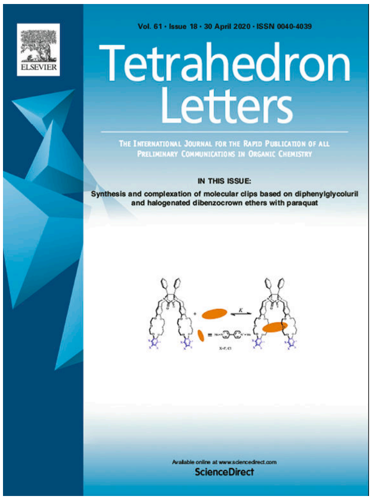

Intramolecular activation of imidate with cationic gold(I) catalyst: a new benzylation reaction of alcohols

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Graphical Abstract

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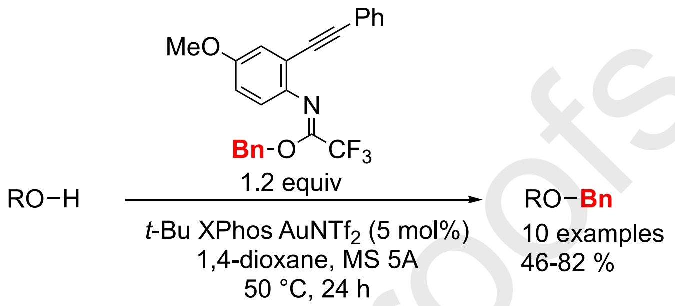

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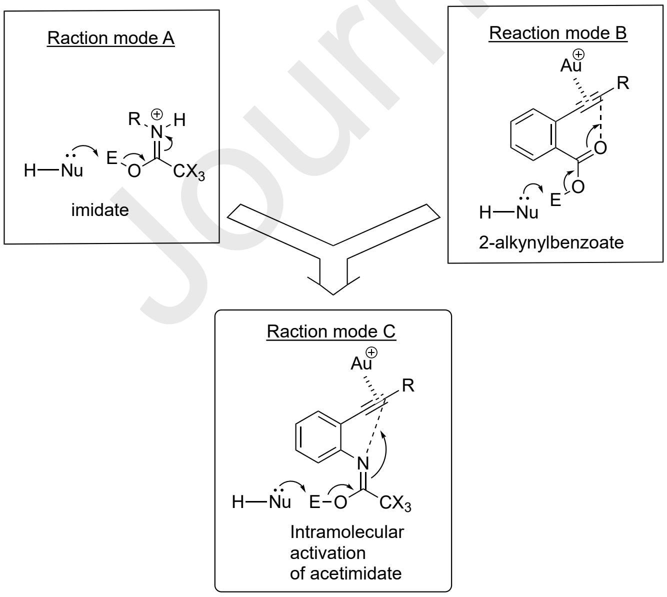
ABSTRACT

Benzylation of alcohols with benzyl (*Z*)-2,2,2-trifluoro-*N*-(2-alkynylphenyl)acetimidates **5a-f** in the presence of a cationic gold(I) catalyst was investigated. Reagent **5f** was the most effective, affording benzyl ethers in good yields. Our results indicate that these gold(I)-activated imidates are effective leaving groups.

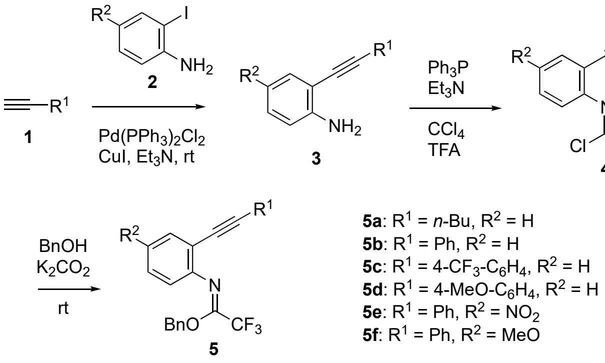
Leaving groups, such as halogens, sulfonates, etc., play vital roles in acid-base reactions, elimination reactions and nucleophilic substitution reactions.[1] Among them, imidates are activated by coordination of a proton or a hard Lewis acid onto the imino nitrogen and are typically used for benzylation and 4-methoxybenzylation under acidic conditions (Scheme 1, reaction mode A).[2-4] On the other hand, 2-alkynylbenzoates are leaving groups that are activated intramolecularly by addition reaction of carbonyl oxygen to the alkyne moiety activated by coordination with a soft Lewis acid, gold(I) (reaction mode B).[5] These two types of leaving groups have been successfully applied to glycosylation reactions.[6] With these two reaction modes in mind, we designed imidates that can be activated by a soft gold(I) catalyst in a mode (reaction mode C) that is a hybrid of reaction modes A and B. Thus, an *N*-(2-alkynyphenyl)acetimidate could undergo coordination with gold(I) catalyst to make the alkyne moiety highly electrophilic, and then the imino moiety would undergo addition reaction to the alkyne moiety to induce electrophilic activation of the imidate moiety. To examine the feasibility of this strategy, we focused initially on benzylation.



Scheme 1. Reaction modes of imidates (A), 2-alkynyl benzoates (B) and the hybrid (C).

First, we synthesized the new imidates **5a-f** (Scheme 2). Sonogashira reaction of terminal alkynes **1** with 2-iodoanilines **2** gave 2-alkynyl anilines **3a-f**, which were exposed to trifluoroacetic acid under appropriate conditions for dehydration and chlorination[7] to afford chloroimines **4a-f**. Finally, **4a-f** were treated with benzyl alcohol in the presence of K_2CO_3[8] as a base to give *O*-benzyl imidates **5a-f**.[9]

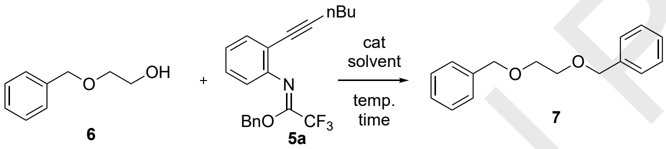
With imidates **5a-f** in hand, appropriate reaction conditions were next examined by employing alcohol **6** and reagent **5a** (Table 1). When alcohol **6** (1.0 equiv) was treated with **5a** (1.2 equiv) and Ph_3PAuCl (5 mol%) in $(CH_2Cl)_2$ at room temperature, no reaction occurred (entry 1). Use of elevated temperature resulted in formation of only a trace of **7** (entries 2 and 3).



Scheme 2. Preparation of imidates **5a**-**f**.

Cationic gold(I) species generated *in situ* by adding AgOTf exhibited higher reactivity. Thus, **7** was not formed at room temperature (entry 4), while the reactions at 50 °C and 80 °C gave **7** in 42% and 50% yields, respectively (entries 5 and 6). Use of 1,4-dioxane as a solvent improved the reactivity, and the reaction proceeded even at room temperature to give **7** in 43% yield although a prolonged reaction time (72 h) was required (entry 7).[10] The reaction was accelerated at higher temperatures, and at 80 °C it was completed within 1 h to afford **7** in 59% yield (entries 8 and 9). Next, other cationic gold(I) catalysts, JohnPhos AuNTf$_2$ and t-Bu XPhos AuNTf$_2$ with MS 5A, were examined. Comparison of JohnPhos AuNTf$_2$ with t-Bu XPhos AuNTf$_2$ **7** in 64% yield (entries 10-12).

Table 1. Gold(I)-catalyzed benzylation of 2-benzyloxyethanol (**6**) using reagent **5a**.



Entry	Conditions	Yield %
1	Ph$_3$PAuCl (5 mol%), (CH$_2$Cl)$_2$, rt, 24 h	0
2	Ph$_3$PAuCl (5 mol%), (CH$_2$Cl)$_2$, 50 °C, 72 h	2
3	Ph$_3$PAuCl (5 mol%), (CH$_2$Cl)$_2$, 80 °C, 72 h	6
4	Ph$_3$PAuCl (5 mol%), AgOTf (5 mol%), (CH$_2$Cl)$_2$, rt, 24 h	0
5	Ph$_3$PAuCl (5 mol%), AgOTf (5 mol%), (CH$_2$Cl)$_2$, 50 °C, 48 h	42
6	Ph$_3$PAuCl (5 mol%), AgOTf (5 mol%), (CH$_2$Cl)$_2$, 80 °C, 0.5 h	50
7	Ph$_3$PAuCl (5 mol%), AgOTf (5 mol%), 1,4-dioxane, rt, 72 h	43
8	Ph$_3$PAuCl (5 mol%), AgOTf (5 mol%), 1,4-dioxane, 50 °C, 24 h	57
9	Ph$_3$PAuCl (5 mol%), AgOTf (5 mol%), 1,4-dioxane, 80 °C, 1 h	59
10	JohnPhos AuNTf$_2$ (5 mol%),[a] 1,4-dioxane, MS 5A, rt, 120 h	30
11	JohnPhos AuNTf$_2$ (5 mol%), 1,4-dioxane, MS 5A, 50 °C, 48 h	58
12	t-Bu XPhos AuNTf$_2$ (5 mol%),[b] 1,4-dioxane, MS 5A, 50 °C, 21 h	64

[a] JohnPhos: 2-(Di-*tert*-butylphosphino)biphenyl

[b] t-Bu XPhos: 2-Di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl

With the catalyst and solvent thus identified, we next examined the other reagents **5b-f** (Table 2). A change of the acetylenic terminal group R^1 from n-butyl (**5a**) to phenyl (**5b**) improved the yield to 72% (Table 1, entry 12 vs Table 2, entry 1), whereas **5c** (R^1 = 4-CF$_3$-C$_6$H$_4$) and **5d** (R^1 = 4-MeO-C$_6$H$_4$) were less effective (entries 2 and 3). As for the R^2 group in the aromatic moiety of reagent **5**, an electron-donating methoxy group was more efficient than an electron-deficient nitro group (entries 4 and 5). Thus, reagent **5f** efficiently benzylated alcohol **6** in the presence of t-Bu XPhos AuNTf$_2$ and MS 5A in 1,4-dioxane to provide product **7** in 82% yield (entry 5).

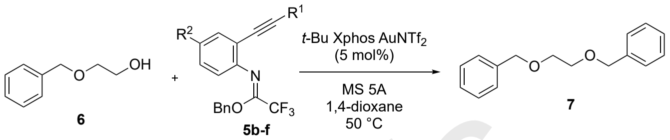
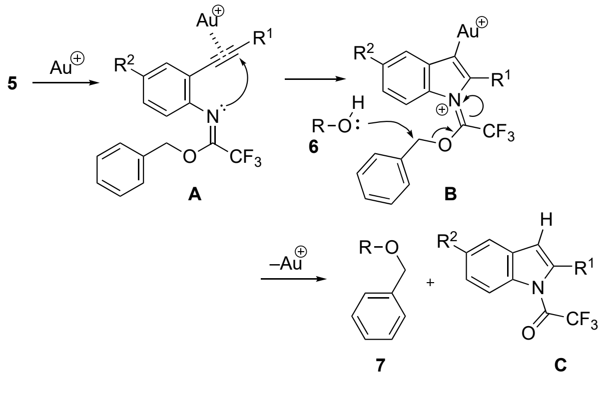


Table 2. Gold(I)-catalyzed benzylation of **6** using **5b-f**.

Entry	Imidate **5**	Time h	Yield %
1	**5b**, R^1 = Ph, R^2 = H	42	72
2	**5c**, R^1= 4-CF$_3$-C$_6$H$_4$, R^2 = H	53	42
3	**5d**, R^1= 4-MeO-C$_6$H$_4$, R^2 = H	16	58
4	**5e**, R^1= Ph, R^2 = NO$_2$	27	10
5	**5f**, R^1= Ph, R^2 = MeO	25	82

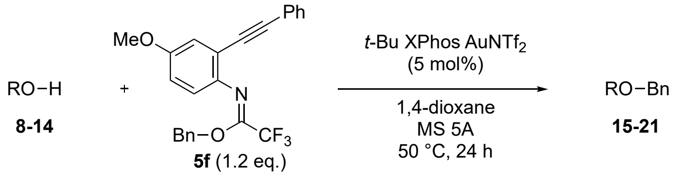
The present gold-catalyzed benzylation is considered to involve the highly reactive indolenium intermediate **B** (Scheme 3). Thus, the gold(I) catalyst coordinates with the acetylene moiety of reagent **5** to form **A**, and then 5-endo-dig cyclization occurs by attack of nitrogen of the imidate moiety on the activated acetylene moiety to give highly activated imidate **B**. Alcohol **6** reacts at the electrophilic benzyl position of **B** and proton transfer takes place to afford **7** and N-acyl indole **C**. The phenyl group as R^1 may facilitate coordination of the cationic gold(I) catalyst, while the methoxy group as R^2 would enhance the nucleophilicity of the imino nitrogen.

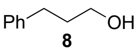
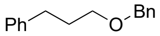
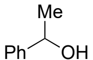
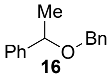
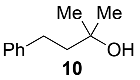
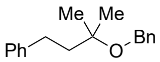
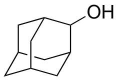
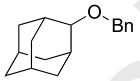
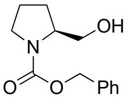
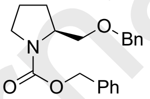
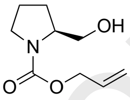
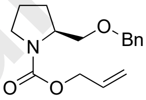
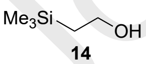
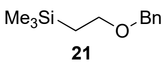


Scheme 3. Plausible mechanism of gold(I)-catalyzed benzylation of alcohol **6** with imidate **5**.

conducted gold(I)-catalyzed benzylation of various alcohols **8-14** (Table 3). Primary (entry 1), secondary (entry 2) and tertiary (entry 3) alcohols **8-10** were benzylated to give **15-17** in 59%, 59% and 46% yields, respectively. 2-Adamantyl alcohol (**11**), a highly hindered secondary alcohol, also reacted under these conditions to afford **18** in 51% yield (entry 4). Carbamates were tolerated, and carbamate-protected amino alcohols **12** and **13** provided benzylated compounds **19** and **20**, respectively, each in 66% yield (entries 5 and 6). β-Silyl alcohol is known to be unstable under acidic conditions because of Peterson elimination, and therefore 2-(trimethylsilyl)ethanol (**14**) cannot be benzylated by acid-catalyzed benzylation with trichloroacetoimidate.[11] In contrast, alcohol **14** underwent benzylation with reagent **5f** to provide **21** in a satisfactory yield (74%) (entry 7).[12]

Table 3. Gold(I)-catalyzed benzylation of various alcohols **8-14** using reagent **5f** and *t*-Bu Xphos $AuNTf_2$.[a]



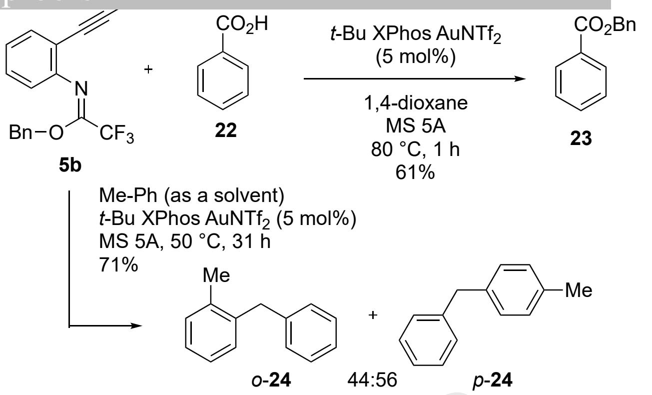
Entry	Alcohol	Product	Yield %
1	 **8**	 **15**	59
2	 **9**	 **16**	59
3	 **10**	 **17**	46
4[b]	 **11**	 **18**	51
5[b]	 **12**	 **19**	66
6[c]	 **13**	 **20**	66
7	 **14**	 **21**	74

[a] Unless otherwise specified, reactions were conducted by using **5f** (1.2 equiv) and *t*-Bu XPhos $AuNTf_2$ (5 mol%) at 50 °C for 24 h.

[b] Reagent **5f** (1.5 equiv) and *t*-Bu XPhos $AuNTf_2$ (6 mol%) were used at 80 °C for 4 h.

[c] Reagent **5f** (1.8 equiv) and *t*-Bu XPhos $AuNTf_2$ (7 mol%) were used at 80 °C for 5 h.

Finally, several other reactions were examined (Scheme 4). Benzoic acid (**22**) was treated with reagent **5b** in the presence of a catalytic amount of *t*-Bu XPhos $AuNTf_2$ and MS 5A in 1,4-dioxane to give benzyl benzoate (**23**) in 61% yield.[13] Reagent **5b**, on exposure to *t*-Bu XPhos $AuNTf_2$ in toluene, underwent Friedel-Crafts reaction with toluene to afford a 44:56 mixture of *o*-**24** and *p*-**24** in 71% yield, indicating the generation of benzyl cation species.



Scheme 4. Ester formation of **22** and Friedel–Crafts reaction with toluene.

In conclusion, we show that a new type of imidate derived from 2-alkynylaniline can be activated by cationic gold(I) catalyst, and can readily benzylate various alcohols. In other words, these gold(I)-activated imidates are effective leaving groups. Further applications of these leaving groups to other cationic reactions, for example glycosylation, are currently under investigation.

Acknowledgments

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12. Kunishima and co-workers also succeeded in benzylation of alcohol **14** under mild acidic conditions; see ref. 4d.
13. The requirement of higher temperature of the reaction of carboxylic acid **22** is probably due to the lower nucleophilicity compared to an alcohol.

Supplementary Material

Experimental details, ^{1}H and ^{13}C NMR spectra of all new compounds are available in the Supplementary Material, at http://dx.doi.org/10.1016/j.tetlet.