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Lewis Acid-Catalyzed Direct Amination of Benzhydryl Alcohols

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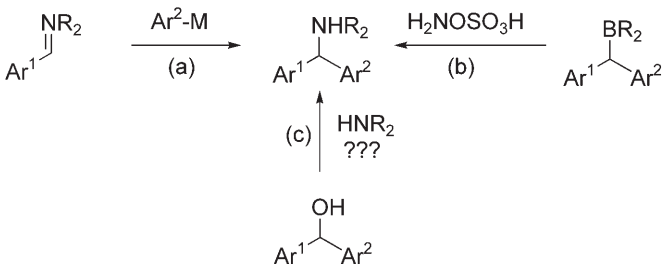
Abstract: The Lewis acid-mediated direct amination of benzylic alcohols is described, providing various benzylic amine derivatives in good yields under mild and environmentally benign conditions. Among the different Lewis acids tested, gold(III) proved to be the catalyst of choice for both chemical (yield, conversion) and practical reasons (a filtration over a silica pad is generally sufficient to obtain the corresponding benzylic amine in analytically pure form).

Keywords: amination; diarylmethylamine; gold; indium; Lewis acid

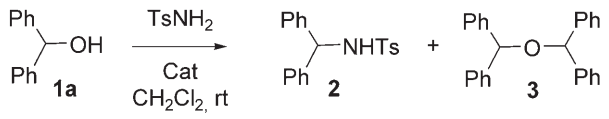
Homo- and hetero-biarylamines are found in a number of biologically active compounds such as cetirizine hydrochloride (histamine H_1-receptor)[1] or SNC80 (an opioid receptor agonist).[2] Traditionally, the syntheses of such compounds have been achieved by the addition of an organometallic compound on a preformed imine [Scheme 1, Eq. (a)][3] or, more recently, by the reaction of organoboranes with hydroxylamine-*O*-sulfonic acid [Scheme 1, Eq (b)].[1]



Scheme 1. Synthesis of diarylamines.

As part of a program directed towards the preparation and applications of new mono- and diamines to the design of new transition metal ligands,[4] we have been interested in developing a rapid and simple access to these compounds. Starting from previously described gold(III)[5] mediated Friedel–Crafts-type reactions[6] and our own experience on gold(III) induced propargylic substitution,[7] we have been exploring the possibility of achieving the direct amination of the corresponding alcohols **1** [Scheme 1, Eq. (c)].

Thus, we began our investigations with benzhydryl alcohol (**1a**; $Ar^1 = Ar^2 = Ph$) in the presence of tosylamine ($TsNH_2$) (Scheme 2). Gratifyingly in the presence of $NaAuCl_4 \cdot 2H_2O$ the amination product **2** was obtained in 95% yield. Due to a complete conversion of the starting material combined with the absence of side-products, analytically pure **2** was easily isolated by simple filtration over a silica pad. In the absence of tosylamine (Table 1, entry 2), the corresponding ether **3** was obtained in quantitative yield. Other salts (Table 1, entries 3–8) were then tested. As previously observed in other examples,[7,8] the less Lewis acidic gold(I) complex was inefficient in this reaction (entry 3, Table 1). With a Ti(III)-base catalyst (entry 4, Table 1), only traces of ether **3** could be detected by ^1H NMR in the crude mixture (entry 4). Other Lewis acids were also tested. Ti(IV) afforded the expected amination product **2** in a poor 37% yield (entry 5), In(III)[9] and $BF_3 \cdot OEt_2$ were equally efficient leading to **2** in 87 and 85% yields, respectively (entries 6 and 7). Slightly lower yields were ob-



Scheme 2. Catalytic amination of diphenylmethanol.

Table 1. Catalyzed amination of benzylic alcohols.

Entry	Cat (5%)	Recovered **1a**	Yield **2** [%]	Yield **3** [%]
1	$NaAuCl_4$	-	95	-
2	$NaAuCl_4$[a]	-	-	Quant.
3	Ph_3PAuCl	100	-	-
4	$TiCl_3$	>95	-	Traces
5	$TiCl_4$	-	37	-[b]
6	$InCl_3$	Traces	87	-
7	BF_3-OEt_2	Traces	85	Traces
8	PTSA	5	31	50

[a] Reaction carried out without $TsNH_2$.
[b] Unidentified by-products.

tained with indium and $BF_3{\cdot}OEt_2$ compared to those obtained with $NaAuCl_4$, mainly due to the presence of traces of both starting material and ether **3** in the crude product (thus also requiring purification by flash chromatography). In addition, such behavior might be problematic with more demanding nucleophiles (vide infra). Gold(III) catalysis then seems, from both chemical (complete conversion, high yield) and practical (isolation by filtration) considerations, to be the catalyst of choice in these reactions.[10]

A recent publication by Sanz and Rodriguez,[11] describing propargylic substitution in the presence of PTSA,[12] prompted us to test these conditions on our model reaction (entry 8). Again conversion was almost complete (5% starting material recovered) and the expected product **2** was obtained along with ether **3** in 31 and 50% yields, respectively, thus precluding the use of these reaction conditions.

We next turned our attention to the introduction of other nitrogen nucleophiles (Table 2). Such nitrogen nucleophiles can be roughly divided in three main classes: (1) basic nitrogen nucleophiles that may interact with and/or poison the catalyst leading to the recovery of the starting material (Table 2, entries 2–4, 14 and 15); (2) non-basic and poor nucleophiles where the aryl ether **3** is obtained as the major product (Table 2, entries 5–13); (3) moderately-basic and better nucleophiles such as 4-nitroaniline, $TMSN_3$ and

Table 2. Amination of benzhydryl alcohol **1a**.[a]

Entry	Amine	Catalyst	Conditions	Product No. (Yield %)	**3**
1	$PhSO_2NH_2$	$NaAuCl_4$	DCM, rt, 16 h	**4** (95)	-
2	BnNHBoc	$NaAuCl_4$	DCM, rt ,16 h	RSM[b]	
3	BnNHBoc	$NaAuCl_4$	MeCN, 60°C, 72 h	RSM[b]	
4	BnNHBoc	$NaAuCl_4$	DCM, reflux, 16 h	RSM[b]	
5	BnNHBoc	$InCl_3$	DCM, rt, 16 h	-	94
6	BnNHTos	$NaAuCl_4$	DCM, rt, 16 h	**5** (10)	80
7	BnNHTos[c]	$NaAuCl_4$	DCM, rt, 72 h	**5** (8)	78
8	BnNHTos	$NaAuCl_4$	110°C, MW,[g] 1 h	-	Quant
9	BnNHTos	$InCl_3$	DCM, rt, 16 h	-	91
10	Phtalimide	$NaAuCl_4$	DCM, rt, 16 h	-	90
11	Phtalimide	$InCl_3$	DCM, rt, 16 h	-	89
12	$BnNHCOCF_3$	$NaAuCl_4$	DCM, rt, 16 h	-	85[c]
13	Potassium phthalimidate	$NaAuCl_4$	DCM, rt, 16 h	RSM[b]	
14	Bn_2NH	$NaAuCl_4$	DCM, rt, 16 h	RSM[b]	
15	Bn_2NH	$InCl_3$	DCM, rt, 16 h	RSM[b]	
16	4-Nitroaniline	$NaAuCl_4$	DCM, rt, 16 h	**6** (91)	-
17	4-Nitroaniline	$InCl_3$	DCM, rt, 16 h	**6** (51)[f]	-
18	4-Nitroaniline	$BF_3{\cdot}OEt_2$	DCM, rt, 16 h	**6** (86)	10
19	2,4-DNPH	$NaAuCl_4$	DCM, rt, 16 h	**7** (60)	15
20	2,4-DNPH	$InCl_3$	DCM, rt, 16 h	-	Quant
21	2,4-DNPH	$BF_3{\cdot}OEt_2$	DCM, rt, 16 h	**7** (<5)[e]	-
22	$TMSN_3$	$NaAuCl_4$	DCM, rt, 16 h	**8** (93)	-
23	$TMSN_3$	$InCl_3$	DCM, rt, 16 h	**8** (64)	Traces
24	$TMSN_3$	$BF_3{\cdot}OEt_2$	DCM, rt, 16 h	**8** (84)	6

[a] Reaction of benzhydryl alcohol **1a** with the amine (2 equivs.) in the presence of 5% of catalyst in CH_2Cl_2 (0.2 M) at room temperature.
[b] The starting diphenylmethanol material was recovered.
[c] 10% of the starting diphenylmethanol was also recovered.
[d] Carried out with 10 equivs. of amine and mixture 10-fold diluted.
[e] Identified by ^1H NMR and mass analysis but obtained as a mixture with unidentified by-products.
[f] 44% of the starting diphenylmethanol was also recovered.
[g] Closed vessel, $P = 10$ bar in CEM Discover device.

2,4-DNPH allowing the formation of the benzylic C–N bond (Table 2, entries 16–24).

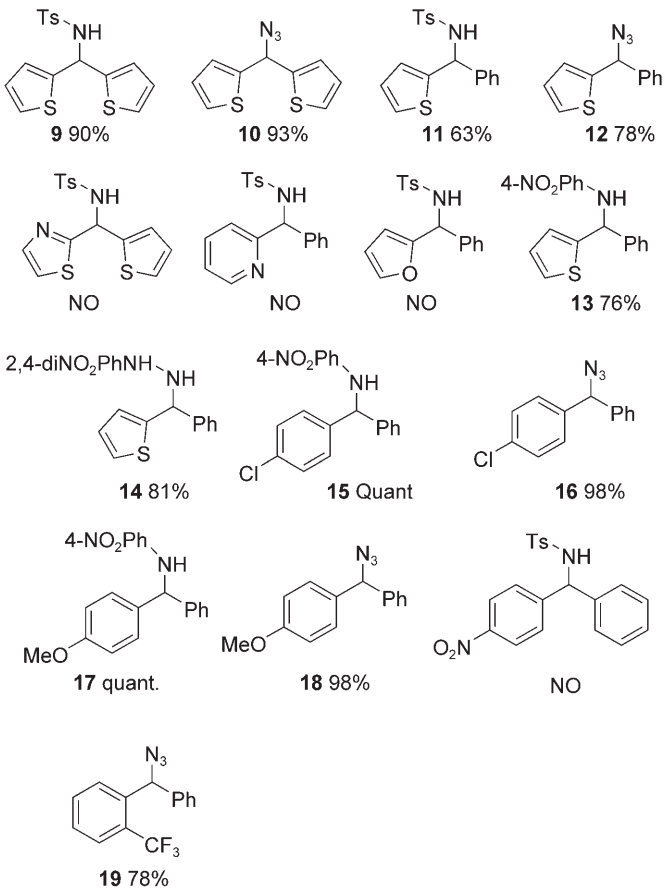
The former class of amines, *N*-benzyl-*N*-bocamine, potassium phthalimide and *N*,*N*-dibenzylamine (entries 2–4 and 13–15), led to a complete recovery of the starting material. No traces of ether **3** could be detected, clearly indicating the lack of catalytic activity. Unexpectedly, moving from Au(III) to In(III) in the reaction between *N*-benzyl-*N*-bocamine and benzhydryl alcohol leads to the exclusive formation of ether **3** (entry 5), evidencing the complementarity of both catalytic systems. In contrast to these results, the use of phthalimide and *N*-benzyltrifluoromethylacetamide under both gold and indium catalysis showed catalytic activity (entries 10–12). Indeed, complete conversions of the starting material were observed, however leading to ether **3** as the sole product in high yields.

Concerning the $NaAuCl_4$-catalyzed reactions of *N*-benzyl-*N*-tosylamine with benzhydryl alcohol (entries 6–9), it is worth noting that the expected amination product **5** was obtained in low yield. Attempts to increase the amount of compound **5** failed even by using prolonged heating times or microwave activation where ether **3** is obtained quantitatively (entry 8).

Finally, several other N nucleophiles including 2,4-dinitrophenylhydrazine, 4-nitroaniline and trimethylsilyl azide (entries 16–24) were successfully tested, allowing the introduction of hydrazine- and aniline-based as well as azido moieties at the benzylic position.

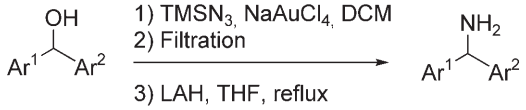
Among the nucleophiles, $TMSN_3$ (Table 2, entries 22–24) is particularly attractive since the azido group can be reduced leading to the free amino group (*vide infra*). As previously observed with $TsNH_2$ (see Table 1), under identical reaction conditions and after complete conversion of the starting material as monitored by TLC, comparisons in various examples (compare entries 16 with 17/18, 19 with 20/21 and 22 with 23/24), clearly evidenced the superiority of gold(III) over indium(III) and $BF_3{\cdot}OEt_2$ in these carbon-nitrogen bond formation reactions.

Scheme 3 contains the results of an aromatic substitution survey for this reaction. Compounds **9–14**, based on one or two π-excessive thiophene units, were efficiently prepared in 63 to 93% yields. As expected, no reaction takes place when moving from thiophene to usual transition metal ligands such as pyridine. Indeed, the lack of reactivity of pyridine-based substrates might be explained either by possible complexation of pyridine by gold or by a lesser stabilization of the electrophilic intermediate due to the presence of an electron-deficient pyridine heterocycle. Substrates involving the basic thiazolyl and the acid-sensitive furyl residues only lead to degradation.



Scheme 3. Gold-catalyzed amination on various aromatic and heteroaromatic substrates. NO: not obtained.

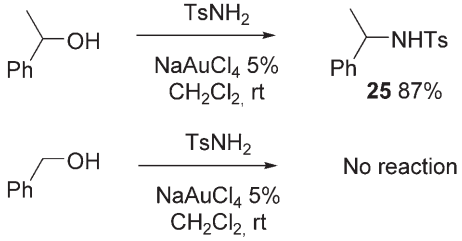
Starting from benzhydryl alcohol as reference, we next examined the influence of the substitution by electron-withdrawing or electron-donating groups on the formation of the carbon-nitrogen bond. As expected, poor results were obtained in the presence of electron-withdrawing groups. Indeed, as shown in Scheme 3, the presence of a strong electron-withdrawing group, such as the nitro group, precludes the formation of C–N bond. In this case neither *N*-tosyl-1-(4-nitrophenyl)-1-phenylmethylamine nor the corresponding ether could be obtained. The influence of a mild electron-withdrawing group, such as CF_3, was next studied. Under classical conditions (16 h, room temperature), a poor conversion (20%) was observed. However, increasing the reaction time to 48 h at room temperature led to 90% conversion, indicating that mild electron-withdrawing groups even when arranged in an *ortho* fashion are tolerated. *N*-Tosyl-1-(2-trifluoromethylphenyl)-1-phenylmethylamine (**19**) was isolated in 78% yield. In sharp contrast with these results, donating groups favored the formation of the carbon-nitrogen bond as illustrated in the efficient synthesis of compounds **15–18** which were isolated in high to quantitative yields.



Scheme 4. Direct access to diarylmethylamines.

Table 3. Access to diarylmethylamines.

Entry	Ar^1	Ar^2	Compound	Yield (%) Two steps
1	Phenyl	Phenyl	**20**	86
2	Thienyl	Phenyl	**21**	55
3	Thienyl	Thienyl	**22**	49
4	4-Cl-C_6H_4	Phenyl	**23**	54
5	2-CF_3-C_6H_4	Phenyl	**24**	49



Scheme 5. Amination of alkylarylmethyl alcohols.

A direct access to di(hetero)arylmethylamines is also valuable in the context of the synthesis of bioactive products. Attempts to develop a one-pot access to di(hetero)arylmethylamines involving $TMSN_3$ amination followed by *in situ* reduction of the azido group led to disappointing results. However, we found that filtration of gold salts over a silica pad after the amination step, followed by the reduction of the azido intermediate using LAH, afforded the desired methylamines. Thus, various diarylmethylamines have been successfully prepared using LAH as the reducing agent in 49 to 82% yields (Scheme 4) and the results are gathered in Table 3.

Finally, the reaction was tested on other benzylic substrates. When 1-phenylethanol was reacted with tosylamine in the presence of $NaAuCl_4$, the desired amination product **25** was obtained in 87% yield. In contrast, benzyl alcohol was recovered unchanged even after prolonged reactions times (Scheme 5).

The formation of the carbon-nitrogen bond is assumed to proceed through an overall S_N1-like mechanism including the generation of a benzylic cation as reactive intermediate, in a first step, and subsequent nucleophilic attack in a second step. This kind of mechanism and intermediate are consistent with the influence of the electronic effects of the substituents as we observed and mechanisms suggested by other related studies.[6]

In conclusion, we have developed an efficient procedure to obtain benzylic amines starting from the corresponding alcohols under mild and environmentally benign catalytic conditions. This methodology tolerates various aromatic or heterocyclic substrates bearing electron-donating but also mild electron-withdrawing groups. Several catalytic systems were compared evidencing the higher selectivity of Au(III) over others. Among the nitrogen-based nucleophiles used, $TMSN_3$ proved useful as intermediate in the amination-reduction sequence leading to the direct preparation of diarylmethylamines.

Experimental Section

General Remarks

Reactions were carried out in round-bottom flasks equipped with a magnetic stirring bar and capped with a septum. Dichloromethane was distilled over CaH_2 and run over neutral alumina to remove any residual alcohol. TLC analyses were performed on Merck silica gel 60 F_{254} TLC plates. FT-IR spectra were recorded with a Perkin–Elmer Spectrum BX spectrometer and ^1H and ^{13}C NMR spectra were recorded with Bruker 200, Avance-300 and 500 spectrometers and referenced to $CDCl_3$ unless otherwise noted. Mass spectra were obtained from the mass spectrometry facilities operated by the Institut de Chimie des Substances Naturelles.

General Procedure for Gold-Catalyzed Amination of Benzylic Alcohols

To a solution of the benzylic alcohol (1 equiv.) in dichloromethane (0.2 M) was added the nucleophile (3 equivs.) followed by the catalyst (5 mol%). The reaction mixture was stirred at room temperature for 16 h. Upon completion, as monitored by ^1H NMR, the mixture was concentrated under vacuum and loaded on to a silica gel column and chomatographed with an appropriate mixture of solvents to give the amination products described below.

***N*-Tosyl-1,1′-diphenylmethylamine (2):** $R_f = 0.38$ (20% AcOEt in cyclohexane); mp 157 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.38$ (s, 3H), 5.24 (d, 1H, $J = 7.1$ Hz), 5.58 (d, 1H, $J = 7.1$ Hz), 7.09–7.23 (m, 12H), 7.57 (d, 2H, $J = 8.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.4$, 61.3, 127.2 (2C), 127.3 (4C), 127.5 (2C), 128.5 (4C), 129.3 (2C), 137.3, 140.5 (2C), 143.2; IR (KBr): $\nu = 3242$, 2656, 2358, 1594, 1491, 1454, 1317, 1161, 1095, 1054, 1021, 938, 818, 698, 674 cm^{-1}; HR-MS (ESI): $m/z =$ 360.1036, calcd. for $[M+Na]^+$: 360.1034; anal. calcd.: C 71.19, H 5.68; found: C 71.07, H 5.75.

General Procedure for Reduction of Methyl Azides

To a stirring solution of diarylazidomethane (0.141 mmol) in 7.0 mL of dry THF were added 14 mg of lithium aluminium hydride (0.351 mmol, 2.5 equivs.). The solution was refluxed for 16 h and the reaction monitored by TLC until disappearance of the starting azide. The yellow solution was allowed to cool to room temperature. The reaction mixture was di-

luted with 15 mL of ethyl acetate, quenched with 5 mL of 1 M HCl and the phases were separated. The aqueous phase was basified with 10 mL of a 1 M solution of NaOH, and the organic phase was extracted with 3×20 mL of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash chromatography.

1-Phenyl-1′-(2-fluorophenyl)-methylamine (24): $R_f = 0.27$ (30% EtOAc in heptane); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 1.87 (bs, 2H), 5.70 (s, 1H), 7.23–7.57 (m, 8H), 7.66 (d, $J =$ 8 Hz, 1H); ^{13}C-{^{1}H} NMR ($CDCl_3$, 75 MHz): $\delta = 54.1$, 115.9, 125.6, 125.7, 126.9, 127.1, 128.5, 132.5, 136.6, 144.3, 145.3; IR (neat): $\nu = 3374$, 3303, 3062, 3028, 2924, 1605, 1583, 1493, 1450, 1308, 1271, 1153, 1105, 1060, 1033, 958, 891, 798, 766, 732, 697, 658, 643 cm^{-1}; HR-MS (ESI): $m/z = 235.0723$, calcd. for $[Ph(o\text{-}CF_3\text{-}C_6H_4)CH]^+$: 235.0735; anal. calcd.: C 66.93, H 4.81; found: C 66.98, H 4.97.

Acknowledgements

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