Communication to the Editor

Gold-Catalyzed Benzylic Azidation of Phthalans and Isochromans and Subsequent $FeCl_3$-Catalyzed Nucleophilic Substitutions

Shota Asai,[a] Yuki Yabe,[a] Ryota Goto,[a] Saori Nagata,[a] Yasunari Monguchi,[a] Yasuyuki Kita,[b] Hironao Sajiki,*[,a] and Yoshinari Sawama*[,a]

[a] *Gifu Pharmaceutical University; 1–25–4 Daigaku-nishi, Gifu 501–1196, Japan: and* [b] *College of Pharmaceutical Sciences, Ritsumeikan University; 1–1–1 Nojihigashi, Kusatsu, Shiga 525–8577, Japan.*

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The benzylic positions of the phthalan and isochroman derivatives (1) as benzene-fused cyclic ethers effectively underwent gold-catalyzed direct azidation using trimethylsilylazide ($TMSN_3$) to give the corresponding 1-azidated products (2) possessing the *N*,*O*-acetal partial structure. The azido group of the *N*,*O*-acetal behaved as a leaving group in the presence of catalytic iron(III) chloride, and 1-aryl or allyl phthalan and isochroman derivatives were obtained by nucleophilic arylation or allylation, respectively. Meanwhile, a double nucleophilic substitution toward the 1-azidated products (2) occurred at the 1-position using indole derivatives as a nucleophile accompanied by elimination of the azido group and subsequent ring opening of the cyclic ether nucleus produced the bisindolylarylmethane derivatives.

Key words azidation; gold catalyst; phthalan; isochroman; iron-catalyzed nucleophilic substitution

Phthalan[1–3] and isochroman[4–8] derivatives are pharmaceutically useful and also utilized as reaction precursors to construct various frameworks.[9–13] We have continuously investigated the iron[14–20]- or gold[21–23]-catalyzed activation at the benzylic position of various skeletons accompanied by the benzylic C–O bond cleavage. During these investigations, the benzylic position of phthalan (**1**; n=1) as a benzene fused cyclic ether was found to be directly azidated in the presence of a gold catalyst and trimethylsilylazide ($TMSN_3$) without the C–O bond cleavage to give the 1-azido phthalan (**2**) (Chart 1). The direct azidations at the benzylic position of phthalan and isochroman (**1**; n=2) were previously accomplished using stoichiometric iodine reagents[9–11] in the presence of azido sources, such as $TMSN_3$ and NaN_3. Although gold catalysts were used for the C–C and C–N bond formation on the benzylic position *via* C–H bond activation,[12,13] the azidation method was never reported in the literature. Azido derivatives are easily transformed into amines[24] and triazoles by the Huisgen cyclization with alkynes.[25,26] Furthermore, the nucleophilic substitution of an azido functionality as a leaving group was also reported in the literature.[27–29] In this report, we have applied 1-azido products (**2**) as key intermediates to the Lewis acid-catalyzed nucleophilic substitution to give highly functionalized phthalan and isochroman derivatives *via* the oxonium ion intermediate (**A**) generated by the chemoselective elimination of the azido group of the *N*,*O*-acetal moiety[30–33] (Chart 1). Consequently, the iron-catalyzed Friedel–Crafts arylation and allylation gave the 1-aryl/allyl phthalan and isochroman derivatives (**3**, **4**) (Chart 2), while the use of highly nucleophilic indole derivatives effectively facilitated the double substitutions *via* elimination of the azido group and the subsequent ring opening of the cyclic ether to give the bisindolylarylmethane derivatives (**5**).[34–39] The obtained product (**3**) could also be converted into the corresponding bisarylindolylmethane derivatives (**6**) by the $FeCl_3$-catalyzed ring-opening indolylation.[40–42] We now report the direct gold-catalyzed azidation of phthalan and isochroman derivatives (Chart 1) and the subsequent unique $FeCl_3$-catalyzed nucleophilic substitutions (Chart 2) to produce the various pharmaceutically useful compounds.

We first examined the catalyst and solvent efficiencies for the direct benzylic azidation of phthalan (**1a**) using $TMSN_3$ (4 eq) as an azido source at room temperature (Table 1). While the use of trivalent $FeCl_3$, $AuCl_3$ and $HAuCl_4 \cdot 3H_2O$ in CH_2Cl_2 gave only trace amounts of the desired 1-azido phthalan (**2a**) (entries 1–3), the combined use of monovalent $(Ph_3P)AuCl$ (10 mol%) and $AgSbF_6$ (10 mol%) improved the reaction efficiency to produce **2a** in 20% yield (entry 4). The solvent significantly influenced the azidation, and **2a** was obtained in 69% yield in 1,4-dioxane in the presence of $(Ph_3P)AuCl$ and $AgSbF_6$ for 5.5 h (entry 8), while CH_2Cl_2, $(CH_2Cl)_2$, benzene and toluene were less effective solvents (entries 4–7). Other combinations of the gold catalyst and silver salts, solvents and azido sources had no influence on the present azidation (see Supplementary Materials). Additionally, the reaction under oxygen atmosphere (entry 9) or using molecular sieves 4A (MS4A) to remove the contaminated H_2O derived from the reagents (entry 10) led to lower yield.

The $(Ph_3P)AuCl$-catalyzed benzylic azidation could be ap-

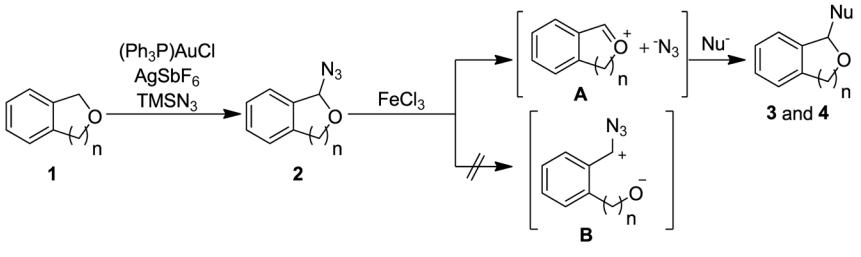


Chart 1. Catalytic Direct Azidation of Phthalans and Isochromans and the Subsequent Lewis Acid-Catalyzed Transformation

* To whom correspondence should be addressed. e-mail: sajiki@gifu-pu.ac.jp; sawama@gifu-pu.ac.jp

plied to various phthalan and isochroman derivatives (**1a**–**d**) possessing a cyclic benzyl ether backbone (Table 2). The non-substituted and 5,6-dichlorophthalans (**1a**, **b**) underwent the direct benzylic azidation to give the corresponding 1-azidated products (**2a**, **b**), respectively. Isochroman and 7-chloroiso-

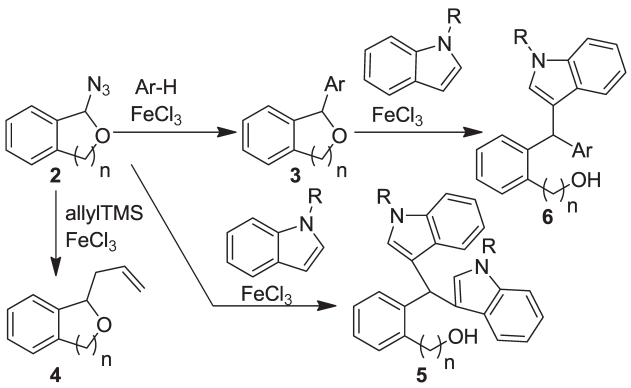
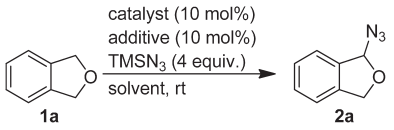


Chart 2. Transformation of Azido Compounds as Key Reaction Intermediates

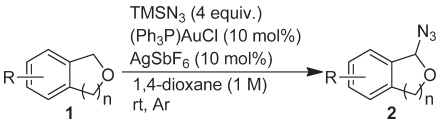
Table 1. Catalyst and Solvent Efficiencies of Direct Benzylic Azidation of Phthalan[a,b]

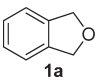
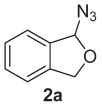
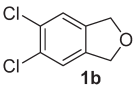
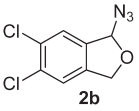
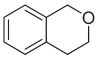
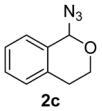
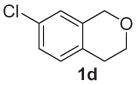
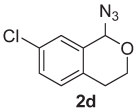
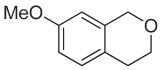
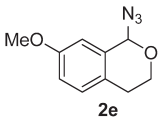


Entry	Catalyst	Additive	Solvent	Time (h)	Yield (%)
1	$FeCl_3$	—	CH_2Cl_2	8	Trace
2	$AuCl_3$	—	CH_2Cl_2	24	Trace
3	$HAuCl_4 \cdot 3H_2O$	—	CH_2Cl_2	24	Trace
4	$(Ph_3P)AuCl$	$AgSbF_6$	CH_2Cl_2	24	20
5	$(Ph_3P)AuCl$	$AgSbF_6$	$(CH_2Cl)_2$	24	28
6	$(Ph_3P)AuCl$	$AgSbF_6$	Benzene	24	48
7	$(Ph_3P)AuCl$	$AgSbF_6$	Toluene	24	44
8	$(Ph_3P)AuCl$	$AgSbF_6$	1,4-Dioxane	5.5	69
9[c]	$(Ph_3P)AuCl$	$AgSbF_6$	1,4-Dioxane	5.5	34
10[d]	$(Ph_3P)AuCl$	$AgSbF_6$	1,4-Dioxane	7	59

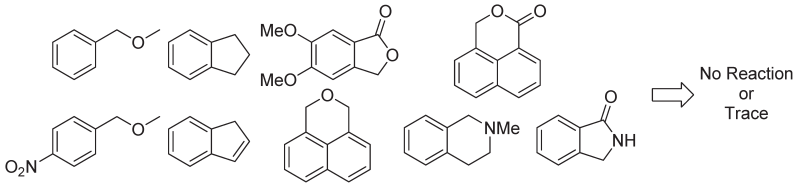
a) Conditions: catalyst (10 mol%), additive (10 mol%), $TMSN_3$ (4 eq), solvent (substrate concentration; 1 M), at rt under Ar. *b*) Optimization details using other catalysts, solvents, solvent concentrations, reaction temperatures, *etc.*, are described in the Supplementary Materials. *c*) The reaction was carried out under O_2 instead of Ar. *d*) The reaction was carried out with MS4A.

Table 2. Scope and Limitation of the Substrates[a]



Entry	Substrate	Product	Time (h)	Yield (%)
1	 **1a**	 **2a**	5.5	69
2	 **1b**	 **2b**	24	41
3	 **1c**	 **2c**	20	48
4	 **1d**	 **2d**	24	36
5	 **1e**	 **2e**	24	0

a) Inapplicable substrates under the present reaction conditions are described below.



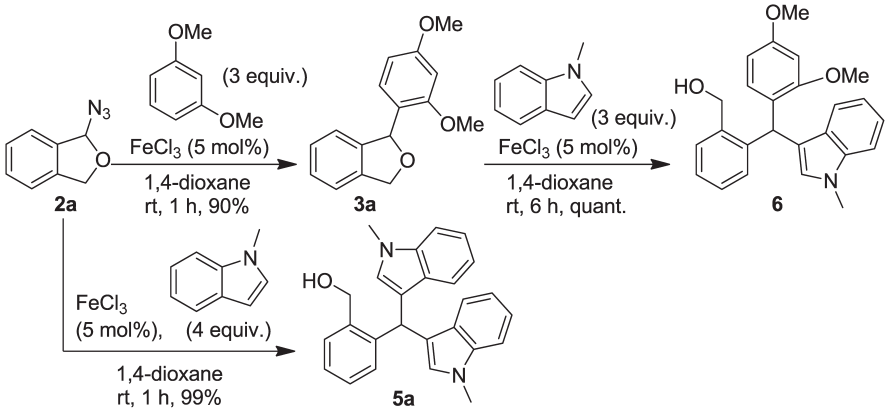


Chart 3. Chemical Modification of the Obtained 1-Azidophthalan (**2a**)

chroman were also reacted with $TMSN_3$ in the presence of $(Ph_3P)AuCl$ and $AgSbF_6$ to give the corresponding 1-azidated products (entries 3, 4) respectively, while 7-methoxyisochroman (**1e**) possessing a relatively electron-rich aromatic nucleus was hardly transformed into the desired azidated product (**2e**). Furthermore, other substrates, such as indane and indene without the corresponding benzylic oxygen atom, benzylmethylether as an acyclic substrate, phthalide derivatives a possessing lactone moiety and nitrogen-containing heterocycles, were also inadequate. Namely, the specific cyclic benzyl ether structures were essential for the present direct benzylic azidation, while the reason and reaction mechanism are still unclear.

The chemical modification of the obtained 1-azido phthalan (**2a**) was next investigated (Chart 3). The *N*,*O*-acetal moiety of **2a** was chemoselectively activated by $FeCl_3$ (5 mol%) (Chart 1) and the subsequent nucleophilic substitution using 1,3-dimethoxybenzene accompanied by elimination of the azido group gave the 1-arylated phthalan (**3a**) in 90% yield.[43] It is noteworthy that the use of *N*-methylindole as a highly nucleophilic reagent gave the bisindolylmethane (**5a**) in 99% yield *via* the elimination of the azido group and the ring opening of the cyclic benzyl ether moiety (in other words, the elimination of the benzyl ether substructure). Additionally, **3a** was also smoothly reacted with *N*-methylindole in the presence of $FeCl_3$ to produce the ring-opened bisarylindolylmethane product (**6**) in quantitative yield.

We next examined the one-pot transformation of phthalan and isochroman derivatives (**1a**–**d**) to **3**, **4** and **5** *via* the 1-azidated phthalan and isochroman derivatives (**2**) as intermediates (Table 3). As the result of the primary gold-catalyzed azidation of phthalan (**1a**) for 6 h and subsequent arylation by the stepwise addition of $FeCl_3$ and 1,3-dimethoxybenzene, 1,3,5-trimethoxybenezene or 1-methoxynaphthalene, the corresponding 1-arylated phthalans (**3a**–**c**) were obtained in good yields (entries 1–3). Meanwhile, the use of *N*-methylindole and indole instead of arenes as nucleophiles gave the bisindolylarylmethane derivatives (**5a**, **b**) by the one-pot azidation, the subsequent nucleophilic substitution accompanying with the elimination of the azido group and the ring opening of the cyclic benzyl ether moiety.[44] Furthermore, allylTMS was also a good nucleophile to form the 1-allylated phthalan (**4**) in 49% yield (entry 6). 5,6-Dichlorophthalan (**1b**) could also be applied in the one-pot reaction to give the corresponding

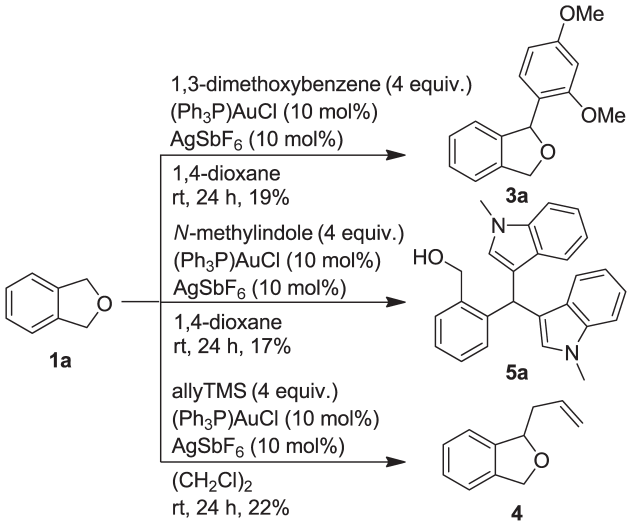


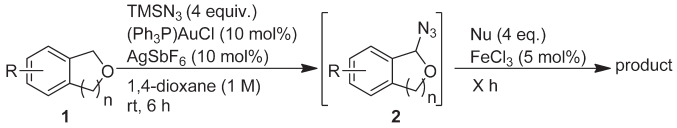
Chart 4. Gold-Catalyzed Direct Arylation, Bisarylation and Allylation of **1a**

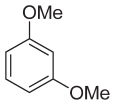
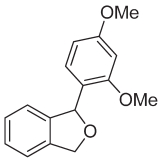
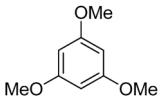
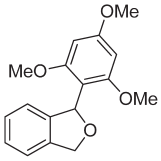
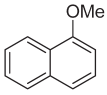
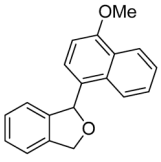
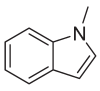
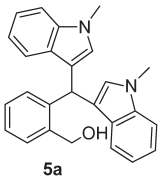
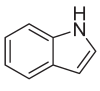
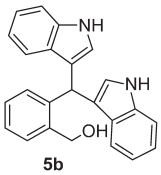
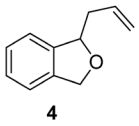
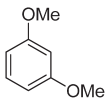
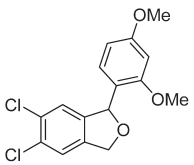
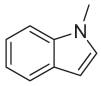
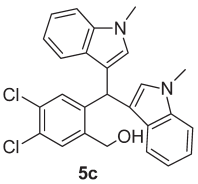
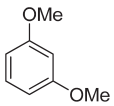
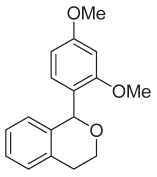
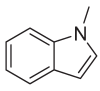
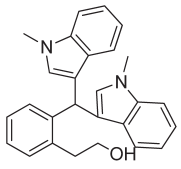
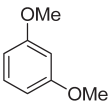
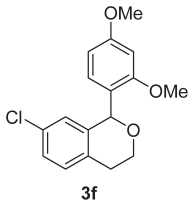
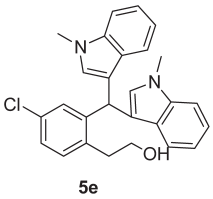
1-arylphthalan derivative (**3d**) with 1,3-dimethoxybenzene and bisindolylarylmethane derivative (**5c**) with *N*-methylindole (entries 7, 8). Isochroman (**1c**) could be converted into the corresponding 1-arylated isochroman (**3e**) by the use of 1,3-dimethoxybenezene as a nucleophile in 56% yield and the bisindolylarylmethane derivative (**5d**) was also obtained by the nucleophilic attack of *N*-methylindole in 57% yield (entries 9, 10). 7-Chloroisochroman could be converted into the corresponding **3f** and **5e**, while the yields were not satisfied (entries 11, 12). Although the $(Ph_3P)AuCl$-catalyzed direct arylation using 1,3-dimethoxybenezene and *N*-methylindole, and allylation using allylTMS of phthalan (**1a**) could slightly proceed without the azidation step and the addition of $FeCl_3$, the reaction efficiencies were not improved (Chart 4).

In conclusion, we have achieved the $(Ph_3P)AuCl$-catalyzed benzylic azidation of phthalan and isochroman derivatives and the subsequent $FeCl_3$-catalyzed nucleophilic substitutions of the azidated products. As a consequence, the 1-aryl and allyl phthalan and isochroman, bisindolylarylmethane and bisarylindolylmethane derivatives possessing unique and pharmaceutically useful skeletons could be easily constructed.

Acknowledgments This work was supported by Grand-

Table 3. One-Pot Synthesis Using Phthalan and Isochroman Derivatives (**1a–d**) as Substrates



Entry	SM	Nucleophile	Product	Time (h)	Yield (%)
1	**1a**		 **3a**	15	64
2	**1a**		 **3b**	15	73
3[a]	**1a**		 **3c**	17	71
4	**1a**		 **5a**	24	93
5	**1a**		 **5b**	24	87
6	**1a**		 **4**	15	49
7[a,b]	**1b**		 **3d**	1	40
8[b]	**1b**		 **5c**	24	43
9[b]	**1c**		 **3e**	3	56
10[b]	**1c**		 **5d**	16	57
11[a,b]	**1d**		 **3f**	29	36
12[b]	**1d**		 **5e**	24	29

a) A total of 50 mol% $FeCl_3$ was used. *b*) The first azidation step was carried out for 24 h.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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30) Although the Lewis acid-mediated ring opening of **2** to generate the intermediate **B** was considerable, the product derived from **B** was never obtained under the presented reaction conditions.
31) While Grignard reagents have been known to chemoselectively facilitate the nucleophilic substitutions of *N*,*O*-acetals composed of the azido group as a leaving group, the Lewis acid-catalyzed Friedel–Crafts type reaction toward *N*,*O*-acetals has not been investigated, see refs. 32 and 33.
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43) $FeCl_3$ was more effective than other Lewis acids [trimethylsilyl trifluoromethanesulfonate (TMSOTf): 71% and $BF_3 \cdot Et_2O$: 53%] and Brønsted acid [trifluoroacetic acid (TFA): trace] in the reaction of **2a** using 1,3-trimethoxybenzene.
44) The yields of **5a** and **b** in the one-pot method were better than the yield of **2a** for the benzylic azidation (Table 2, entry 1). During the direct azidation of the phthalan (**1a**, **b**) and isochroman (**1c**, **d**) derivatives and their work-up process, the *N*,*O*-acetal moiety of the azidated products, which are generally acid-labile, may be partially decomposed.