

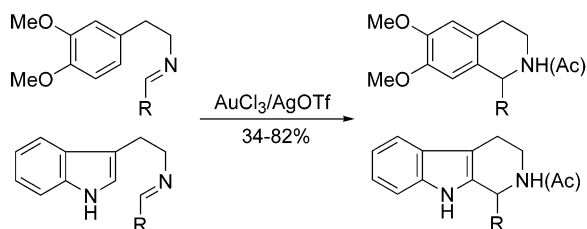
Development of the Pictet–Spengler Reaction Catalyzed by AuCl₃/AgOTf

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Mild and efficient AuCl₃/AgOTf-catalyzed Pictet–Spengler reactions were developed to afford in good yields a variety of tetrahydroisoquinoline and tetrahydro- β -carboline ring systems, which constitute important motifs in biologically active natural and synthetic organic compounds.

The Pictet–Spengler reaction¹ has been shown to be useful and important for the synthesis of tetrahydroisoquinoline and tetrahydro- β -carboline ring systems, which are present in numerous natural and synthetic organic compounds possessing various biological activities.² Strong Brønsted acids³ are most commonly employed to promote the Pictet–Spengler reaction, involving the cyclization of an electron-rich aromatic ring onto an imine. The few recent examples of Lewis acid catalyzed Pictet–Spengler reaction involved highly reactive species such as nitron,⁴ or ionic liquid and microwave irradiation to enhance the reactivity.^{3c,5} Recently, gold⁶ has been shown to catalyze a variety of C–C bond-forming reactions. In the quest to develop a mild and practical protocol, we envisioned the potential application of such a catalytic system for the desired Pictet–

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TABLE 1. Optimization Studies for the Pictet–Spengler Reaction of **1a**^a

entry	catalyst	additive	yield (%) ^b
1	PdCl ₂	—	—
2	—	AgOTf	20
3	AuCl	—	<10
4	—	AgOTf	trace
5	AuCl ₃	—	20
6	—	AgOTf	40
7	—	AgOTf ^c	30
8	—	AgSbF ₆	20
9	—	AgBF ₄	—
10	—	AgClO ₄	—
11	—	Ag(O ₂ CCF ₃)	20
12	AuBr ₃	AgOTf	20
13	Sc(OTf) ₃	—	20
14	AlCl ₃	—	15
15	CeCl ₃ ·7H ₂ O	—	15
16	—	AgOTf	trace
17	ZnCl ₂	—	<5
18	—	AgOTf	<20

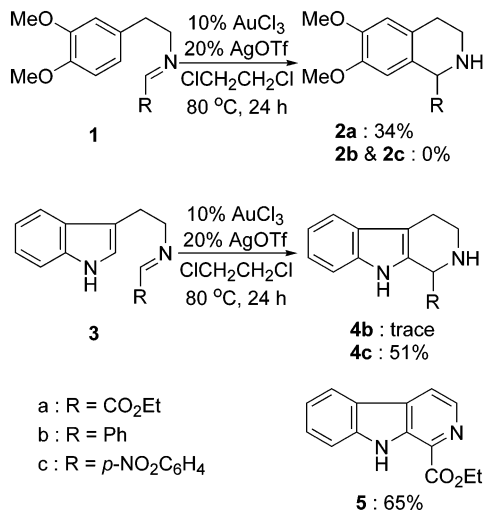
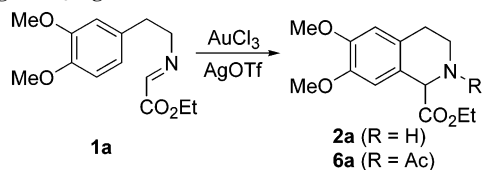
^a All reactions were carried out with catalyst (10 mol %) and additive (20 mol %) in ClCH₂CH₂Cl (0.02 M) at 60 °C for 24 h, unless otherwise noted. ^b Determined by ¹H NMR using trichloroethylene as an internal standard. ^c Using 30 mol % of AgOTf.

Spengler reaction. Herein we report the efficient Pictet–Spengler reaction catalyzed by AuCl₃/AgOTf.

At the outset of the studies, a broad spectrum of potential metal salts and complexes were tested in the cyclization of **1a**, and the effects of silver salt additives were determined (Table 1; for complete data, see Supporting Information). With the exception of AuCl₃, Sc(OTf)₃, AlCl₃, and CeCl₃·7H₂O, most of the metal complexes examined did not show the ability to produce the desired product **2a**. Analysis of the crude reaction mixture by ¹H NMR showed that nearly all of the complexes tested induced some degree of imine hydrolysis. In an attempt to increase the electrophilicity at the metal centers by giving the weakly coordinating counterions, reactions were run in the presence of silver salt additives. As a general trend, it was found that the conversion of **1a** increased upon the addition of silver salt; however, the amount of imine hydrolysis also increased. Among them AgOTf showed outstanding effects, and a control experiment has shown that AgOTf itself is not responsible for the catalytic activation (see Supporting Information).

We were delighted to identify an exciting lead, which unambiguously stood out in the array of experiments. The combination of AuCl₃ and AgOTf was optimal in this reaction system to produce **2a** in 40% yield (Table 1, entry 6). Decreasing the amount of catalyst and reaction temperature caused lower yields. To boost the reactivity, TMSCl^{4,5} was added to the reaction mixture; however, the addition of TMSCl (0.1 equiv) had only a marginal effect.

Product **2a** could be obtained in the presence of 10 mol % AuCl₃ and 20 mol % AgOTf at 80 °C in 34% isolated yield, whereas no desired products were produced with the substrates derived from benzaldehyde (**1b**) and *p*-nitrobenzaldehyde (**1c**), even with the addition of stoichiometric amount of TMSCl along

SCHEME 1. Pictet–Spengler Reactions Catalyzed by AuCl₃/AgOTfTABLE 2. Optimization for the Acyl–Pictet–Spengler Reaction of 1a Using AuCl₃/AgOTf^a

entry	acylating agent	solvent	yield (%) ^b	
			2a	6a
1	AcCl	ClCH ₂ CH ₂ Cl	trace	62
2	Ac ₂ O	ClCH ₂ CH ₂ Cl	14	45
3	ClCO ₂ Et	ClCH ₂ CH ₂ Cl	27	40 ^c
4	AcCl	toluene	20	50
5	AcCl	CH ₃ CN	16	74
6	AcCl	1,4-dioxane	19	71
7	AcCl	THF	11	43
8	AcCl	CH ₂ Cl ₂	20	60
9	AcCl	THF/CH ₂ Cl ₂ (1:4)	8	50
10 ^d	AcCl	CH ₃ CN	<10	87(81)

^a All reactions were carried out with AuCl₃ (10 mol %), AgOTf (20 mol %), and acylating agent (1 equiv) in solvent (0.02 M) at room temperature for 24 h, unless otherwise noted. ^b Yields were determined by ¹H NMR using trichloroethylene as an internal standard; isolated yield is given in parentheses. ^c R = CO₂Et. ^d Performed with 1 mol % AuCl₃ and 2 mol % AgOTf.

with complete hydrolysis (Scheme 1). The similar reactions of 3a and 3c gave the corresponding β-carbolines, 5, which precursor (4a) is known to be very unstable,⁷ and 4c, respectively, whereas once again 3b showed very low reactivity to give only a trace amount of 4b (Scheme 1).

These results led us to explore more reactive variants of the Pictet–Spengler reaction. The challenge of the Pictet–Spengler reaction appears to be associated with the low reactivity of the imine substrate. Therefore, strong Brønsted acid,³ highly reactive substrates,⁴ high reaction temperature, or microwave irradiation^{3c,5} have been employed to promote the reaction. Meanwhile, a general strategy to enhance the reactivity of imine involves generation of the corresponding *N*-acyliminium ions^{8a} due to the electron-withdrawing effect of the *N*-acyl group, and this

TABLE 3. Acyl–Pictet–Spengler Reactions Catalyzed by AuCl₃/AgOTf^a

entry	substrate	product	yield (%) ^b
1	1a (R = CO ₂ Et) ^c	6a	81
2	1b (R = Ph)	6b	73
3	1c (R = <i>p</i> -NO ₂ C ₆ H ₄)	6c	78
4	1d (R = <i>p</i> -MeOC ₆ H ₄)	6d	82
5	1e (R = 2-(5-methylfuran-2-yl))	6e	66
6	1f (R = 2-(6-methylpyridin-2-yl))	6f	56
7	1g (R = cinnamyl)	6g	74
8	1h (R = <i>n</i> -Pent) ^c	6h	35
9	3a (R = CO ₂ Et) ^c	7a	61
10	3b (R = Ph)	7b	65
11	3c (R = <i>p</i> -NO ₂ C ₆ H ₄)	7c	66
12	3d (R = <i>p</i> -MeOC ₆ H ₄)	7d	63
13	3e (R = 2-(5-methylfuran-2-yl))	7e	73
14	3f (R = 2-(6-methylpyridin-2-yl))	7f	48
15	3g (R = cinnamyl)	7g	77
16	3h (R = <i>n</i> -Pent)	7h	55

^a All reactions were carried out with AuCl₃ (1 mol %), AgOTf (2 mol %), AcCl (1 equiv), and 2,6-lutidine (1 equiv) in CH₃CN (0.02 M) at room temperature for 12 h, unless otherwise noted. ^b Isolated yields. ^c Performed without 2,6-lutidine.

methodology has been reported to promote the Pictet–Spengler reaction.^{3a,8b–c}

With the preliminary results of the Pictet–Spengler reaction in the presence of AuCl₃/AgOTf, we set out to explore the scope of acyl–Pictet–Spengler reactions. Compound 1a underwent cyclization in the presence of acetyl chloride and AuCl₃/AgOTf in 1,2-dichloroethane at room temperature to provide 6a in 62% yield (Table 2, entry 1). On the other hand, acetic anhydride and ethyl chloroformate were less effective (Table 2, entries 2 and 3). Interestingly, it was also found that any base such as NEt₃, pyridine, 2,6-lutidine, etc. afforded only trace amount of desired product 6a along with decomposition. Various solvents were examined, and CH₃CN appeared preferable. Gratifyingly, the reaction also provided an excellent yield even when the amount of AuCl₃/AgOTf was reduced to 1 mol % (Table 2, entry 10).

We proceeded to examine the substrate scope of AuCl₃/AgOTf-catalyzed acyl–Pictet–Spengler reactions. In some previous reports, only special imines, such as an aliphatic imine^{8c} and *N*-protected tryptamine derivative,^{3a} were successful. Waldmann^{8b} reported that several days are required for aromatic imines and the reaction did not proceed with α,β-unsaturated imine. In contrast, in our reaction system various imines obtained by condensation of 3,4-dimethoxyphenethylamine or tryptamine with aldehydes were used without further purification, and yields were equally good with both electron-deficient and electron-

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rich aromatic imines as well as aliphatic imines (Table 3). Heteroaromatic imines (Table 3, entries 5, 6, 13, and 14), α,β -unsaturated imines (Table 3, entries 7 and 15), and free (NH) indole-derived imines (Table 3, entries 9–16) were all successful in this reaction. It should be noted that a base such as 2,6-lutidine was required for optimal conversion in most cases, except for **1a**, **1h**, and **3a**.

In summary, we have developed the Pictet–Spengler reaction catalyzed by AuCl₃/AgOTf. To enhance the reactivity of imine, an acylating agent was involved. It is likely that this reaction proceeds an electrophilic pathway involving imine activation by coordinating gold(III) complex. The process is mild and efficient and can be used to synthesize a variety of tetrahydroisoquinoline and tetrahydro- β -carboline derivatives that constitute important motifs in biologically active natural and synthetic organic compounds.

Experimental Section

General Procedure for Pictet–Spengler Reactions Using AuCl₃/AgOTf. A mixture of 10 mol % AuCl₃ and 20 mol % AgOTf in ClCH₂CH₂Cl was stirred vigorously for 1 h. To the resulting solution was added the imine substrate (**1a–c** or **3a–c**) dissolved in ClCH₂CH₂Cl (0.02 M). After 24 h at 80 °C, the solvent was

evaporated, and the residue was purified by column chromatography on silica gel (EtOAc/*n*-hexanes = 1:1 to EtOAc only) to give the corresponding product (**2a**, **4c**, **5**).

General Procedure for Acyl-Pictet–Spengler Reactions Using AuCl₃/AgOTf. A mixture of 1 mol % AuCl₃ and 2 mol % AgOTf in CH₃CN was stirred vigorously for 1 h. To a resulting solution was added the imine substrate (**1a–h** or **3a–h**) dissolved in CH₃CN (0.02 M), AcCl (1 equiv), and 2,6-lutidine (if required, 1 equiv) successively at room temperature. After 12 h, the solvent was evaporated, and the residue was purified by column chromatography on silica gel (EtOAc/*n*-hexanes = 3:1 to EtOAc only) to give the corresponding product (**6a–h** or **7a–h**).

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Supporting Information Available: Full experimental details, complete data for the systematic screening, and spectral characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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