Direct substitution of the hydroxy group with highly functionalized nitrogen nucleophiles catalyzed by Au(III)

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バージョン：

Direct substitution of the hydroxy group with highly functionalized nitrogen nucleophiles catalyzed by Au(III)†

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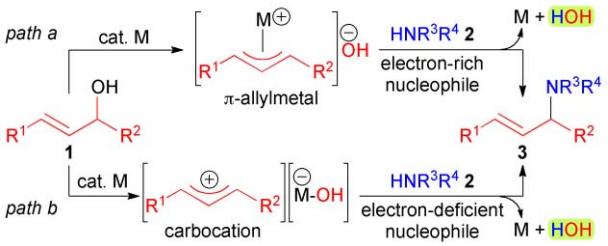
A direct catalytic substitution of various allylic and benzylic alcohols with synthetically useful, but acid-sensitive Boc, Bus, and Dios protected amine nucleophiles, which have not been well utilized for Lewis acid catalysis, with various functionalities (OTBS, OTHP, etc.) were efficiently catalyzed by 1 mol% of Au(III) under mild conditions.

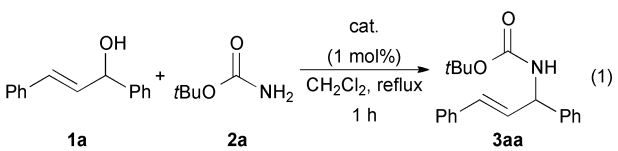
The development of a direct and reliable synthetic methodology to attain a wide variety of amine derivatives has attracted considerable attention because of their relevance as synthetic tools for various pharmaceuticals and fine chemicals. Nucleophilic substitution of allylic substrates represents one of the most powerful methods for producing allylamines.[1] From both environmental and economic points of view, the direct catalytic amination of *underivatized* allylic alcohols **1**, which forms water as the sole coproduct, is desirable (Scheme 1). Because of the poor leaving ability of the hydroxyl group, such direct reactions have been rarely explored except for several palladium-catalyzed direct aminations of **1** *via* a π-allylpalladium intermediate (*path a*).[2] We recently reported that platinum complexes bearing DPEphos or Xantphos ligand are efficient catalysts for direct amination of **1** with high monoallylation selectivity and broad substrate generality.[3] Although these reactions efficiently proceed with electron-rich amines, electron-deficient nitrogen nucleophiles are not good substrates due to their low nucleophilicity.[2e] The reaction with electron-deficient nitrogen nucleophiles was efficiently catalysed by various Lewis acids (Re,[4] Ru,[5] rare earth metals,[6] Au,[7] In,[8] Bi,[9] Fe,[10] Ag,[11] Mo,[12] Hg[13] etc.) and Brønsted acid[14] *via* a carbocation intermediate (*path b*).[15] Thus, acid-catalyzed direct amination is a counterpart of late transition metal-catalyzed amination;[16] nucleophiles of the reported acid-catalyzed reaction, however, are limited to rather stable nitrogen compounds such as 4-nitroaniline, tosylamide, methyl carbamate, and simple amides. In particular, there is almost no access to more useful but acid-sensitive nucleophiles such as *tert*-butyl carbamate.[8b,10e,12a] Here, we report that direct substitutions of allylic and benzylic alcohols with synthetically useful *tert*-butoxycarbonyl (Boc), thiophenesulfonyl,[17] *tert*-butylsulfonyl (Bus),[18] and 2-(1,3-dioxan-2-yl)ethylsulfonyl (Dios)[19] protected amine nucleophiles are efficiently catalyzed by 1 mol% of $NaAuCl_4•2H_2O$ under mild conditions (rt to 40 ˚C). Reactions with more acid-sensitive functional groups such as TBS and THP groups were achieved using dichloro(pyridine-2-carbozylato)gold (III) (**4**)[20] as a catalyst. Moreover, we found



Scheme 1 Direct catalytic amination of allylic alcohol **1**.

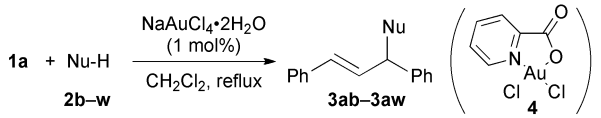
unusual positive effects of added thiophene in the gold-catalyzed direct amination reactions.

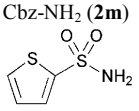
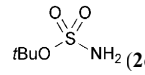
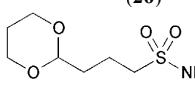
Using the protocol based on Pt-Xantphos,[3] substrate generality was not expandable to electron-deficient amines. The reaction of 1,3-diphenylprop-2-en-1-ol (**1a**) with electron-deficient Boc-amide **2a** (eq 1) using the Pt catalyst gave product **3aa** in low yield (<14%).† We are interested in the use of Au(I) and Au(III) salts,[21] which are respectively isoelectronic to Pt(0) and Pt(II). Both AuCl and $AuCl_3$ became catalysts for the reaction of **1a** with **2a** and product **3aa** was obtained in 92% and 94% yield, respectively, after optimization of the reaction conditions.† The use of $NaAuCl_4•2H_2O$,[7a,b,e,f] also gave a high yield (96%) and thus we decided to use more stable and easier to handle $NaAuCl_4•2H_2O$ as the catalyst for further studies.



Under the optimized conditions, direct amination of **1a** with various *N*-substituted Boc-amides was examined (Table 1, Entries 1–13). Benzyl, allyl, phenethyl, and carbonylmethyl substituted Boc-amides **2b–g** were good nucleophiles to give the desired products in high yield (Entries 1–6), except for the reaction with a sterically congested **2h** (R = *c*Hex) (Entry 7). Under the present reaction conditions, several functionalities such as nitrile (Entry 3), TBS ether of phenol (Entry 5), and ester (Entry 6) remained intact. We further examined the compatibility of other functional groups under the $NaAuCl_4$-catalyzed conditions (Entries 8–13). Nucleophiles with acetoxy (Entry 8) and MEM ether (Entry 9) functionalities reacted smoothly to give the product in excellent yield, whereas TBS (Entry 10) and highly acid-sensitive THP

Table 1 Direct catalytic substitution of **1a** with various *N*-nucleophile.[a]

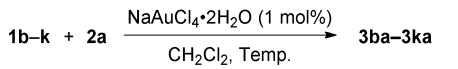


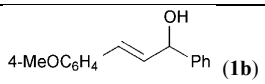
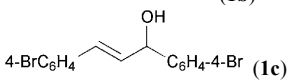
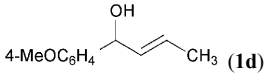
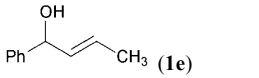
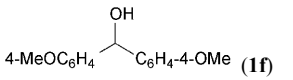
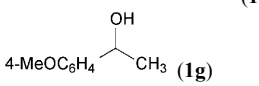
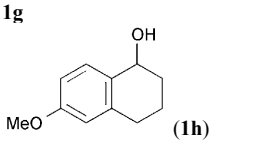
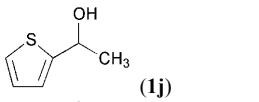
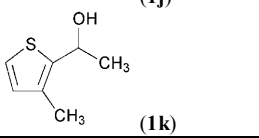
Entry	Nucleophile **2** (Nu-H)	Time (h)	Yield (%)[b]
1	Boc-NH-CH_2Ph (**2b**)	1	88
2	Boc-NH-$CH_2C_6H_4$-4-CH_3 (**2c**)	3	91
3	Boc-NH-$CH_2C_6H_4$-4-CN (**2d**)	1	92
4	Boc-NH-$CH_2CH{=}CH_2$ (**2e**)	1	86
5	Boc-NH-$CH_2CH_2C_6H_4$-4-OTBS (**2f**)	2	79
6	Boc-NH-CH_2CO_2Et (**2g**)	1	90
7[c]	Boc-NH-*c*Hex (**2h**)	24	31
8	Boc-NH-$(CH_2)_4$-OAc (**2i**)	3	93
9	Boc-NH-$(CH_2)_6$-OMEM (**2j**)	1.5	99
10	Boc-NH-$(CH_2)_6$-OTBS (**2k**)	1	50
11[d]	**2k**	7	99
12	Boc-NH-$(CH_2)_6$-OTHP (**2*l***)	1.5	44
13[d]	**2*l***	4	71
14	Cbz-NH_2 (**2m**)	1	94
15	 (**2n**)	3	81
16	 (**2o**)	5	70
17	 (**2p**)	1	95
18	Ph-NHCONH-Ph (**2q**)	1	84
19	Ph-NHCONH_2 (**2r**)	7	74
20	PhCONH_2 (**2s**)	6	>99
21	4-O_2N-C_6H_4-NH_2 (**2t**)	0.3	92
22	4-NC-C_6H_4-NH_2 (**2u**)	3	98
23	4-F_3C-C_6H_4-NH_2 (**2v**)	30	92
24	Ph-NH_2 (**2w**)	36	48

[a] Reaction conditions: **1a** (1 mmol), **2** (1.5 mmol, 1.5 equiv), $NaAuCl_4$•$2H_2O$ (0.01 mmol, 1 mol%), CH_2Cl_2 (2 mL), reflux. [b] Isolated yield. [c] Toluene (reflux) was used instead of CH_2Cl_2. [d] Au(III)-picolinate complex **4** was used instead of $NaAuCl_4$•$2H_2O$.

(Entry 12) ethers of aliphatic alcohol partially decomposed during the reactions, resulting in only moderate yield of the products. Such undesired decompositions were successfully suppressed by the use of milder Au(III)-picolinate complex **4**[20] as the catalyst, affording the products **3ak** and **3a*l*** in 99% (Entry 11) and 71% (Entry 13) yields, respectively. We next examined the reaction of **1a** with different types of nitrogen nucleophiles (Entries 14–24). The reaction with Cbz-amide **2m** afforded the corresponding product **3am** in 94% yield (Entry 14). Synthetically useful thiophenesulfonyl (Entry 15),[17] Bus (Entry 16),[18] and Dios (Entry 17)[19] amides, which are readily deprotected by Mg, TFA with anisole, and aq. TFA, respectively, to give the corresponding amines, were first utilized in the direct catalytic amination reaction. They smoothly reacted with **1a** to give the product **3an**–**ap** in 70–95% yield, leaving thienyl, *tert*-butyl, and acetal functionalities intact. When ureas **2q** (Entry 18) and **2r** (Entry 19) were used, only mono allylation occurred in both cases. Although amide **2s** was less reactive than the above nucleophiles, the desired product **2as** was obtained in >99% yield (Entry 20). Electron-deficient aniline derivatives **2t**–**v** were also good nucleophiles (Entries 21–23). Electron-rich aniline (**2w**) is a challenging substrate for the acid-catalyzed direct substitution reaction with a few excellent exceptions.[4a] Under the present conditions, the desired product **3aw** was obtained, though the yield was moderate (Entry 24).

Table 2 Direct catalytic substitution of various alcohols with **2a**.[a]



Entry	Alcohol **1**	Temp.	Time (h)	Yield (%)[b]
1	 (**1b**)	reflux	2	96[c]
2	 (**1c**)	rt	8	94
3	 (**1d**)	reflux	3	77[d]
4	 (**1e**)	rt	12	44[d]
5[e]	**1e**	rt	12	75[d]
6	 (**1f**)	reflux	0.3	99
7	 (**1g**)	reflux	19	66
8[e]	**1g**	rt	3	>99
9	 (**1h**)	reflux	5	88
10	Ph_3C-OH (**1i**)	reflux	10	80
11[e]	**1i**	reflux	4	91
12	 (**1j**)	rt	24	80
13	 (**1k**)	rt	24	85

[a] Reaction conditions: **1a** (1 mmol), **2** (1.5 mmol, 1.5 equiv), $NaAuCl_4$•$2H_2O$ (0.01 mmol, 1 mol%), CH_2Cl_2 (2 mL), reflux. [b] Isolated yield. [c] A mixture of regioisomers (ca. 1:1) was obtained. [d] α-Methyl cinnamylamine derivative was obtained. [e] The reaction was performed with thiophene (**5**, 1 mmol, 1.0 equiv).

The scope of the reaction with respect to alcohols **1** was further examined (Table 2). The reactions of 1,3-diphenyl substituted allylic alcohols with both electron-donating (Entry 1) and electron-withdrawing (Entry 2) groups proceeded smoothly to afford products **3ba** and **3ca** in 96% and 94% yields, respectively. The reactivity of alkyl substituted allylic alcohols **1d** (Entry 3) and **1e** (Entry 4) was lower than that of **1a**–**c** due to the formation of less reactive α-methyl cinnamyl alcohols, and S_N2' products (cinnamylamine derivatives) were obtained regioselectively. Benzylic alcohols **1f** (Entry 6), **1h** (Entry 9), and **1i** (Entry 10) smoothly reacted with **2a**, though related benzylic alcohol **1g** (Entry 7) was less reactive. This gold catalysis was also applicable to thiophenemethanol derivatives **1j** (Entry 12) and **1k** (Entry 13), affording the corresponding products in high yield. Because the thiophene unit is rarely utilized in gold catalysis[7b,21] due to the high affinity of gold to soft sulfur atom, the high yields

using **2n** (Table 1), **1j**, and **1k** were interesting. Contrary to our expectation, thiophene (**5**) had positive effects on the gold-catalysis and the above-mentioned unsatisfactory results using **1e** and **1g** were greatly improved by the addition of 1 equiv of **5**, giving products **3ea** (Entry 5) and **3ga** (Entry 8) in 75% and >99% yields, respectively. Notably, the addition of **5** prevented the undesired isomerization of **1e** to cinnamyl alcohol derivatives. Positive effects of added **5** were also observed in the reaction of trityl alcohol (**1i**) (Entry 11). Finally, crossover experiments indicated that the reaction is reversible under the reaction conditions.[9b]† The reaction using optically active **1h** gave only the racemic product **3ha**, suggesting carbocation intermediate.†

In summary, we developed a direct catalytic substitution of various allylic and benzylic alcohols with synthetically useful, but acid-sensitive Boc, Bus, and Dios-protected amine nucleophiles, which have not been well utilized for Lewis acid catalysis, promoted by 1 mol% of $NaAuCl_4 \cdot 2H_2O$ under mild conditions (rt to 40 ˚C). The use of a milder Au(III)-picolinate complex as a catalyst enables reactions with more acid-sensitive functional groups, such as TBS and THP groups. Furthermore, a thiophene unit showed unusual positive effects on the present gold catalysis and improved the yield of less reactive substrates.

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Notes and references

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† Electronic Supplementary Information (ESI) available: experimental procedures, characterization of the products, and other detailed results. See DOI: 10.1039/b000000x/

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