Watanabe in 1981,[11] the field progressed.[8,9,11−16] Current transition-metal-catalyzed dehydrative *N*-alkylation methods (Scheme 1) include direct amination reactions (path a)[8] and borrowing hydrogen or hydrogen autotransfer methodology (path b),[9,11−16] with the latter being one of the most significant ways for amine derivative synthesis.[1−5] Direct amination reactions proceed through a nucleophilic substitution of the alcohol's hydroxy group by amines/amides **2** via Lewis acid[8b−k] or transition metal complex-catalyzed[8l−p] dehydrative formation of a carbocation or coordinated cationic allylic-metal complexes. In contrast, the borrowing hydrogen[9a−e]/hydrogen autotransfer[9f,g] methodology is usually held to allow the reactions to proceed at lower temperatures via a transition-metal-mediated dehydrogenative alcohol activation to yield aldehydes **4** with generation of the hydridometal species (MH or MH_2) (path b, step i) that serves as the reducing agent in subsequent reduction of intermediate

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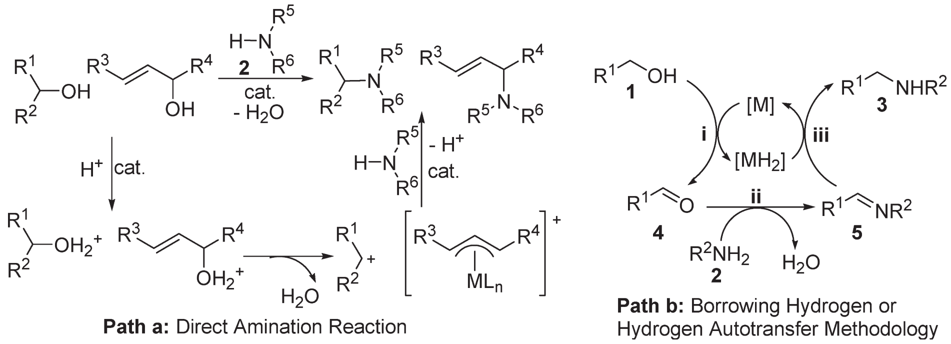
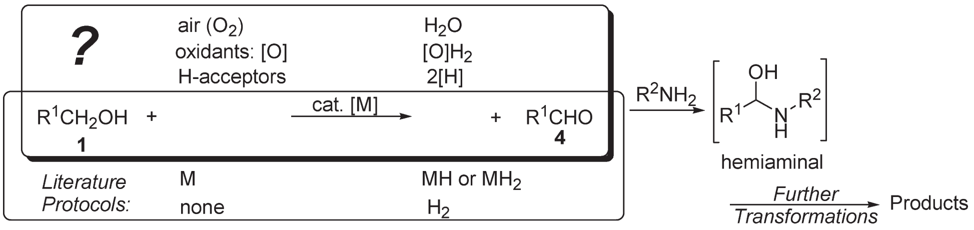
Scheme 1. Literature Protocols for *N*-Alkylation of Amines and Amides with Alcohols



Scheme 2. Literature and Potential Protocols for in Situ Alcohol Activation/Oxidation in Alcohol-Based Tandem Multistep Reactions

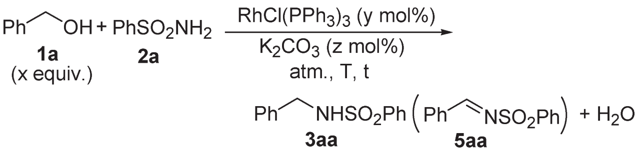


imines **5** to afford product amines **3** (path b, step iii), thus furnishing the borrowed hydrogen and regenerating the cycle.

The dehydrogenative activation of alcohols to aldehydes and the generation of the hydridometal species (Scheme 1, path b, step i) in the borrowing hydrogen reactions are thermodynamically unfavorable processes,[9c] and thus, noble metal complexes derived from ruthenium and iridium or addition of capricious ligands for catalyst activation are usually required.[9,11−13] Therefore, developing more economical and efficient methods that can be carried out under greener and milder conditions is highly desirable. Only recently, a few less expensive metals have been found suitable for some substrates.[14,15] To our knowledge, never a different methodology or a new mechanism that is greener and more efficient has been discovered and proposed up to date.[17,18]

The metal-mediated dehydrogenation of alcohols to aldehydes is by nature an alcohol oxidation reaction.[9a,b] The oxidation of alcohols for aldehyde and ketone syntheses has been the focus of numerous reviews and reports,[19,20] and since metal-catalyzed versions of the reaction are recognized as one of the greenest processes,[20] we therefore considered an alcohol-based tandem multistep reaction sequence (Scheme 2), as an alternative to the borrowing hydrogen strategy[9,11−16] and the acceptorless processes.[9b,21,22] We envisioned that this new protocol should utilize other oxidants[19,20] or hydrogen acceptors[23−25] that can convert the alcohol to the aldehyde. However, despite the above-mentioned literature background[19,20] and the parallel methods found in C−C bond constructions,[24,25] amine activation-functionalization reactions (the cross-dehydrogenative couplings),[26] and aerobic imine preparations from alcohols and amines,[27] they have not been accepted in the field yet.[9,11−16] Although a few *N*-alkylation reactions have been carried out under aerobic conditions and found more efficient than the anaerobic reactions,[15] the role air played in the reactions and how it promoted the reactions remains to be fully clarified and recognized. Only recently, we[17] and Crabtree[18] became aware of air's crucial influence on aerobic C−N and C−C bond-forming reactions and utilized it with purpose.

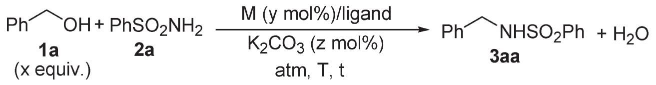
Table 1. Condition Screening and Optimization[a]



run	*x*, *y*, *z*	atm, *T*, *t*	**3aa** % yield[b]
1[c,d]	6, 5, 100	N_2, 100−120 °C, 8 h	ND[f]
2[c]	6, 5, 100	N_2, 120 °C, 24 h	(67)[g]
3[c]	6, 5, 100	air, 120 °C, 4 h	99 (96)[h]
4[e]	1.33, 0.5, 10	air, 135 °C, 24 h	90 (83)
5[e]	1.1, 0.5, 10	air, 135 °C, 36 h	95

[a] Abbreviations used in the table: *x*, equivalents of added **1a** to **2a**; *y*, percent catalyst loading based on **2a**; *z*, percent base loading based on **2a**; atm, air or N_2 atmosphere; *T*, reaction temperature; *t*, reaction time. [b] Reactions monitored by TLC and/or GC−MS. GC yields (isolated yields in parentheses) based on **2a**. **3aa**/**5aa** ratios measured from GC are usually >99/1. Undegassed commercial **1a** (containing trace amount of benzaldehyde **4a** as confirmed by GC) was used unless otherwise noted. [c] **1a** (*x* mmol, *x* equiv) and **2a** (1 mmol) in a 50 mL Schlenk tube. [d] Absolute **1a** (dried over CaH_2, degassed, distilled, and stored under nitrogen in a Schlenk flask, without any contaminants as proved by GC analysis) was used. [e] **1a** (3*x* mmol, *x* equiv) and **2a** (3 mmol) in a 20 mL Schlenk tube. [f] Monitored by TLC (ND, not detected). [g] Undegassed commercial **1a** was directly added. [h] 92% GC yield in 2 h.

Table 2. Scope of Metal Catalysts in the Air-Promoted Metal-Catalyzed Aerobic *N*-Alkylation Reactions



run	M	*x*, *y*, *z*	ligand (mol %)	atm, *T*, *t*	**3aa** % yield[a]
1[b]	$RhCl_3 \cdot 3H_2O$	6, 5, 100		air, 120 °C, 8 h	83
2[b]	$RhCl_3 \cdot 3H_2O$	6, 5, 100		N_2, 120 °C, 8 h	ND[d]
3[b]	$RhCl_3 \cdot 3H_2O$	6, 5, 100	PPh_3 (15)	air, 120 °C, 8 h	99
4[b]	$RhCl_3 \cdot 3H_2O$	6, 5, 100	PPh_3 (15)	N_2, 120 °C, 8 h	81
5[b]	$RhCl_3 \cdot 3H_2O$	6, 5, 100	$Ph_3P(O)$ (15)	air, 120 °C, 8 h	83
6[b]	$RhCl_3 \cdot 3H_2O$	6, 5, 100	$Ph_3P(O)$ (15)	N_2, 120 °C, 8 h	trace[d]
7[b]	$RhCl_3 \cdot 3H_2O$	4, 5, 100		air, 120 °C, 8 h	89
8[c]	$RhCl_3 \cdot 3H_2O$	1.33, 0.5, 10		air, 135 °C, 24 h	90
9[c]	$RhCl_3 \cdot 3H_2O$	1.33, 0.5, 10		N_2, 135 °C, 24 h	trace
10[b]	Rh_2O_3	4, 5, 100		air, 120 °C, 8 h	99
11[c]	Rh_2O_3	1.33, 0.5, 10		air, 135 °C, 36 h	80
12[c]	Rh_2O_3	1.33, 0.5, 10		N_2, 135 °C, 36 h	67
13[b]	$Rh_2(OAc)_4$	4, 5, 100		air, 120 °C, 8 h	84
14[c]	$Rh_2(OAc)_4$	1.33, 0.5, 10		air, 135 °C, 24 h	92
15[c]	$Rh_2(OAc)_4$	1.33, 0.5, 10		N_2, 135 °C, 24 h	trace
16[c]	$RuCl_3 \cdot nH_2O$	1.3, 1, 20		air, 135 °C, 8 h	69
17[c]	$RuCl_3 \cdot nH_2O$	1.3, 1, 20		N_2, 135 °C, 8 h	trace
18[c]	$RuCl_3 \cdot nH_2O$	1.3, 1, 20	PPh_3 (5)	N_2, 135 °C, 8 h	94
19[c]	RuO_2	1.33, 0.5, 10		air, 135 °C, 36 h	99
20[c]	RuO_2	1.33, 0.5, 10		N_2, 135 °C, 36 h	61
21[c]	$IrCl_3$	1.5, 1, 20		air, 135 °C, 24 h	95
22[c]	$IrCl_3$	1.5, 1, 20		N_2, 135 °C, 24 h	trace
23[c]	$IrCl_3$	1.5, 1, 20	PPh_3 (5)	N_2, 135 °C, 24 h	95
24[c]	$IrCl_3$	1.5, 1, 10		air, 135 °C, 29 h	93
25[c]	$IrCl_3$	1.5, 0.5, 20		air, 135 °C, 24 h	83
26[c]	IrO_2	1.33, 0.5, 10		air, 135 °C, 36 h	90
27[c]	IrO_2	1.33, 0.5, 10		N_2, 135 °C, 36 h	55

[a] Reactions monitored by TLC and/or GC−MS. GC yields based on **2a**. [b] **1a** (*x* mmol, *x* equiv) and **2a** (1 mmol) in a 50 mL Schlenk tube. [c] **1a** (3*x* mmol, *x* equiv) and **2a** (3 mmol) in a 20 mL Schlenk tube. [d] Not detected (ND) or trace as monitored by TLC.

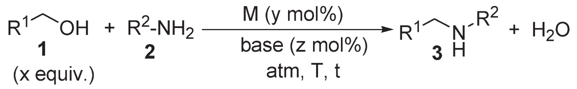
Herein we report in detail our findings in the area by providing a mild, efficient, and potentially useful air-promoted metal-catalyzed aerobic *N*-alkylation methodology,[17] which is rather general in catalyst and substrate scope that uses many simpler, cheaper, more available, and ligand-free metal catalysts, and a wide range of amines, amides and alcohols behave more effectively in activities and reactivities than those under the conventional anaerobic conditions. Moreover, based on a thorough mechanistic study and also supported by a broad background of literature, an unprecedented mechanism in the metal-catalyzed *N*-alkylation reactions is presented for the first time for the aerobic *N*-alkylation reactions.

■ RESULTS AND DISCUSSION

Discovery and Condition Screening of a Rhodium-Catalyzed Aerobic *N*-Alkylation Reaction of Sulfonamides with Alcohols. Our interests in pharmaceutically significant sulfonamide derivatives[28] led us to undertake a study of metal-catalyzed *N*-alkylation reactions of simple sulfonamides using alcohols. Alcohols are good candidates as the alkylating agents[9] because they are abundant, inexpensive, and varied in structure and because they are good reagents for green chemistry. Although ruthenium and iridium[9,11−13] have been used as metal catalysts in *N*-alkylation reactions, catalysis by rhodium was almost completely unknown. Only a few Rh catalysts have been briefly mentioned by Grigg[11a] and Tanaka.[29] Thus, we started our study by investigating the reactions of sulfonamides and alcohols using the famous Wilkinson's catalyst $RhCl(PPh_3)_3$ (Table 1).[17]

Initially, no target product was detected when the mixture of benzenesulfonamide **2a** and benzyl alcohol **1a** was heated (100−120 °C) under nitrogen in the presence of $RhCl(PPh_3)_3$ and K_2CO_3 (Table 1, run 1). Subsequent attempts under a series of anaerobic conditions even using solvents to promote the reaction failed. Instead, surprisingly, when undegassed commercial **1a** was accidentally added, the reaction dramatically afforded 67% isolated yield of the target *N*-benzylbenzenesulfonamide **3aa** in high selectivity (run 2). Another reaction using commercial substrates without any treatments was directly heated under air, affording almost quantitative yield of the product in only 4 h (run 3). Beside the observed crucial role of air, catalyst $RhCl(PPh_3)_3$ and base were also found indispensable for the reaction. Without catalyst, no product could be detected.[30] Without base, the byproduct (also an intermediate) imine *N*-benzylidenebenzenesulfonamide **5aa** was observed.[27,30,31] The best results were

Table 3. Air-Promoted Metal-Catalyzed Aerobic *N*-Alkylation Reactions of Amides and Amines with Alcohols



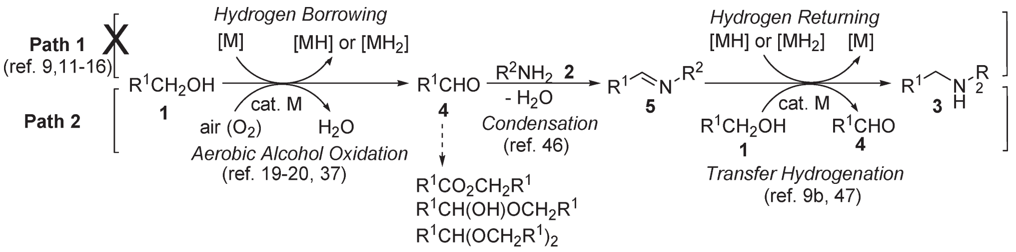
run	1	2	M	*x*, *y*, *z*	atm, *T*, *t*	3 % yield[a]
1[b]	$PhCH_2OH$ (**1a**)	$PhSO_2NH_2$ (**2a**)	$RhCl(PPh_3)_3$	1.33, 0.5, 10	air, 135 °C, 24 h	**3aa**: 90 (83)
2[b]	*p*-$ClC_6H_4CH_2OH$ (**1b**)	**2a**	$RhCl(PPh_3)_3$	2, 0.5, 10	air, 135 °C, 36 h	**3ba**: 99
3[b]	*m*-$ClC_6H_4CH_2OH$ (**1c**)	**2a**	$RhCl(PPh_3)_3$	2, 0.5, 10	air, 135 °C, 36 h	**3ca**: 99
4[b]	*p*-$CH_3OC_6H_4CH_2OH$ (**1d**)	**2a**	$RhCl(PPh_3)_3$	2, 0.5, 10	air, 135 °C, 36 h	**3da**: 92 (78)
5[b]	*o*-$CH_3OC_6H_4CH_2OH$ (**1e**)	**2a**	$RhCl(PPh_3)_3$	2, 0.5, 10	air, 135 °C, 36 h	**3ea**: 89
6[b]	$Ph(CH_2)_2OH$ (**1f**)	**2a**	$IrCl_3$	3, 5, 50	air, 150 °C, 24 h	**3fa**: 99 (78)
7[b]	**1f**	**2a**	$IrCl_3$	3, 5, 50	N_2, 150 °C, 24 h	**3fa**: 69
8[b]	$Ph(CH_2)_3OH$ (**1g**)	**2a**	$IrCl_3$	2, 5, 50	air, 150 °C, 24 h	**3ga**: 74
9[b]	**1g**	**2a**	$IrCl_3$	2, 5, 50	N_2, 150 °C, 24 h	**3ga**: trace
10[b]	**1a**	*p*-$CH_3C_6H_4SO_2NH_2$ (**2b**)	$RhCl(PPh_3)_3$	1.33, 0.5, 10	air, 135 °C, 36 h	**3ab**: 99 (86)
11[b]	**1a**	*o*-$CH_3C_6H_4SO_2NH_2$ (**2c**)	$RhCl(PPh_3)_3$	1.33, 0.5, 10	air, 135 °C, 36 h	**3ac**: 98 (86)
12[b]	**1a**	*p*-$ClC_6H_4SO_2NH_2$ (**2d**)	$RhCl(PPh_3)_3$	1.33, 0.5, 10	air, 135 °C, 36 h	**3ad**: 99 (83)
13[b]	**1a**	*o*-$ClC_6H_4SO_2NH_2$ (**2e**)	$RhCl(PPh_3)_3$	1.33, 0.5, 10	air, 135 °C, 36 h	**3ae**: 74
14[b]	**1a**	*p*-$CH_3OC_6H_4SO_2NH_2$ (**2f**)	$RhCl(PPh_3)_3$	1.33, 0.5, 10	air, 135 °C, 36 h	**3af**: 98
15[b]	**1a**	2-naphthalene-sulfonamide (**2g**)	$RhCl(PPh_3)_3$	1.33, 0.5, 10	air, 135 °C, 36 h	**3ag**: 80
16[b]	**1a**	$CH_3SO_2NH_2$ (**2h**)	$RhCl(PPh_3)_3$	1.33, 0.5, 10	air, 135 °C, 36 h	**3ah**: 99 (65)
17[b]	**1a**	**2h**	$RhCl(PPh_3)_3$	1.33, 0.5, 10	N_2, 135 °C, 36 h	**3ah**: 52
18[b]	**1b**	**2b**	$RhCl(PPh_3)_3$	1.5, 0.5, 10	air, 135 °C, 36 h	**3bb**: 99
19[b]	**1c**	**2b**	$RhCl(PPh_3)_3$	1.5, 0.5, 10	air, 135 °C, 36 h	**3cb**: 99
20[b]	**1d**	**2b**	$RhCl(PPh_3)_3$	1.5, 0.5, 10	air, 135 °C, 36 h	**3db**: 95
21[b]	**1e**	**2b**	$RhCl(PPh_3)_3$	1.5, 0.5, 10	air, 135 °C, 36 h	**3eb**: 75
22[b]	2-thiophenemethanol (**1h**)	**2b**	$RhCl_3 \cdot 3H_2O$	3, 2, 20	air, 135 °C, 24 h	**3hb**: 78
23[b]	**1h**	**2b**	$RhCl_3 \cdot 3H_2O$	3, 2, 20	N_2, 135 °C, 24 h	**3hb**: 50
24[b]	**1b**	**2f**	$RhCl(PPh_3)_3$	1.5, 0.5, 10	air, 135 °C, 36 h	**3bf**: 99
25[c]	**1a**	$PhCONH_2$ (**2i**)	$RhCl(PPh_3)_3$	6, 5, 100	air, 180 °C, 4 h	**3ai**: 90
26[c]	**1a**	**2i**	$RhCl(PPh_3)_3$	6, 5, 100	N_2, 180 °C, 4 h	**3ai**: 43
27[b]	**1a**	**2i**	$RhCl(PPh_3)_3$	2, 1, 20	air, 180 °C, 36 h	**3ai**: 64
28[c]	**1a**	**2i**	$RuCl_2(PPh_3)_3$	6, 5, 100	air, 120 °C, 48 h	**3ai**: 76
29[c]	**1a**	**2i**	$RuCl_2(PPh_3)_3$	6, 5, 100	N_2, 120 °C, 24 h	**3ai**: trace
30[c]	**1a**	**2i**	$RuCl_2(PPh_3)_3$	6, 5, 100	air, 150 °C, 16 h	**3ai**: 74
31[c]	**1a**	**2i**	$RuCl_2(PPh_3)_3$	6, 5, 100	N_2, 150 °C, 16 h	**3ai**: trace
32[c]	**1a**	**2i**	$RuCl_2(PPh_3)_3$	6, 5, 100	N_2, 180 °C, 4 h	**3ai**: 73
33[b]	**1a**	**2i**	$RuCl_3$	1.5, 1, 20	air, 150 °C, 24 h	**3ai**: 66
34[b]	**1a**	**2i**	$RuCl_3$	1.5, 0.5, 10	air, 150 °C, 24 h	**3ai**: 66
35[b]	**1a**	**2i**	$RuCl_3$	1.5, 1, 20	air, 150 °C, 24 h	**3ai**: 65
36[c]	**1a**	**2i**	$IrCl_3$	6, 5, 100	air, 135 °C, 20 h	**3ai**: 86
37[c]	**1a**	**2i**	$IrCl_3$	6, 5, 100	air, 150 °C, 12 h	**3ai**: 99
38[b]	**1a**	**2i**	$IrCl_3$	1.5, 1.5, 20	air, 135 °C, 32 h	**3ai**: 74 (53)
39[b]	**1a**	2i	$IrCl_3$	1.5, 1.5, 20	air, 150 °C, 20 h	**3ai**: 82
40[b]	**1a**	2i	$IrCl_3$	1.5, 1.5, 10	air, 135 °C, 28 h	**3ai**: 72
41[b]	**1a**	**2i**	$IrCl_3$	1.5, 1.5, 10	air, 150 °C, 12 h	**3ai**: 74
42[b]	**1a**	**2i**	$IrCl_3$	1.5, 1, 10	air, 150 °C, 36 h	**3ai**: 89
43[b]	**1b**	**2i**	$IrCl_3$	3, 5, 100	air, 150 °C, 12 h	**3bi**: 81 (75)
44[b]	**1d**	**2i**	$IrCl_3$	3, 5, 100	air, 150 °C, 12 h	**3di**: (69)
45[b]	**1a**	*p*-$CH_3OC_6H_4CONH_2$ (**2j**)	$IrCl_3$	3, 5, 100	air, 150 °C, 12 h	**3aj**: 58
46[b]	**1a**	nicotinamide (**2k**)	$IrCl_3$	3, 5, 100	air, 180 °C, 12 h	**3ak**: 74
47[b]	**1a**	2-aminopyrimidine (**2l**)	$RhCl(PPh_3)_3$	1.3, 0.5, 20	air, 150 °C, 20 h	**3al**: 80
48[b]	**1a**	**2l**	$RhCl(PPh_3)_3$	1.3, 1, 20	N_2, 150 °C, 24 h	**3al**: 67
49[c]	**1a**	2-aminopyridine (**2m**)	$RhCl(PPh_3)_3$	6, 5, 100	air, 120 °C, 12 h	**3am**: (67)
50[b]	**1a**	**2m**	$RhCl(PPh_3)_3$	1.5, 1, 20	air, 135 °C, 36 h	**3am**: 85

Table 3. Continued

run	1	2	M	*x*, *y*, *z*	atm, *T*, *t*	3 % yield[a]
51[b]	**1a**	**2m**	$RhCl(PPh_3)_3$	1.3, 0.5, 20	air, 135 °C, 24 h	**3am**: 70
52[b]	**1a**	**2m**	$RhCl_3\cdot3H_2O$	1.3, 0.5, 20	air, 135 °C, 24 h	**3am**: 82
53[b]	**1a**	**2m**	$RhCl_3\cdot3H_2O$	1.3, 0.5, 20	N_2, 135 °C, 24 h	**3am**: 75
54[b]	**1b**	**2m**	$RhCl_3\cdot3H_2O$	1.5, 1, 40	air, 135 °C, 36 h	**3bm**: 82 (90)
55[b]	**1d**	**2m**	$RhCl_3\cdot3H_2O$	1.5, 1, 40	air, 135 °C, 36 h	**3bm**: 89 (55)
56[b]	**1a**	2-amino-5-chloropyridine (**2n**)	$RhCl_3\cdot3H_2O$	1.5, 1, 40	air, 135 °C, 36 h	**3an**: 90
57[b,d]	**1a**	3-aminopyridine (**2o**)	$RhCl(PPh_3)_3$	1.5, 1, 40	air, 135 °C, 12 h	**3ao**: 92
58[b,d]	**1a**	**2o**	$RhCl(PPh_3)_3$	1.5, 1, 40	N_2, 135 °C, 36 h	**3ao**: 92
59[b,d]	**1a**	**2o**	$RhCl_3\cdot3H_2O$	1.5, 1, 40	air, 135 °C, 12 h	**3ao**: 99 (79)
60[b,d]	**1a**	**2o**	$RhCl_3\cdot3H_2O$	1.5, 1, 40	N_2, 135 °C, 36 h	**3ao**: 99
61[b,e]	**1a**	$PhNH_2$ (**2p**)	$IrCl_3$	1.5, 5, 40	air, 150 °C, 24 h	**3ap**: 99
62[b,e]	**1a**	**2p**	$IrCl_3$	1.5, 5, 40	N_2, 150 °C, 24 h	**3ap**: 99
63[b,e]	**1a**	*p*-$EtOC_6H_4NH_2$ (**2q**)	$IrCl_3$	1.5, 5, 40	air, 150 °C, 24 h	**3aq**: 99
64[b,e]	**1a**	**2q**	$IrCl_3$	1.5, 5, 40	air, 150 °C, 24 h	**3aq**: 98

[a] Reactions monitored by TLC and/or GC−MS. GC yields (isolated yields in parentheses) based on **2**. Unless otherwise noted, K_2CO_3 was used as the base. [b] **1** (3*x* mmol, *x* equiv) and **2** (3 mmol) in a 20 mL Schlenk tube. [c] **1** (*x* mmol, *x* equiv) and **2** (1 mmol) in a 50 mL Schlenk tube. [d] NaOH was used as the base. [e] CsOH was used as the base.

Scheme 3. Possible One-Pot and Multistep Tandem Processes for *N*-Alkylation of Amides/Amines with Alcohols



obtained when the reaction was carried out under solvent-free conditions. K_2CO_3 was determined to be the best base.[30] Reactions at a lower temperature or with lesser amounts of substrate and catalyst loadings were still effective,[30] but under these conditions, a higher temperature (such as 135 °C) gave much better results. Thus, alcohol loading could be reduced to only 1.1−1.33 equiv, $RhCl(PPh_3)_3$ to 0.5 mol %, and K_2CO_3 to 10 mol % (runs 4 and 5). It is worth noting that, in our hands, the volume of the reaction vessel related to the amount of air was also found to have an effect, with 20 mL tubes being the optimum size.[30]

Scope of Metal Catalysts and Substrates in the Air-Promoted Metal-Catalyzed Aerobic *N*-Alkylation Reactions. Since almost all metal-catalyzed *N*-alkyaltion reactions were previously carried under an inert atmosphere,[9,11−16] the above surprising observation that the Rh-catalyzed reaction did not take place under nitrogen but could proceed in a dramatically efficient way under air prompted us to examine the mechanism (vide infra) and the catalyst and substrate scopes (Tables 2 and 3) of the reaction.

We identified several simpler, less expensive, more available, and ligand-free metal catalysts derived from Rh, Ru, and Ir that were inactive under borrowing hydrogen conditions, but that were found to be very active catalysts under aerobic conditions, giving the product in yields comparable to $RhCl(PPh_3)_3$ and with high selectivities (Table 2, runs 1, 7, 8, 13, 14, 16, 21, 24, and 25). In contrast, the corresponding parallel anaerobic reactions were ineffective, affording no or only trace amounts of product (runs 2, 9, 15, 17, and 22).

During the catalyst screening studies, the usually ineffective anaerobic reactions of $RhCl_3$, $RuCl_3$, and $IrCl_3$ (Table 2, runs 2, 17, and 22) gave high yields of the product if a phosphine ligand such as PPh_3 was added (runs 4, 18, and 23). These ligand-promoted reactions are hallmarks of the borrowing hydrogen reactions, in which external ligands are employed for catalyst activation to achieve effective reactions with simple catalysts.[9,11−13] Possibly, the ligands first activate the metal catalysts, and then the in situ generated metal complexes activate the alcohol and thus promote the whole reaction.[9] Notably, the yields of these ligand-assisted reactions are comparable with those carried out under air (runs 1, 16, and 21). These results indicate that catalyst activation by adding ligands can be avoided by simply carrying out the reactions under air. In other words, by simply conducting the reactions under air, many less reactive, cheaper, more available, and ligand-free metal catalysts can be used instead of the preformed metal complexes or the activation of catalysts by the addition of capricious ligands, most probably because alcohol activation to aldehyde could be achieved more easily under air as we deduced (Scheme 2) and proved (vide infra). In contrast, the corresponding phosphine oxide $Ph_3P(O)$ showed no activating capacity at all (runs 1 and 2 vs runs 5 and 6).

In reactions catalyzed by metal oxides such as Rh_2O_3, RuO_2, and IrO_2, although the anaerobic reactions (Table 2, runs 12, 20, and 27) were somewhat less effective than the corresponding aerobic ones (runs 11, 19, and 26), they were still more efficient than reactions conducted with other catalysts (runs 2, 9, 15, 17,

Table 4. Metal-Catalyzed Aerobic Alcohol Oxidation

$$\underset{\mathbf{1a}}{PhCH_2OH} \xrightarrow[K_2CO_3\ (z\ mol\%),\ air]{M\ (y\ mol\%)} \underset{\mathbf{4a}}{PhCHO}$$

run	M	y, z	additive (mol %)	T, t	yield %[a]
1[b]	$RhCl(PPh_3)_3$	2.5, 50		120 °C, 2 h	29
2[b]	$RhCl(PPh_3)_3$	2.5, -		120 °C, 2 h	22
3[c]	$RhCl(PPh_3)_3$	2.5, 17		rt, 24 h	3.91
				48 h	3.93
4[c]	$RhCl(PPh_3)_3$	2.5, 17	**2a** (17)	rt, 24 h	0
				48 h	0
5[d]	$RuCl_3$	2.5, 17		rt, 24 h	15.0
				48 h	23.1
6[d]	$RuCl_3$	2.5, 17	**2a** (17)	rt, 24 h	1.40
				48 h	1.96

[a] Absolute **1a** (100% purity as confirmed by GC) was used. Reactions monitored by GC−MS. GC yields based on **1a**. [b] **2a** (2 mmol) was heated in a sealed 50 mL Schlenk tube. Yields are combined yields of **4a** and other oxidation products such as $PhCO_2CH_2Ph$ and $PhCH(OH)OCH_2Ph$. [c] **1a** (2 mmol) and additives were stirred in a Schlenk tube open to air. [d] **1a** (6 mmol) was stirred in a Schlenk tube open to air.

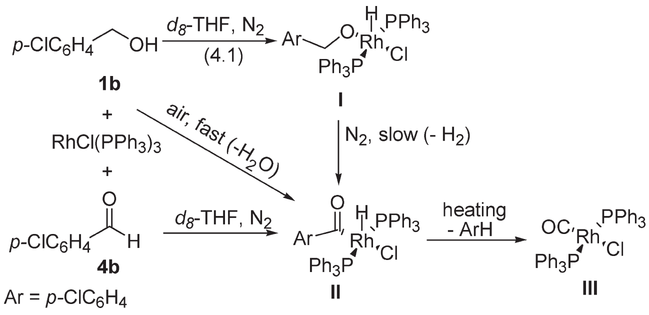
and 22). Possibly, these metal oxides are also good catalysts/oxidants for alcohol oxidation as documented in the literature.[19,20] This idea is also consistent with our deductions (Scheme 2) and findings that external oxidants can facilitate the reaction by oxidizing the alcohol to the aldehyde (Table 7).[32]

All of these results showed that these aerobic reactions are milder, more convenient, and more efficient than many recently reported *N*-alkylaltion reactions of sulfonamides,[12−16] for example, lower in alcohol loading, lower in reaction temperature, higher in reaction efficiency, and avoids inert atmosphere protection and the use of activating ligands and solvents, revealing the advantages of employing the aerobic protocol.

We then applied the new metal-catalyzed aerobic *N*-alkylation protocol to reactions of various sulfonamides, carboxamides, and aromatic and heteroaromatic amines with a series of benzylic, heterobenzylic, and aliphatic alcohols (Table 3). High selectivities (>99/1) of the products were usually obtained. For benzylic alcohols and sulfonamides (Table 3, runs 1−5, 10−24), Rh-catalyzed aerobic reactions under the optimized condition gave generally high yields of the products. As in previous observations, anaerobic reactions conducted with either methanesulfonamide **2h** or 2-thiophenemethanol **1h** gave much lower product yields (runs 17 and 23) than the aerobic ones (runs 16 and 22). With aliphatic alcohols **1f**−**g**, $IrCl_3$ was found to be a better catalyst (runs 6 and 8), and their corresponding anaerobic reactions were also less effective (runs 7 and 9).

In contrast with the sulfonamides, the Rh-catalyzed reactions with carboxamides such as benzamide **2i** were less efficient and required higher temperatures (Table 3, runs 25−27). Again, the aerobic reaction (run 25) was more efficient than the anaerobic one (run 26). In reactions with **2i**, $RuCl_2(PPh_3)_3$ was found to be a more active catalyst (runs 28−32). When the typical borrowing hydrogen catalyst[9,12] $RuCl_2(PPh_3)_3$ was used, the ineffective anaerobic reactions[9f,33] conducted at lower temperatures (runs 29 and 31) were promoted greatly by conducting them under air (runs 28 and 30). These results indicated that, under the aerobic conditions, these Ru-catalyzed *N*-alkylation reactions of benzamide **2i** may also follow a new mechanism other than the borrowing hydrogen pathway. Similarly, ligand-free catalysts $IrCl_3$ and $RuCl_3$ could also catalyze the reactions of carboxamides **2i**−**k** under aerobic conditions, giving moderate to high yields of the products (runs 33−46).

Scheme 4. Alcohol and Aldehyde Decarbonylation in the Absence of Sulfonamides



This aerobic method is also suitable for aromatic and heteroaromatic amines (Table 3, runs 47−64). With 2-aminopyrimidine **2l** and aminopyridines **2m**−**o** (runs 47−60), the aerobic reactions (runs 47, 52, 57, and 59) were generally more efficient than the corresponding anaerobic ones (runs 48, 53, 58, and 60) with respect to catalyst loadings, yields, and reaction times, but the differences between the two conditions were less pronounced. Indeed, with anilines **2p**−**q**, the aerobic and anaerobic reactions were indistinguishable (runs 61−64). Thus, the reactions can be readily performed under aerobic conditions, greatly simplifying the operations.

Individual Reactions of the Metal-Catalyzed Aerobic *N*-Alkylation Sequence. Our dramatically opposite results obtained in the aerobic and anaerobic reactions (Tables 1−3) clearly revealed the crucial role that air (oxygen) played in the reactions. Since the literature[8] also revealed that the transition-metal-catalyzed *N*-alkylation reactions may not always follow the borrowing hydrogen mechanism, and the typical borrowing hydrogen reaction is conducted under an inert atmosphere with the generation of the active hydridometal species,[9,11−16] which are known prone to react with and deactivated by molecular oxygen, our experiments suggested that these aerobic *N*-alkylation reactions may not proceed via the borrowing hydrogen sequence (Scheme 3, path 1) but another path involving air (oxygen) participating in one of its individual reactions such as the aldehyde generation step (path 2), which could therefore be easily inhibited by the absence of air (oxygen). Although air may also activate the Wilkinson's catalyst, which is still unclear at present and may not be the case with most of the other catalysts, it is more possible for air to oxidize the alcohol to aldehyde via the metal-catalyzed way.[20] As having been pointed out,[9b] the mechanism of a reaction may also depend on the substrates, catalysts, and/or the conditions employed, *the challenge therefore is to define catalysts and conditions that lead to the same transformations under milder conditions*.[9b] Regarding the related literature as mentioned above,[9b,15,17−20,24−27] we decided to investigate the mechanistic aspects of the aerobic reactions in an unprecedented manner to get deeper insights into the aerobic reactions.

Several observations permitted us to exclude the possibility that the reaction undergoes a Lewis acid- catalyzed direct amination process:[8] (1) Instead of detecting an ether that is usually generated under Lewis acid catalyzed conditions,[8,34] we always observed small amounts of byproducts, aldehyde **4a** and

Scheme 5. Alcohol and Aldehyde Decarbonylation in the Presence of Sulfonamides

$$\text{RhCl(PPh}_3)_3 + \underset{\textbf{4b}}{p\text{-ClC}_6\text{H}_4\text{CHO}} + \underset{\textbf{2b}}{p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NH}_2} \xrightarrow[\substack{70\ ^{\circ}\text{C, 2 h}\\ 99\%}]{d_8\text{-THF, N}_2} \underset{\textbf{III}}{\text{RhCl(CO)(PPh}_3)_2} \quad (5.1)$$

$$\text{RhCl(PPh}_3)_3 + \underset{\textbf{1b}}{p\text{-ClC}_6\text{H}_4\text{CH}_2\text{OH}} + \underset{\textbf{2b}}{p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NH}_2} \cancel{\xrightarrow[70\text{-}120\ ^{\circ}\text{C}]{d_8\text{-THF, N}_2}} \textbf{III} \quad (5.2)$$

$$\text{RhCl(PPh}_3)_3 + \underset{\textbf{1b}}{p\text{-ClC}_6\text{H}_4\text{CH}_2\text{OH}} + \underset{\textbf{2b}}{p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NH}_2} \xrightarrow[70\ ^{\circ}\text{C, 5 h}]{d_8\text{-THF, air}} \textbf{III} \quad (5.3)$$

Table 5. Metal-Promoted Condensation of Sulfonamide and Aldehyde

$$\underset{\textbf{2a}}{\text{PhSO}_2\text{NH}_2} + \underset{\substack{\textbf{4a}\\ (x\ \text{equiv.})}}{\text{PhCHO}} \xrightleftharpoons[\substack{\text{K}_2\text{CO}_3\ (z\ \text{mol\%})\\ \text{atm., T, t}}]{\text{M}\ (y\ \text{mol\%})} \underset{\textbf{5aa}}{\text{PhSO}_2\text{N=CHPh}} + \text{H}_2\text{O}$$

run	M	*x, y, z*	atm, *T*, *t*	yield %[a]
1[b]		6, 0, 0	N_2, 120 °C, 8 h	65
2[b]	$RhCl(PPh_3)_3$	6, 5, 0	N_2, 120 °C, 8 h	97
3[b]	$RhCl(PPh_3)_3$	6, 5, 0	air, 120 °C, 8 h	96
4[b]		6, 0, 100	N_2, 120 °C, 8 h	84
5[b]		6, 0, 100	air, 120 °C, 8 h	99
6[c]	$RhCl(PPh_3)_3$	1.33, 1, 0	N_2, 100 °C, 2 h	68
7[c]	$RhCl(PPh_3)_3$	1.33, 1, 20	air, 100 °C, 2 h	67

[a] GC yields based on **2a**. [b] **2a** (1 mmol) and **4a** (6 mmol, 6 equiv) in a 50 mL Schlenk tube. [c] **2a** (3 mmol) and **4a** (4 mmol, 1.33 equiv) in a 20 mL Schlenk tube.

Table 6. Rh-Catalyzed Transfer Hydrogenation of Intermediate Imine to Product Amide by Alcohol

$$\underset{\substack{\textbf{1a}\\ (x\ \text{equiv.})}}{\text{PhCH}_2\text{OH}} + \underset{\textbf{5aa}}{\text{PhSO}_2\text{N=CHPh}} \xrightarrow[\substack{\text{K}_2\text{CO}_3\ (z\ \text{mol\%})\\ \text{atm., T, t}}]{\text{RhCl(PPh}_3)_3\ (y\ \text{mol\%})} \underset{\textbf{3aa}}{\text{PhSO}_2\text{NHCH}_2\text{Ph}} + \underset{\textbf{4a}}{\text{PhCHO}}$$

run	*x, y, z*	atm, *T*, *t*	**3aa**% yield[a]	**4a** % yield[a]	**4a**/**3aa**[f]
1[b]	6, 5, 100	N_2, 100 °C, 2 h	82	14	
2[b]	6, 5, 100	air, 100 °C, 4 h	83	13	
3[c]	1.3, 1, 10	N_2, 120 °C, 4 h	98	36	
4[c]	1.3, 1, 10	air, 120 °C, 4 h	87	31	
5[c,d]	1.3, 1, 20	N_2, 100 °C, 2 h	45 (49)[e]	23 (55)[e]	1.12/1
		4 h	76 (86)[e]	28 (78)[e]	0.91/1

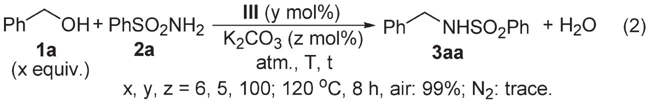
[a] Reactions monitored by GC−MS. GC yields based on **5aa**. [b] **5aa** (1 mmol) and **1a** (6 mmol, 6 equiv) in a 50 mL Schlenk tube. [c] **1a** (3x mmol, *x* equiv) and **5aa** (3 mmol) in a 20 mL Schlenk tube. [d] Catalyst $RhCl(CO)(PPh_3)_2$ (**III**) was used. [e] Yields in parentheses was calculated based on proton integrations of the ^1H NMR spectra. [f] **4a**/**3aa** ratios based on ^1H NMR spectroscopic analysis.

imine **5aa**,[27,31] which may be the intermediates of the reaction (Scheme 3). (2) Ester and hemiacetal byproducts that were possibly generated due to aerobic oxidation of alcohol **1a** to aldehyde **4a**[20] were also detected in minor amounts in many cases. (3) In reactions with reduced alcohol loadings, relatively lower ratios of **3aa**/**5aa** were detected at the beginning of the reaction[35] that were gradually enhanced as the reaction progressed. (4) Similarly, large amounts of **5aa** instead of **3aa** were detected under aerobic base-free conditions.[27,30] These results indicated that the reaction most probably proceeds via path 2 of Scheme 3 involving aldehydes **4** and imines **5** as the intermediates, which may also be generated prior to product amine **3**. In an effort to clarify the mechanism for the present aerobic *N*-alkylation reactions, we investigated the details of the corresponding individual reactions as shown in Scheme 3, path 2.

The first step of the reaction, the metal-catalyzed aerobic alcohol oxidations, has been well-studied.[19,20] Indeed, the metal-catalyzed aerobic oxidation of alcohols to intermediate aldehydes could possibly be another means to activate the alcohol[36] (Schemes 2 and 3) in present aerobic *N*-alkylation reactions.[37] This activation/oxidation is also supported by our own experimental results as shown in Table 4.

When Rh-catalyzed aerobic alcohol oxidation reactions were heated at 120 °C in the absence of sulfonamide **2a**, considerable amounts of benzaldehyde **4a** and oxidation byproducts were afforded in either the presence or the absence of base (Table 4, runs 1 and 2), confirming the occurrence of the Rh-catalyzed aerobic alcohol oxidation step[37] and also showing that base is not essential in the oxidation. Other metal catalysts behaved similarly, generating **4a** in considerable amounts.[30] Moreover, room temperature stirring of pure alcohol **1a** in open air with $RhCl(PPh_3)_3$ gave a detectable amount of aldehyde **4a** (run 3), which was totally inhibited by the addition of sulfonamide **2a** (run 4). Also worth noting is that the efficient $RuCl_3$-catalyzed oxidation (run 5)[20] was also greatly inhibited by **2a** (run 6). These results[30] can only be explained by deactivation of the metal catalysts by the sulfonamides and that this deactivation can be a general phenomenon for various metal catalysts.[38,39] Although this catalyst deactivation has seldom been taken into account in the past,[9,12,13] our NMR spectroscopic analyses support its occurrence.

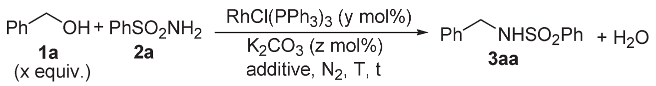
As shown in Scheme 4, in the absence of sulfonamides **2**, the reactions of *p*-chlorobenzyl alcohol (**1b**)[9b,40,41] or *p*-chlorobenzaldehyde (**4b**)[9b,41,42] with $RhCl(PPh_3)_3$ easily afforded the final carbonylated Rh complex **III**[43] via intermediates **I** and **II** under several aerobic or anaerobic conditions (Scheme 4). The catalytic activity of **III** was also found to be similar (eq 2) with that of $RhCl(PPh_3)_3$, showing that alcohol decarbonylation and the presence of a CO ligand on Rh do not affect Rh's catalytic activity. Furthermore, the corresponding anaerobic reactions were ineffective, giving only trace amounts of product (eq 2).



x, y, z = 6, 5, 100; 120 °C, 8 h, air: 99%; N_2: trace.
x, y, z = 1.5, 0.5, 20; 135 °C, 24 h, air: 93%; N_2: trace.

However, a completely different outcome occurred upon addition of sulfonamide **2** (Scheme 5). Although decarbonylation and formation of **III** from the mixture of $RhCl(PPh_3)_3$ and

Table 7. Rh-Catalyzed *N*-Alkylation of Sulfonamide in the Presence of Initiators

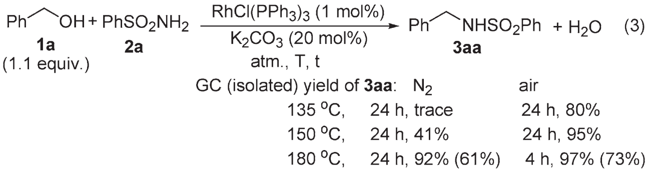


run	*x*, *y*, *z*	additive	*T*, *t*	**3aa** % yield[a]
1[b]	6, 5, 100	air (6 mL, O_2: 2.5% v/v, 5.6 mol %)	120 °C, 24 h	64
			48 h	99
2[b]	6, 5, 100	air (20 mL, O_2: 8.4% v/v, 18.8 mol %)	120 °C, 13 h	88
3[b]	6, 5, 100	**4a** (5 mol %)	120 °C, 12 h	84
4[c]	1.1, 1, 20	**4a** (10 mol %)	135 °C, 24 h	79
5[b]	6, 5, 100	$PhCH{=}NSO_2Ph$ **5aa** (10 mol %)	120 °C, 16 h	88
6[c]	1.3, 1, 10	**5aa** (10 mol %)	135 °C, 18 h	80
7[c]	1.3, 1, 30	$PhI(OAc)_2$ (10 mol %)	135 °C, 24 h	81
8[c]	2, 1, 50	$PhI(OAc)_2$ (20 mol %)	135 °C, 24 h	98
9[c]	1.3, 1, 20	TEMPO (20 mol %)	135 °C, 24 h	99
10[c]	1.5, 0.5, 10	$CH_2{=}CHCOOEt$ (20 mol %)	135 °C, 36 h	63
11[c]	1.5, 0.5, 10	$PhCH{=}CH_2$ (20 mol %)	135 °C, 36 h	81

[a] Reactions monitored by TLC and/or GC−MS. GC yields (isolated yields in parentheses) based on **2a**. [b] **2a** (1 mmol) and **1a** (*x* mmol, *x* equiv) in a 50 mL Schlenk tube. [c] **1a** (3*x* mmol, *x* equiv) and **2a** (3 mmol) in a 20 mL Schlenk tube.

4b in the presence of **2b** were easily detected after heating the reaction mixture under nitrogen (eq 5.1), the corresponding reaction of alcohol **1b** and $RhCl(PPh_3)_3$ did not take place, even when heated to 120 °C (eq 5.2), revealing that under anaerobic conditions, decarbonylation and **III**'s formation from alcohol and $RhCl(PPh_3)_3$ can be greatly inhibited by **2**, supporting the idea that the lone Rh catalyst is incapable of dehydrogenating the alcohol under an inert atmosphere. In contrast, the same mixture under air using solvent that had not been degassed gave **III** smoothly at 70 °C (eq 5.3), showing that, even in the presence of sulfonamide **2**, alcohol dehydrogenation (oxidation) followed by the inevitable decarbonylation can be facilitated by air (oxygen). The observation in eq 5.2 is (1) consistent with previously observed inhibition in aerobic alcohol oxidations (Table 4), (2) a great contrast with easy decarbonylation of the alcohol in the absence of sulfonamides (Scheme 4), and (3) a great contrast with easy anaerobic aldehyde decarbonylation (eq 5.1) and aerobic alcohol decarbonylation (eq 5.3) in the presence of **2**. Besides, **2a** and **2b** were very helpful in dissolving $RhCl(PPh_3)_3$ in d_8-THF, resulting in total solvation of $RhCl(PPh_3)_3$ to give a transparent NMR solution at room temperature.[38,44,45]

Anaerobic dehydrogenative alcohol activation is known as a thermodynamically unfavorable process.[9c] In contrast, the aerobic oxidation of alcohol resulting in the production of water is an exothermic process that may serve as the driving force for the reaction. Thus, the reaction is thermodynamically more favorable because the energy required for aldehyde formation can be compensated by this oxidation, and it can promote the reaction to occur at a relatively lower temperature. Vice versa, the anaerobic reactions should be able to occur at higher temperatures because the energy required can be achieved by high-temperature heating. Thus, as we observed, the anaerobic reaction of **1a** and **2a** at 180 °C is also very effective (eq 3), whereas the reactions below 180 °C gave only poor yields of the product. In comparison, the same reactions under air were much faster, giving much higher product yields.



(3)

GC (isolated) yield of **3aa**:	N_2	air
135 °C,	24 h, trace	24 h, 80%
150 °C,	24 h, 41%	24 h, 95%
180 °C,	24 h, 92% (61%)	4 h, 97% (73%)

Furthermore, condensation of **2** with **4** giving intermediate imines **5**, a standard organic reaction,[46] was easily confirmed (Table 5). According to the above analysis, aerobic alcohol oxidation to aldehyde[20,37] and subsequent condensation with **2**[27] should be responsible for the formation of intermediate **5**. However, it is not clear if metal catalysts promote this reaction.[9b] The assumption implicit in the borrowing hydrogen concept that metals do not affect this step may not hold because aldehyde binding to an electrophilic metal fragment should greatly increase the electrophilicity of the carbonyl carbon and thus enhance nucleophilic attack.[9b] This idea may be true, since metal insertions into aldehydes are indeed very common with many metals.[9b,41,42] The above NMR studies and the results of the controlled condensations as summarized in Table 5 may also support this point. Thus, without metal catalysts and base, **2a** and **4a** gave moderate yield of **5aa** under the reaction condition (Table 5, run 1), showing that neither catalyst nor base are essential in this reaction. However, complete conversion of **2a** did not occur, even after 8 h, supporting the condensation equilibrium.[15a,b,46] Reactions in the presence of the Rh catalyst and/or the base showed that each additive could facilitate the reaction independently (runs 2−5) and cooperatively.[30] Furthermore, reactions at a lower temperature and/or with reduced aldehyde and catalyst loadings were still efficient in a very short time (runs 6 and 7).[30]

We then investigated the transfer hydrogenation step of the reaction (Scheme 3). Transition-metal-catalyzed transfer hydrogenation reactions using alcohols as the reducing agent have been well-documented in the literature.[9b,47,48] They serve as a good alternative for conventional hydrogenations and have been widely adopted in asymmetric synthesis.[47,49] In the present reactions (Table 6), no reaction occurred without Rh catalyst and base.[30] With the lone Rh catalyst under air, no reaction occurred at the reaction temperature,[50] but with the hydrolysis of imine **5aa** and the oxidation of alcohol **1a** to aldehyde **4a**, resulting in the detection of a large amount of **4a**.[30] Base was then found crucial to promote the transfer hydrogenation as Bäckvall had pointed out.[50d] Thus, in the presence of RhCl(PPh_3)$_3$ and K_2CO_3, reduction of **5aa** by **1a** proceeded efficiently to give a high yield of **3aa** with considerable **4a** regenerated.[30] With a large excess of alcohol, the reaction is very fast even at a lower temperature (runs 1 and 2). With reduced alcohol loadings, the reaction is still fast at 120 °C (runs 3 and 4). Catalyst **III** also showed good activity in the reaction (run 5), in which the amount of byproduct **4a** was also measured by ^{1}H NMR spectroscopic analysis, showing that quantitative **4a** could be regenerated.[30] On the basis of the above Rh-catalyzed alcohol activation/oxidation studies, this transfer hydrogenation reaction most probably does not involve the demanding formation of RhH or RhH_2 species, whereas according to the mechanistic studies of the transfer hydrogenation reactions,[9b,47] it is also possible to proceed via a six-membered cyclic Meerwein–Pondorf–Verley-type transition state.

Although bases are similarly required in borrowing hydrogen reactions,[9,11–16] it was *still unclear which catalytic step requires base*.[9b] In contrast, results of above controlled individual reactions clearly showed that, unlike the alcohol oxidation and condensation steps that can both take place under base-free conditions, transfer hydrogenation is the only base-dependent step in the present reactions. This is also exemplified by the formation of imine **5aa** under aerobic and base-free conditions.[30]

Alternative Protocols for Alcohol Activation/Oxidation and Potential Initiators for the Metal-Catalyzed Anaerobic *N*-Alkylation Reactions. Our examinations of the individual reactions revealed that path 2 of Scheme 3, involving the aerobic oxidation of the alcohol, is the most probable route for the present aerobic *N*-alkylation reactions. Although both condensation and transfer hydrogenation reactions can be conducted under air, they can also take place with great ease at lower temperatures and/or under nitrogen, indicating that the rate-limiting step of the reaction should be initiation of the aldehyde formation. Thus, only the alcohol activation step should require air to facilitate the reaction, which is consistent with above findings on catalyst deactivation and alcohol oxidation studies (Table 4, Schemes 4 and 5). The quantitative regeneration of aldehyde **4** during the transfer hydrogenation step is a further indication that if aldehyde **4** could be recycled to condense with amide/amine **2**, then generation of only catalytic amounts of **4** is sufficient for the whole reaction. Thus, only catalytic amounts of air (oxygen) should be necessary to produce the catalytic amounts of starting **4**.[51] Otherwise, large amount of byproducts **4** or **5** may be produced, even becoming the major products in the presence of a large excess of air (oxygen).[15,20,27] Similar to air, as we deduced, catalytic amounts of external oxidants[19] or hydrogen acceptors[23–25] should initiate the reaction by converting the alcohol to aldehyde under anaerobic conditions (Scheme 2). Indeed, the above hypothesis is consistent with previous findings and the following control reactions (Table 7).

For example, addition of ~6.3 mol % O_2 (21% v/v) to 3 mmol substrates in a typical 20 mL Schlenk tube has been found crucial for an efficient reaction (Table 1, run 4). Similarly, when 6 mL of air was carefully introduced under nitrogen to a 50 mL Schlenk tube containing degassed substrates (1 mmol), the reaction afforded 64% and 99% **3aa** in 24 and 48 h, respectively (Table 7, run 1). Another reaction with 20 mL air proceeded much faster, giving 88% product yield in 13 h (run 2). In comparison, the reaction under the original conditions is the fastest (50 mL air; O_2: 21% v/v; 47 mol %), giving 92% product in only 2 h (Table 1, run 3).

Aldehydes are also good initiators.[51] Under the original conditions, a reaction with 5 mol % **4a** could give **3aa** in 84% yield in 12 h (Table 7, run 3). With reduced **1a** loading, the reaction became slower (run 4) but was still a good contrast to the ineffective anaerobic reactions (eq 3). Similarly, the reactions in the presence of imine **5aa**, which can regenerate **4a** via transfer hydrogenation, also afforded high yield of the product under nitrogen (runs 5 and 6).

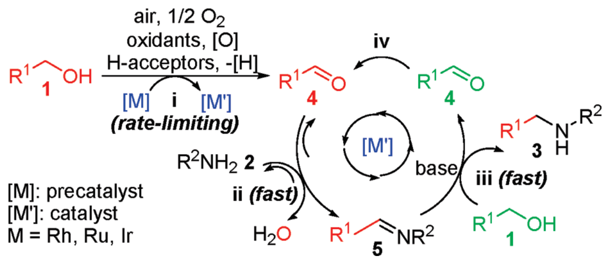
The well-known oxidants of alcohols, such as PhI(OAc)$_2$ (Table 7, runs 7 and 8) and TEMPO (run 9),[19,20] and hydrogen acceptors, such as the activated alkenes ethyl acrylate and styrene (runs 10 and 11),[23–25] can also initiate the reaction effectively in the presence of the catalyst, giving much higher product yield than the blank reaction (eq 3). Herein, easy formation of aldehyde **4a** from alcohol **1a** via dehydrogenation by ethyl acrylate was also confirmed, giving large amounts of **4a** efficiently at only 50 °C (eq 4).

$$\underset{\textbf{1a}}{PhCH_2OH} \xrightarrow[\substack{K_2CO_3\ (7.5\ mol\%) \\ CH_2{=}CHCOOEt\ (2\ equiv) \\ 50\ ^{o}C,\ 8\ h,\ 61\%}]{RhCl(PPh_3)_3\ (0.38\ mol\%)} \underset{\textbf{4a}}{PhCHO} \begin{array}{l} +\ CH_3CH_2COOEt \\ +\ byproducts \end{array} \quad (4)$$

Mechanism of the Air-Promoted Metal-Catalyzed Arobic *N*-Alkylation Methodology. The above studies on the individual reactions and alternative routes to aldehyde generation confirmed our previous deductions that air, external oxidants, and hydrogen acceptors are all potentially useful alcohol activation protocols (Scheme 2). In comparison, performing the reactions under air is clearly the greenest and most advantageous protocol regarding convenience, efficiency, economy, environmental considerations, etc. The ability of various catalysts, regardless of their valence states or the presence of ligands, to catalyze the reactions of various substrates (Tables 2 and 3) also indicates that the reactions possibly have no inherent correlation with the valence state of the metal or the presence of the ligands.[52] Thus, a new mechanistic route as presented in Scheme 6 was proposed for the air-promoted metal-catalyzed aerobic *N*-alkylation reactions.[17] Since all the individual reactions of this new mechanism are in fact supported by related independent reactions, i.e., alcohol oxidation (i),[19,20,37] condensation (ii),[46] and transfer hydrogenation (iii),[47–50] this mechanism is the most probable and natural route for the aerobic *N*-alkylation reactions.[53] To our best knowledge, it should be a new mechanism in metal-catalyzed *N*-alkylation reactions that has never been proposed before.[17,18]

As shown in Scheme 6, due to a potentially general metal catalyst deactivation by the strong ligating amines/amides that has seldom been considered in the past and just disclosed in present research, the efficiency of the lone catalyst to abstract hydrogens from the alcohol to afford aldehyde and to provide a hydridometal species is reduced greatly, making it the rate-limiting step of the whole reaction. Therefore, air, oxidants, or H-acceptors can facilitate the metal-catalyzed oxidative aldehyde formation step (Scheme 6, step i) to occur at lower temperatures (such as 100–135 °C), during which a new catalyst [M′] may be generated.[54] These measures were found to be relatively more effective for activating the alcohol than the anaerobic dehydrogenation protocol, for in the latter cases, heating at a much higher temperature or adding an activating ligand will be required to achieve an efficient reaction.[9,11–13] [M′] then catalyzes the condensation (step ii) and transfer hydrogenation (step iii) reactions efficiently even at lower temperatures and the aldehyde will be

Scheme 6. Simplified Reaction Path for the Air-Promoted Metal-Catalyzed Aerobic *N*-Alkylation Reaction of Amides/Amines with Alcohols[53,54]



regenerated quantitatively and recovered (step iv) for the next *N*-alkylation cycle. Interestingly, the latter alcohol **1** (in green) transfers its own hydrogen atoms to the preceding alcohol **1** (in red, in its imine form **5** via aldehyde **4**) with itself being oxidized to **4** and will then (also in imine form) receive new hydrogen atoms from an even later alcohol in the next cycle; the process is analogous to a relay race game with the "handing off" of hydrogen atoms.

Besides, reactions should be more likely to proceed via an easier route that holds the lower energy barrier and requires the least energy. In present reactions, since condensation and transfer hydrogenation can both take place easily at lower temperatures, and rate-limiting step is the generation of the initiating aldehyde in alcohol activation, it indicates that, once the reaction is initiated by trace aldehdye that is generated via either route, it will require no longer high temperature heating for the difficult anaerobic dehydrogenative formation of aldehyde and hydridometal species by the lone catalysts. On the contrary, the reaction can cycle itself, with the aldehdye being continuously regenerated in the transfer hydrogenation and recycled until completion of the reaction even at the lower temperatures. That is indeed the case as we have observed in present reactions.

Moreover, condensation of the carbonyl compounds with amines followed by reduction of the generated imines (Scheme 6, steps ii + iii) have been long defined as reductive amination reactions.[2] The above aldehyde-initiated reactions (Table 7) can also be taken as one of such reactions. However, conventional reductive amination reactions usually require more than stoichiometric amounts of hazardous reducing reagents such as hydrogen gas or metal borohydrides.[2] In the present reactions, we adopted a reducing alcohol that can be converted to the reactant aldehyde by transfer hydrogenation, resulting in the requirement of only catalytic amounts of the starting aldehyde. Thus, the present method can also be considered as a rare case of the reductive amination of carbonyl compounds.[2,49] This may also be another support to the new mechanism we proposed in present research.

■ CONCLUSION

In summary, by employing aerobic alcohol oxidation as a more effective alcohol activation protocol than the conventional anaerobic dehydrogenative processes, a milder, greener, more efficient, and advantageous air-promoted metal-catalyzed *N*-alkylation methodology has been developed for the versatile amide/amine derivative sythesis. This aerobic method is rather general in catalyst and substrate scopes in that it is suitable for many simple, less expensive, readily available, and ligand-free metal catalysts and a wide range of amides, amines, and alcohols, avoiding inert atmosphere protection and the use of expensive preformed metal complexes, activating ligands, and solvents. Mechanistic studies revealed that, contrary to the conventional borrowing hydrogen or hydrogen autotransfer mechanism, a new mechanism analogous to a relay race game that has never been proposed in metal-catalyzed *N*-alkylation reactions should be involved in the aerobic reactions. In light of the related literature background,[9b,18−20,24−27,37−39,45,47−50] our present conclusions, and Crabtree's opinion, *some previous conclusions in aerobic systems may need to be re-examined.*[18] Further extensions and deeper mechanistic insights of these air-promoted metal-catalyzed reactions are under way.

■ EXPERIMENTAL SECTION

General Methods and Materials. Substrates and catalysts are all purchased. In reactions carried out under air, substrates, solvents and catalysts were used as purchased without further purification and degassing. In reactions under N_2 and mechanistic studies, absolute alcohols (**1**) (dried over CaH_2, newly distilled, degassed, and stored under nitrogen in a Schlenk flask) and aldehydes (**4**) (100% purity without any contaminants as proved by GC analysis) were used unless otherwise noted. Reactions were carried out in sealed Schlenk tubes and monitored by TLC and/or GC−MS. Products were purified by column chromatography on silica gel using petroleum ether and ethyl acetate as eluent and identified by usual physical methods, i.e., NMR, MS, HRMS, etc. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded on a 500 MHz spectrometer (500 MHz for ^1H, 125.4 MHz for ^{13}C, and 202.4 MHz for ^{31}P NMR spectroscopy) or a 300 MHz spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C NMR spectroscopy). Unless otherwise noted, $CDCl_3$ was used as the solvent. Chemical shift values for ^1H and ^{13}C were referred to internal Me_4Si (0 ppm), and that for ^{31}P was referred to H_3PO_4 (85% solution in D_2O, 0 ppm).

Typical Procedure for Metal-Catalyzed Aerobic *N*-Alkylation of Amides/Amines with Alcohols. A mixture of benzenesulfonamide **2a** (0.471 g, 3.0 mmol), $RhCl(PPh_3)_3$ (0.0139 g, 0.015 mmol, 0.5 mol %), and K_2CO_3 (0.041 g, 0.3 mmol, 10 mol %) in benzyl alcohol **1a** (0.4 mL, 4.0 mmol, 1.33 equiv) was stirred at 135 °C under air in a sealed 20 mL Schlenk tube and monitored by TLC and/or GC−MS. The reaction was then quenched with ethyl acetate, and the product was purified by column chromatography with ethyl acetate and petroleum ether (60−90 °C) as eluent, giving *N*-benzylbenzenesulfonamide **3aa** in 83% isolated yield. Constant but low amounts of intermediate benzaldehyde **4a** (2−8%) and trace *N*-benzylidenebenzenesulfonamide **5aa** (0%∼0.5%) were observed in reaction mixtures of **1a** and **2a** according to GC−MS analysis.

Typical Procedure for Anaerobic Reactions. A mixture of benzenesulfonamide **2a** (0.157 g, 1.0 mmol), $RhCl(PPh_3)_3$ (0.0463 g, 0.05 mmol, 5 mol %), and K_2CO_3 (0.138 g, 1.0 mmol, 1 equiv) was degassed under vacuum and refilled with pure nitrogen for 3−5 times. Then newly distilled, degassed, and dried benzylic alcohol **1a** (0.6 mL, 6.0 mmol, 6 equiv) was added under nitrogen, and the tube was then sealed heated at 100 or 120 °C. No reaction occurred as monitored by TLC. In cases where different equivalents of the substrates were added and other catalysts were used, trace product may be detected with large amounts of the substrates remaining unreacted. Solvents were also degassed prior to use in the anaerobic reactions.

***N*-Benzylbenzenesulfonamide (3aa).** White solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, J = 7.4 Hz, 2H), 7.54−7.42 (m, 3H), 7.20−7.17 (m, 5H), 5.29 (b, 1H), 4.09 (d, J = 6.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.8, 136.2, 132.5, 129.0, 128.5, 127.72, 127.66, 126.9, 47.1. MS (EI): m/z (%) 246 (0.3), 143 (6), 141 (4), 125 (6), 106

(100), 104 (12), 91 (15), 79 (21), 78 (14), 77 (39), 51 (15). This compound was known.[16c]

_N_-(4-Chlorobenzyl)benzenesulfonamide (3ba). White solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.82 (d, J = 7.6 Hz, 2H), 7.60−7.45 (m, 3H), 7.20−7.09 (m, 4H), 5.36 (bt, J = 6.3 Hz, 1H), 4.08 (d, J = 6.3 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 139.6, 134.8, 133.5, 132.7, 129.14, 129.09, 128.7, 126.9, 46.4. MS (EI): m/z (%) 281 (0.09), 280 (0.11), 142 (32), 140 (100), 138 (13), 125 (18), 113 (8), 89 (6), 77 (46). This compound was known.[8c]

_N_-(3-Chlorobenzyl)benzenesulfonamide (3ca). White solid. ^{1}H NMR (500 MHz, CDCl$_3$): δ7.85−7.84 (m, 2H), 7.60−7.57 (m, 1H), 7.52−7.49 (m, 2H), 7.21−7.15 (m, 3H), 7.09−7.07 (m, 1H), 5.06 (bt, J = 6.0 Hz, 1H), 4.12 (d, J = 6.5 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 139.8, 138.3, 134.5, 132.8, 129.9, 129.2, 128.1, 128.0, 127.0, 125.9, 46.6. MS (EI): m/z (%) 281 (1), 142 (33), 140 (100), 125 (13), 113 (8), 78 (14), 77 (46), 51 (12). This compound was known.[55]

_N_-(4-Methoxybenzyl)benzenesulfonamide (3da). White solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.83 (d, J = 7.6 Hz, 2H), 7.58−7.44 (m, 3H), 7.08 (d, J = 8.2 Hz, 2H), 6.75 (d, J = 8.2 Hz, 2H), 5.32 (b, 1H), 4.04 (d, J = 5.5 Hz, 2H), 3.73 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 159.0, 139.8, 132.5, 129.1, 128.9, 128.2, 126.9, 113.8, 55.1, 46.5. MS (EI): m/z (%) 277 (5), 141 (2), 135 (100), 121 (29), 77 (26). This compound was known.[56]

_N_-(2-Methoxybenzyl)benzenesulfonamide (3ea). White solid. ^{1}H NMR (500 MHz, CDCl$_3$): δ7.77−7.75 (m, 2H), 7.48 (t, J = 7.5 Hz 1H), 7.39 (t, J = 8.0 Hz, 2H) 7.19−7.16 (m, 1H), 7.06−7.04 (m, 1H), 6.79 (t, J = 7.5, 1H), 6.71 (d, J = 5.5 Hz, 1H), 5.20 (bt, J = 6.0 Hz, 1H), 4.16 (d, J = 6.5 Hz, 2H), 3.72 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 157.2, 140.3, 132.2, 129.8, 129.3, 128.7, 126.9, 124.2, 120.5, 110.1, 55.1, 44.0. MS (EI): m/z (%) 277 (5), 137 (9), 136 (100), 134 (21), 121 (15), 119 (14), 107 (12), 91 (24), 77 (29). HRMS calcd for $C_{14}H_{15}NO_3S$ $(M + Na)^+$: 300.0670, found 300.0664.

_N_-(2-Phenylethyl)benzenesulfonamide (3fa). White solid. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.81 (d, J = 8.0 Hz, 2H), 7.54 (t, J = 7.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 2H), 7.24−7.16 (m, 3H), 7.18 (d, J = 7.0 Hz, 2H), 4.96 (bt, J = 5.5 Hz, 1H), 3.21−3.17 (q, J = 7.0 Hz, 2H), 2.74 (t, J = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 139.8, 137.6, 132.5, 129.0, 128.6, 128.5, 126.9, 126.6, 44.2, 35.7. MS (EI): m/z (%) 261 (1), 171 (9), 170 (100), 142 (7), 141 (97), 104 (18), 92 (9), 91 (48), 78 (9), 77 (89), 65 (18). This compound was known.[57]

_N_-(3-Phenylpropyl)benzenesulfonamide (3ga). Yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.87−7.85 (m, 2H), 7.57−7.54 (m, 1H), 7.50−7.47 (m, 2H), 7.23 (t, J = 7.5 Hz, 2H), 7.16 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 7.5 Hz, 2H), 5.03 (bt, J = 6.0 Hz, 1H), 2.96 (q, J = 6.5 Hz, 2H), 2.58 (t, J = 7.5 Hz, 2H), 1.78−1.75 (m, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 140.8, 139.9, 132.5, 129.0, 128.4, 128.3, 127.0, 126.0, 42.6, 32.6, 31.0. MS (EI): m/z (%) 276 (1), 275 (2), 170 (8), 141 (42), 134 (8), 119 (11), 118 (100), 117 (23), 105 (11), 104 (12), 91 (29), 77 (84). This compound was known.[58]

_N_-Benzyl-_p_-toluenesulfonamide (3ab). White solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.75 (d, J = 7.9 Hz, 2H), 7.29−7.21 (m, 7H), 5.21 (b, 1H), 4.10 (d, J = 6.2 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 143.4, 137.0, 136.5, 129.7, 128.6, 127.9, 127.8, 127.2, 47.2, 21.5. MS (EI): m/z (%) 261 (0.1), 260 (0.2), 157 (3), 107 (10), 106 (100), 92 (13), 91 (39), 79 (17), 77 (11). This compound was known.[12a]

_N_-Benzyl-_o_-toluenesulfonamide (3ac). White oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.96 (d, J = 7.9 Hz, 1H), 7.47−7.42 (m, 1H), 7.31−7.15 (m, 7H), 5.28 (bt, J = 6.0 Hz, 1H), 4.11 (d, J = 6.2 Hz, 2H), 2.61 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 138.0, 137.1, 136.5, 132.8, 132.6, 129.5, 128.6, 127.9, 127.8, 126.2, 47.1, 20.3. MS (EI): m/z (%) 261 (0.13), 157 (2), 155 (1), 106 (100), 91 (50), 77 (12), 65 (18). This compound was known.[59]

_N_-Benzyl-4-chlorobenzenesulfonamide (3ad). White solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.74 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.25−7.15 (m, 5 H), 5.38 (bt, J = 5.7 Hz, 1H), 4.12 (d, J = 6.1 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 139.0, 138.5, 136.0, 129.2, 128.6, 128.5, 127.81, 127.78, 47.1. MS (EI): m/z (%) 281 (0.1), 280 (0.2), 112 (6), 111 (16), 107 (8), 106 (100), 104 (15), 91 (15), 79 (19), 77 (15), 75 (10). This compound was known.[12a]

_N_-Benzyl-2-chlorobenzenesulfonamide (3ae). White solid. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.07 (d, J = 7.5 Hz, 1H), 7.50−7.46 (m, 2H), 7.41−7.38 (m, 1H), 7.26−7.17 (m, 5H), 5.30 (br, 1H), 4.12 (d, J = 6.0 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 137.2, 135.7, 133.7, 131.5, 131.3, 131.2, 128.6, 128.0, 127.9, 127.2, 47.5. MS (EI): m/z (%) 281 (0.1), 280 (0.2), 176 (5), 159 (5), 111 (13), 106 (100), 104 (15), 91 (17), 79 (18), 77 (18), 75 (10). This compound was known.[16c]

_N_-Benzyl-4-methoxybenzenesulfonamide (3af). White solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.78 (d, J = 8.4 Hz, 2H), 7.23−7.20 (m, 5H), 6.93 (d, J = 8.7 Hz, 2H), 5.23 (bt, J = 5.7 Hz, 1H), 4.08 (d, J = 6.0 Hz, 2H), 3.85(s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 162.7, 136.3, 131.3, 129.1, 128.5, 127.7, 127.6, 114.1, 55.5, 47.0. MS (EI): m/z (%) 277 (3), 212 (1), 171 (4), 155 (14), 127 (2), 123 (20), 108 (26), 106 (100), 91 (15), 79 (13), 77 (28), 64 (8). This compound was known.[12a]

_N_-Benzyl-2-naphthalenesulfonamide (3ag). White solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.45 (s, 1H), 7.95−7.83 (m, 4H), 7.68−7.60 (m, 2H), 7.20−7.17(m, 5H), 5.25 (bt, J = 6.1 Hz, 1H), 4.16 (d, J = 6.2 Hz, 2H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 136.5, 136.1, 134.7, 132.0, 129.4, 129.1, 128.7, 128.49, 128.45, 127.8, 127.7, 127.4, 122.2, 47.2. MS (EI): m/z (%) 298 (2), 297 (11), 192 (5), 175 (2), 144 (8), 128 (50), 127 (57), 115 (8), 106 (100), 91 (16), 79 (11), 77 (19). This compound was known.[12a]

_N_-Benzylmethanesulfonamide (3ah). White solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.35 (m, 5H), 4.94 (br, 1H), 4.30 (d, J = 6.1 Hz, 2H), 2.84 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 136.7, 128.9, 128.1, 127.9, 47.2, 41.1. MS (EI): m/z (%) 185 (1), 107 (8), 106 (100), 105 (18), 104 (45), 91 (29), 79 (32), 78 (13), 77 (23), 51 (12). This compound was known.[16c]

_N_-(4-Chlorobenzyl)-_p_-toluenesulfonamide (3bb). White solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.59 (d, J = 8.2 Hz, 2H), 7.16−6.99 (m, 6H), 5.44 (bt, J = 6.3 Hz, 1H), 3.93 (d, J = 6.3 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 143.5, 136.6, 134.9, 133.4, 129.6, 129.1, 128.5, 127.0, 46.3, 21.4. MS (EI): m/z (%) 295 (0.06), 157 (4), 142 (30), 140 (100), 139 (10), 125 (12), 113 (7), 91 (37), 77 (12), 65 (17). This compound was known.[16c]

_N_-(3-Chlorobenzyl)-_p_-toluenesulfonamide (3cb). White solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.70 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 7.9 Hz, 2H), 7.17−7.07 (m, 4H), 5.38 (bt, J = 5.8 Hz, 1H), 4.07 (d, J = 6.2 Hz, 2H), 2.41(s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 143.6, 138.6, 136.9, 134.4, 129.9, 129.7, 127.9, 127.8, 127.1, 126.0, 46.6, 21.5. MS (EI): m/z (%) 295 (0.11), 294 (0.46), 155 (4), 142 (31), 140 (100), 125 (7), 113 (7), 91 (43), 77 (13), 65 (19). This compound was known.[16c]

_N_-(4-Methoxybenzyl)-_p_-toluenesulfonamide (3db). White solid; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.74 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.6 Hz, 2H), 4.89 (bt, J = 5.7 Hz, 1H), 4.03 (d, J = 6.1 Hz, 2H), 3.76 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 159.1, 143.3, 136.8, 129.6, 129.1, 128.2, 127.0, 113.9, 55.1, 46.6, 21.4. MS (EI): m/z (%) 292 (1), 291 (4), 155 (2), 136 (99), 135 (100), 134 (56), 121 (30), 109 (11), 91 (27), 77 (12), 65 (15). This compound was known.[60]

_N_-(2-Methoxybenzyl)-_p_-toluenesulfonamide (3eb). White oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.66 (d, J = 8.2 Hz, 2H), 7.21−7.17 (m, 3H), 7.06 (d, J = 7.0 Hz, 1H), 6.82−6.71 (m, 2H), 5.17 (b, 1H), 4.13 (d, J = 6.4 Hz, 2H), 3.73 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 157.2, 143.0, 137.3, 129.8, 129.4, 129.2, 127.1, 124.4, 120.5, 110.1, 55.2, 43.9, 21.4. MS (EI): m/z (%) 292 (1), 291 (3), 155 (2), 136 (100), 134 (14), 121 (13), 119 (9), 107 (11), 91 (39), 77 (8), 65 (15). This compound was known.[12a]

N-(2-Thiophenylmethyl)-p-toluenesulfonamide (3hb). Yellow solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.74 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.17–7.16 (m, 1H), 6.87–6.84 (m, 2H), 5.14 (bt, J = 5.8 Hz, 1H), 4.30 (d, J = 6.1 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 143.5, 138.9, 136.6, 129.6, 127.1, 126.7, 126.3, 125.6, 41.9, 21.4. MS (EI): m/z (%) 267 (0.17), 266 (1), 157 (3), 139 (6), 112 (100), 111 (16), 97 (20), 91 (25), 85 (18), 65 (12). This compound was known.[16c]

N-(4-Chlorobenzyl)-4-methoxybenzenesulfonamide (3bf). White solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.74 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 8.1 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 5.26 (bt, J = 5.8 Hz, 1H), 4.04 (d, J = 6.2 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 162.9, 135.0, 133.5, 131.3, 129.2, 128.7, 114.2, 55.6, 46.4. MS (EI): m/z (%) 311 (0.12), 142 (33), 140 (100), 125 (18), 105 (2), 77 (47). This compound was known.[61]

N-Benzylbenzamide (3ai). White solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.79 (d, J = 7.4 Hz, 2H), 7.51–7.26 (m, 8H), 6.70 (b, 1H), 4.61 (d, J = 5.6 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 167.4, 138.2, 134.3, 131.5, 128.7, 128.5, 127.8, 127.5, 126.9, 44.0. MS (EI): m/z (%) 211 (8), 210 (54), 106 (29), 105 (100), 91 (10),79 (6), 77 (61), 51 (16). This compound was known.[62]

N-(4-Chlorobenzyl)benzamide (3bi). White solid. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.77–7.79 (m, 2H), 7.50 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 7.31–7.26 (m, 4H), 6.56 (br, 1H), 4.59 (d, J = 5.5 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 167.4, 136.8, 134.2, 133.4, 131.7, 129.2, 128.9, 128.6, 126.9, 43.4. MS (EI): m/z (%) 247 (11), 246 (9), 245 (35), 210 (3), 140 (9), 125 (5), 106 (11), 105 (100), 77 (42). This compound was known.[62]

N-(4-Methoxybenzyl)benzamide (3di). White solid. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.77 (d, J = 7.5 Hz, 2H), 7.49–7.41 (m, 3H), 7.26–7.29 (m, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.40 (br, 1H), 4.57 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 167.2, 159.1, 134.5, 131.5, 130.3, 129.3, 128.5, 126.9, 114.2, 55.3, 43.6. MS (EI): m/z (%) 242 (9), 241 (59), 210 (2), 136 (41), 121 (26), 109 (13), 105 (100), 77 (54).This compound was known.[62]

N-Benzyl-4-methoxybenzamide (3aj). White solid. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.70–7.67 (m, 2H), 7.27–7.20 (m, 5H), 6.84–6.82 (m, 2H), 6.33 (br, 1H), 4.54 (d, J = 5.5 Hz, 2H), 3.76 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 166.9, 162.2, 138.4, 128.7, 127.9, 127.5, 126.7, 113.8, 55.4, 44.1. MS (EI): m/z (%) 242 (6), 241 (36), 211 (1), 136 (10), 135 (100), 107 (12), 92 (10), 77 (17). This compound was known.[63]

N-Benzylnicotinamide (3ak). White solid. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.81 (d, J = 1.0 Hz, 1H), 8.47 (d, J = 4.5 Hz, 1H), 8.00 (t, J = 1.0 Hz, 1H), 7.45 (br, 1H), 7.15–7.19 (m, 6H), 4.47 (d, J = 4.5 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 165.5, 151.8, 147.9, 137.8, 135.2, 130.1, 128.6, 127.7, 127.5, 123.3, 43.9. MS (EI): m/z (%) 212 (55), 211 (17), 182 (2), 168 (4), 167 (2), 155 (7), 107 (10), 106 (100), 104 (5), 91 (22), 79 (24), 78 (55), 65 (11), 51 (23). This compound was known.[64]

N-Benzyl-(2-pyrimidyl)amine (3al). White solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.02(br, 2H), 7.37–7.25 (m, 5H), 6.70 (br, 1H), 6.40 (t, J = 4.8 Hz, 1H), 4.61 (d, J = 5.6 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 162.2, 157.8, 139.0, 128.4, 127.5, 127.0, 110.3, 45.3. MS (EI): m/z (%) 186 (12), 185 (90), 184 (63), 157 (5), 144 (3), 129 (3), 108 (19), 106 (100), 91 (47), 79 (40), 77 (13), 65 (28). This compound was known.[65]

N-Benzyl-(2-pyridyl)amine (3am). White solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.10 (d, J = 4.9 Hz, 1H), 7.43–7.20 (m, 6H), 6.64–6.57 (m, 1H), 6.37 (d, J = 8.4 Hz, 1H), 4.88 (s, 1H), 4.51 (d, J = 5.7 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 158.6, 148.2, 139.2, 137.5, 128.7, 127.4, 127.3, 113.2, 106.8, 46.3. MS (EI): m/z (%) 184 (14), 183 (100), 182 (47), 153 (5), 127 (5), 116 (2), 106 (34), 79 (11), 66 (4). This compound was known.[13a]

N-(4-Chlorobenzyl)-(2-pyridyl)amine (3bm). White solid. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.08 (d, J = 5.0 Hz, 1H), 7.40–7.38 (m, 1H), 7.31–7.27 (m, 4H), 6.61–6.59 (m, 1H), 6.34 (d, J = 8.5 Hz, 1H), 4.91(br, 1H), 4.47 (d, J = 6.0 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 158.4, 148.2, 137.6, 132.9, 128.8, 128.7, 113.4, 106.9, 45.6. MS (EI): m/z (%) 220(16), 219 (12), 218 (51), 217 (19), 183 (5), 142 (33), 140 (100), 125 (43), 113 (7), 107 (12), 89 (23), 79 (42), 78 (31). This compound was known.[13a]

N-(4-Methoxybenzyl)-(2-pyridyl)amine (3dm). White solid. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.10–8.09 (m, 1H), 7.41–7.37 (m, 1H), 7.29–7.26 (m, 2H), 6.88–6.86 (m, 2H), 6.59–6.56 (m, 1H), 6.36 (d, J = 8.5 Hz, 1H), 4.85 (br, 1H), 4.42 (d, J = 5.5 Hz, 2H), 3.79 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 158.8, 158.6, 148.2, 137.4, 131.2, 128.7, 114.0, 113.0, 106.8, 55.2, 45.8. MS (EI): m/z (%) 214 (34), 213 (6), 199 (40), 136 (25), 122 (9), 121 (100), 105 (7), 91 (9), 77 (11). This compound was known.[13a]

N-Benzyl-[2-(5-chloropyridyl)]amine (3an). White solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.93 (d, J = 2.1 Hz, 1H), 7.32–7.23 (m, 6H), 6.27 (d, J = 8.8 Hz, 1H), 5.30 (br, 1H), 4.44 (d, J = 5.8 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 156.9, 146.4, 138.7, 137.2, 128.6, 127.3, 119.8, 107.5, 46.4. MS (EI): m/z (%) 220 (14), 219 (12), 218 (42), 217 (22), 183 (3), 141 (13), 112 (14), 106 (100), 91 (89), 79 (12), 65 (26). This compound was known.[66]

N-Benzyl-(3-pyridyl)amine (3ao). Yellow solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.07 (d, J = 2.9 Hz, 1H), 7.97–7.95 (m, 1H), 7.36–7.26 (m, 5H), 7.09–7.04 (m, 1H), 6.89–6.88 (m, 1H), 4.34 (br, 2H), 4.17 (br, 1H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 144.0, 138.8, 138.5, 136.0, 128.8, 127.5, 127.4, 123.7, 118.6, 47.9. MS (EI): m/z (%) 184 (38), 183 (5), 92 (9), 91 (100), 78 (7), 77 (2), 65 (13), 51 (6). This compound was known.[67]

N-Benzylaniline (3ap). Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.42–7.37 (m, 4H), 7.34–7.31 (m, 1H), 7.24–7.21 (m, 2H), 6.78–6.75 (m, 1H), 6.69–6.67 (m, 2H), 4.30 (s, 2H), 3.99 (br, 1H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 147.8, 138.0, 132.7, 129.2, 128.6, 127.4, 117.7, 112.8, 47.5. MS (EI): m/z (%) 183 (56), 182 (21), 106 (22), 104 (11), 92 (9), 91 (100), 77 (18), 65 (15), 51 (7). This compound was known.[68]

N-Benzyl-4-ethoxyaniline (3aq). Yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.37–7.25 (m, 4H), 6.76 (d, 2H), 6.59–6.56 (m, 2H), 4.26 (s, 2H), 3.93 (q, J = 7.0 Hz, 2H), 1.35 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 151.5, 142.3, 139.6, 128.5, 127.6, 127.1, 115.8, 114.2, 64.1, 49.3, 15.0. MS (EI): m/z (%) 228 (8), 227 (51), 226 (3), 198 (19), 196 (5), 136 (11), 108 (30), 91 (100), 81 (5), 77 (2), 65 (10). This compound was known.[69]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental procedures, condition screening tables, details of mechanism studies, product characterization and spectra of new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For recent heterogeneous examples, see: (a) Alonso, F.; Foubelo, F.; González-Gómez, J. C.; Martínez, R.; Ramón, D. J.; Riente, P.; Yus, M. *Mol. Divers.* **2010**, *14*, 411. (b) Shimizu, K.; Nishimura, M.; Satsuma, A. *ChemCatChem.* **2009**, *1*, 497. (c) Shi, F.; Tse, M. K.; Zhou, S.; Pohl, M. M.; Radnik, J.; Hübner, S.; Jähnisch, K.; Brückner, A.; Beller, M. *J. Am. Chem. Soc.* **2009**, *131*, 1775. (d) Shimizhu, K.-I.; Sato, R.; Satsuma, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 3982. (e) Gonzalez-Arellano, C.; Yoshida, K.; Luque, R.; Gai, P. L. *Green Chem.* **2010**, *12*, 1281. (f) Martínez, R.; Ramón, D. J.; Yus, M. *Org. Biomol. Chem.* **2009**, *7*, 2176. (g) Yamaguchi, K.; He, J.; Oishi, T.; Mizuno, N. *Chem.—Eur. J.* **2010**, *16*, 7199. (h) Kim, J. W.; Yamaguchi, K.; Mizuno, N. *J. Catal.* **2009**, *263*, 205. (i) Cui, X.; Zhang, Y.; Shi, F.; Deng, Y. *Chem.—Eur. J.* **2011**, *17*, 1021. (j) He, L.; Lou, X.-B.; Ni, J.; Liu, Y.-M.; Cao, Y.; He, H.-Y.; Fan, K.-N. *Chem.—Eur. J.* **2010**, *16*, 13965.

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(28) (a) Hansch, C.; Sammes, P. G.; Taylor, J. B. *Comprehensive Medicinal Chemistry*; Pergamon Press: Oxford, 1990; Vol. 2, Chapter 7.1. (b) Connor, E. E. *Primary Care Update OB/GYN* **1998**, *5*, 32. (c) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances, Synthesis, Patents, Applications*; Thieme: Stuggart, 1999.

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(30) See Supporting Information for experimental detail and results.

(31) Constant but low amount of benzaldehyde **4a** (2−8%) and traces of intermediate imine *N*-benzylidenebenzenesulfonamide **5aa** (0−0.5%) were often detected by GC−MS in reactions of **1a** and **2a**. Similarly, these intermediates were also frequently observed in the literature. See refs 9,11−16.

(32) Metal oxides are generally considered to be heterogeneous catalysts. However, whether the reactions of heterogeneous catalysts undergo borrowing hydrogen mechanisms as those of the homogeneous catalysts was questioned by Crabtree (see ref 9b). Therefore, the anaerobic reactions of these metal oxides are also more likely to undergo the new mechanism we proposed (Scheme 6).

(33) Watanabe, Y.; Ohta, T.; Tsuji, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2647.

(34) In our hands, by using FeCl$_2$ or FeCl$_3$ as the catalyst (known and used as Lewis acids, see refs 8e−8g), reactions of **1a** and **2a** in the absence of base did not give **3aa** but afforded dibenzyl ether as the major product. With base added, ether was not detected and no or only trace **3aa** could be observed.

(35) Similar detection of more intermediate imine than product amine at the begining of the reaction and gradual enhancement in product amine/intemediate imine selectivity has been observed in aerobic heterogeneous *N*-alkylation reactions. See refs 15c and 16h.

(36) In conventional borrowing hydrogen reactions, metal-mediated anaerobic dehydrogenative alcohol activation to aldehydes is by nature an alcohol oxidation reaction. See refs 9a, 9b.

(37) For examples of Rh-catalyzed aerobic alcohol oxidations, see refs 20i, 20q−20s. For examples of $Rh-O_2$ complex, see: (a) Ahijado, M.; Braun, T.; Noveski, D.; Kocher, N.; Neumann, B.; Stalke, D.; Stammler, H.-G. *Angew. Chem., Int. Ed.* **2005**, *44*, 6847. (b) Meier, G.; Braun, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 3280. As to the products of the oxidation, hydrogen peroxide was possibly firstly generated and then decomposed to give water and oxygen. See also ref 20.

(38) In fact, it has been documented that amides and amines, including the sulfonamides, are good ligands having strong ligating abilities toward metals: (a) Chohan, Z. H.; Shad, H. A.; Nasim, F.-H. *Appl. Organometal. Chem.* **2009**, *23*, 319 and references therein. (b) Cejudo-Marín, R.; Alzuet, G.; Ferrer, S.; Borrás, J. *Inorg. Chem.* **2004**, *43*, 6805. (c) Zhang, T.; Wang, W.; Gu, X.; Shi, M. *Organometallics* **2008**, *27*, 753. (d) Liang, J.; Lipscomb, W. N. *Biochemistry* **1989**, *28*, 9734. (e) Evelhoch, J. L. E.; Bocian, D. F.; Sudmeier, J. L. *Biochemistry* **1981**, *20*, 4951. (f) Dimroth, J.; Keilitz, J.; Schedler, U.; Schomäcker, R.; Haag, R. *Adv. Synth. Catal.* **2010**, *352*, 2497.

(39) Although complexation of amines with Ru and Ir catalysts had been taken into account by Watanabe and Yamaguchi, in most cases[9,11−16] it was ignored: (a) Watanabe, Y.; Morisaki, Y.; Kondo, T.; Mitsudo, T. *J. Org. Chem.* **1996**, *61*, 4214. (b) Watanabe, Y.; Tsuji, Y.; Ige, H.; Ohsugi, Y.; Ohta, T. *J. Org. Chem.* **1984**, *49*, 3359. (c) Fujita, K.-I.; Enkoi, Y.; Yamaguchi, R. *Tetrahedron* **2008**, *64*, 1943.

(40) Alcohol insertion onto transition metals and subsequent alcohol dehydrogenation are commonly recognized in the literature. See refs 9b, 12, 13.

(41) Reactions of alcohols with $RhCl(PPh_3)_3$: (a) Baird, M. C.; Mague, J. T.; Osborn, J. A.; Wilkinson, G. *J. Chem. Soc. A* **1967**, 1347. (b) Tsuji, J.; Ohno, K. *Tetrahedron Lett.* **1965**, *6*, 3969. Conversion of **I** to **II** possibly proceeds via dehydrogenation of the alcohol moiety with extrusion of molecular hydrogen. See also ref 21.

(42) For aldehyde insertion onto transition metals, addition and decarbonylation reactions and recent advances: (a) Baird, M. C.; Nyman, C. J.; Wilkinson., G. *J. Chem. Soc. A* **1968**, 348. (b) Milstein, D. *Chem. Commun.* **1982**, 1357. (c) Milstein, D. *Organometallics* **1982**, *1*, 1549. (d) Wills, M. C. *Chem. Rev.* **2010**, *110*, 725 and references therein. (e) Allen, C. L.; Williams, J. M. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1724 and references therein. (f) Garralda, M. A. *Dalton Trans.* **2009**, 6535 and references therein.

(43) The formation of complex **III**, formed as yellow crystals from the above solutions, was confirmed by comparison with an authentic sample. See Supporting Information for detail.

(44) In contrast, solubility of $RhCl(PPh_3)_3$ in d_8-THF was found to be rather low in the presence of **1a,b** or **4a,b**. Most $RhCl(PPh_3)_3$ cannot be dissolved, giving suspensions only.

(45) Possibly an Rh-sulfonamide complex was generated, but this remains to be clarified at present. Various sulfonamide−metal complexes have been developed by other groups. See refs 13b, 20r, 38.

(46) (a) Layer, R. W. *Chem. Rev.* **1963**, *63*, 489. (b) Sprung, M. M. *Chem. Rev.* **1940**, *26*, 297.

(47) For reviews and mechanistic details on transfer hydrogenation: (a) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226. (b) Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237. (c) Saluzzo, C.; Lemaire, M. *Adv. Synth. Catal.* **2002**, *344*, 915. (d) Bäckvall, J.-E. *J. Organomet. Chem.* **2002**, *652*, 105. (e) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045. (f) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (g) Zassinocivh, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051.

(48) Transfer hydrogenation of intermediate imines by alcohols to give product amines was also frequently employed to confirm the *N*-alkylation path in borrowing hydrogen reactions, albeit indirectly in our opinion. See refs 9, 12−16.

(49) A series of reductive (transfer hydrogenative) asymmetric carbonyl allylation, propargylation, and vinylation reactions using isopropanol as the reducing alcohol has been achieved by Krische and co-workers: (a) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34. (b) Bechem, B.; Patman, R. L.; Hashmi, A. S. K.; Krische, M. J. *J. Org. Chem.* **2010**, *75*, 1795. (c) Han, S. B.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 1760. (d) Zhang, Y. J.; Yang, J. H.; Kim, A. H.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 4562.

(50) It has been reported that the early base-free transition-metal-catalyzed transfer hydrogenations had to be conducted at much higher temperatures (ref a−c), while Bäckvall and co-workers found that dramatic enhancement of the reaction efficiency can be achieved by addition of small amounts of base (ref d). Base possibly works to deprotonate the alcohol and promotes its coordination with transition metal catalysts, enhancing the catalyst's activity. (a) Sasson, Y.; Blum, J. *Tetrahedron Lett.* **1971**, 2167. (b) Sasson, Y.; Blum, J. *J. Org. Chem.* **1975**, *40*, 1887. (c) Maitlis, P. *J. Organomet. Chem.* **1985**, *289*, 385. (d) Chowdhury, R. L.; Bäckvall, J. E. *Chem. Commun.* **1991**, 1063.

(51) This may also indicate that slight contamination of the alcohols by corresponding aldehydes or incomplete degassing of air by inert gases may lead to rather different results and mechanistic conclusions. Thus, in our work, degassed even newly distilled alcohol free of both aldehyde (as confirmed by GC analysis) and air was used in the control reactions and mechanistic studies.

(52) Similarly, it can also be easily drawn from corresponding literature[9,11−16] that conventional borrowing hydrogen reactions can also be catalyzed by various homogeneous and heterogeneous catalysts without defined valences and ligations.

(53) On the other hand, how every individual reaction proceeds and in what way does not affect the overall sequence and final outcome of the whole reaction. See also refs 9b, 20, 37, 47 and 48.

(54) Although a coordinating CO ligand may be present in the case of Rh catalysts as has been observed, the situation is still not clear with other metals. Thus, [M] and [M′] are used on behalf of precatalysts and catalysts. It seems this catalyst variation does not affect the results of reactions.

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