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Gold (III) Chloride-Catalyzed 6-*endo-trig* Oxa-Michael Addition Reactions for Diastereoselective Synthesis of Fused Tetrahydropyranones

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Abstract

Alkynones were treated with boron trifluoride diethyl etherate to generate α -iodoallenolates, which underwent intramolecular aldol reactions to produce cycloalkenyl alcohols. Diastereoselective oxa-Michael ring closure could then be induced by treatment with a catalytic amount of gold(III) chloride, affording highly functionalized tetrahydropyran-containing ring systems.

Keywords

gold; oxa-Michael; cyclization; tetrahydropyranone

The tetrahydropyran heterocycle is a common structural motif found in pharmacologically active small molecules.^[1] The development of effective diastereoselective strategies for synthesizing oxadecalins^[2] and other bicyclic tetrahydropyran ring systems will help expand the synthetic toolbox, especially if the oxacyclic products contain multiple functional handles. While a 6-*endo-trig* oxa-Michael addition has been used to prepare a number of tetrahydropyran targets,^[3–9] the strongly acidic reaction conditions commonly employed can compromise diastereoselectivity and destroy sensitive functionality. In this update, we describe a mild protocol for inducing 6-*endo-trig* oxa-Michael reaction using catalytic AuCl₃, and demonstrate the application of the method to the synthesis of highly functionalized tetrahydropyran-4-ones.

In 2009, we reported a three-step cascade cyclization involving α -iodoallenolates **2** (Scheme 1).^[10] Alkynones of type **1** could be treated with BF₃·OEt₂/tetra-*n*-butylammonium iodide to afford oxacycles **4**, via the 6-*endo-trig* oxa-Michael addition of cycloalkenyl alcohols of type **3**. (Scheme 1). Since reporting these findings, we have systematically prepared and cyclized a series of alkynones **1** with different R¹, R² and R³ substituents (Table 1), and found that while the α -iodoallenolate formation and intramolecular aldol cyclization steps are efficient in all cases, the enone substitution pattern has a profound effect on oxa-Michael addition behavior.

Experiments varying the R² substituent revealed that fused tetrahydropyran-4-ones of type **4** were formed efficiently when R²=Me or *p*-methoxyphenyl (entries 1 and 3, Table 1), but not at all when R²=phenyl or *tert*butyl (entries 2 and 4). In disubstituted enone substrates

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($R^1=H$), oxa-Michael addition only occurred when R^2 =methyl (entry 5). Oxadecalin formation was not observed in cyclizations of alkynones where R^2 =aryl (entries 6-8). Similarly, the oxadecalin products **4** were not observed in cyclizations of alkynones with alkyl substituents at R^3 (entries 9 and 10).

The fact that the oxa-Michael ring closure is not observed in substrates **1b**, **1d** and **1f-1j** suggests that it is difficult to activate enones with extended conjugation. Substrate **1c** (Table 1, entry 3), which is most able to support carbocationic character at the enone α -carbon, was the only α -aryl enone that underwent oxa-Michael ring closure. Oxa-Michael closure also failed in substrate **1d** (entry 4), indicating that steric bulk at the enone terminus can also hinder the cyclization.

Substrates **1i** and **1j**, which contain β -substituted enones, could not be converted to oxadecalins either (Table 1, entries 9 and 10). It is possible that A-1,3 strain between R^3 and the Lewis acid prevents rotation of **3i** and **3j** from the *s-cis* conformer to the *s-trans* conformer required for oxa-Michael ring closure (Figure 1).

It was also possible to access two novel cycloalkene ring systems from alkynones **1k** and **1l**, using $BF_3 \cdot OEt_2$ as a promoter (equations 1 and 2). When alkynone **1k** was treated with $BF_3 \cdot OEt_2$ at $-40^\circ C$, cyclobutenyl alcohol **3k** was generated in 64% yield (equation 1). However, we were unable to manufacture the [4,6]-system because the cyclobutane ring opened under Lewis acidic conditions at temperatures higher than $-40^\circ C$. Indene **3l** could be prepared in high yield from **1l** in just 10 min using $BF_3 \cdot OEt_2$ at $-40^\circ C$ (equation 3), but formation of the corresponding oxadecalin was inefficient (vide infra.)

(1)

(2)

This study highlights the limitations associated with 6-*endo-trig* oxa-Michael additions in highly functionalized substrates: only a handful of cycloalkenyl alcohols can be cyclized using $BF_3 \cdot OEt_2$.^[10] A complex mixture of products is obtained from many of these reactions, and the cyclohexenols decompose upon exposure to protic acids.^[11] We wanted to identify an alternative promoter that could selectively activate the enone toward oxa-Michael ring closure without destroying the other functionality in the molecule. We chose to examine $AuCl_3$, which is a strong Lewis acid known for its oxophilic character (Table 2).^[12]

Indeed, treatment of **3a** with 10 mol % of $AuCl_3$ in dichloromethane furnished oxadecalin **4a** in 92% yield (Table 2, entry 1). In contrast, cyclization of **3a** could not be promoted using $(Ph_3P)AuCl$, $Au[P(t-Bu)_2(o-biphenyl)](MeCN)SbF_6$, $(Ph_3P)AuCl/AgSbF_6$, or

AgSbF₆, which is consistent with the hypothesis that a strongly oxophilic, Lewis acidic catalyst is required. The reaction carried out with AuCl₃ was also faster than the BF₃·OEt₂ induced cyclization (30 min vs. 3 h).^[13] We also treated alkynone **1a** with AuCl₃/*n*-Bu₄NI in an attempt to initiate the two-step α -iodoallenolate-mediated cyclization, but **1a** was inert to these reaction conditions, even at elevated temperatures.

These mild, catalytic conditions were then tested on other substrates. Cyclization of substrates **3e** and **3m** could be achieved with either BF₃·OEt₂ (1.3 equiv) or AuCl₃ (10 mol %). The yield of the oxacycle **4** was comparable for the two protocols, but the reaction rate was much faster for the AuCl₃-catalyzed reactions (Table 2, entries 2 and 3). The oxa-Michael ring closure of substrate **3l** using BF₃·OEt₂ required elevated temperatures, and **4l** was obtained in only 36% yield. In contrast, when **3l** was treated with 10 mol % AuCl₃, oxacycle **4l** was obtained in 77% yield (Table 2, entry 4). Substrates **3b** and **3n**, which did not cyclize in the presence of BF₃·OEt₂, underwent oxa-Michael addition upon exposure to catalytic AuCl₃, producing oxacycles **4b** and **4n** in moderate yields (entries 5 and 6). Oxadecalin **4b** was obtained in moderate yield (40%) as a single diastereomer, and the structure was confirmed by nOe analysis (see supporting information). Tertiary alcohol **1o** could not be induced to undergo oxa-Michael ring closure using either BF₃·OEt₂ or AuCl₃ (entry 7): the only reaction observed was elimination of the tertiary alcohol.

In the context of substrate **3p**,^[14] a key intermediate in our approach to phomactin A,^[15-17] the AuCl₃ protocol was especially valuable. While BF₃·OEt₂ (1.3 equiv) produced target oxadecalin **4p** in only 20% yield, treatment of **3p** with 10 mol% AuCl₃ catalyzed the desired oxa-Michael ring closure to afford **4p** in 50% yield (Table 2, entry 8).

In every case, the 6-*endo-trig* oxa-Michael ring closures occurred diastereoselectively, with the larger enone α -substituent emerging *trans* to the ring junction (cf. tetrahydropyrans **4b**, **4c**, and **4e**). A number of studies have indicated that most acid-catalyzed 6-*endo-trig* oxa-Michael reactions are thermodynamically controlled, and deliver the most stable tetrahydropyranone product.^[18] However, Gouverneur has demonstrated that 6-*endo-trig* oxa-Michael additions catalyzed by cationic palladium(II) and aluminium Lewis acid complexes are kinetically controlled.^[5] Our experimental and computational results suggest that the AuCl₃-catalyzed oxa-Michael cyclization also occurs irreversibly, with the high diastereoselectivity arising from a kinetically controlled ring closure.^[4,19-20] Given the importance of stereoelectronic effects in other oxa-Michael *endotrig* cyclizations,^[21] we tentatively attribute the stereoselectivity of the reaction to enhanced O $\cdots$ C π orbital overlap in the transition state leading to the observed *trans* isomer, relative to the *cis*.

In summary, we have shown that AuCl₃ is an effective catalyst for 6-*endo-trig* oxa-Michael addition. Relative to cyclization results obtained using stoichiometric BF₃·OEt₂ as promoter, the reactions are faster and the substrate scope is broader. The reaction is highly diastereoselective, and the conditions are mild enough to be used on substrates with acid-sensitive functionality. Application to the synthesis of the bicyclo[9.3.1]pentadecane core of the phomactin natural products demonstrates the utility of the protocol.

Experimental Section

General

Reactions were carried out in oven-dried glassware under an argon atmosphere. Reagents were used as obtained from commercial supplier without further purification. Solvents were purchased from Fisher and dispensed using the Glass Contour solvent purification system. ACS grade hexanes and ethyl acetate were used for column chromatography. Thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 glass-supported

plates (EMD product). Column chromatography was carried out on 60Å silica gel (230-400 mesh) (EMD product). Visualization on thin layer chromatography was done with a UV lamp followed by staining with either potassium permanganate/heat or *p*-anisaldehyde/heat. Low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were measured by Mass Spectrometry Lab of the University of Illinois, Urbana, and at the Chemistry Instrumentation Center at the University of Buffalo. Infrared spectra (IR) were recorded on 8400S Shimadzu FTIR (MIRacle™ ATR diamond) spectrometer. Absorbance frequencies are given in cm^{-1} at the peak maximum.

General Procedure for β -Iodoallenolate Cyclizations Run with $\text{BF}_3\cdot\text{OEt}_2$

Tetra-*n*-butylammonium iodide (1.0 equiv) was added to a stirred solution of the alkynone 1 in dry CH_2Cl_2 (0.10 M) at -40°C . Boron trifluoride diethyl etherate (1.3 equiv) was then added dropwise. The reaction was carried out at the indicated temperature and time. After completion of the reaction, the mixture was diluted with ethyl acetate, quenched with saturated NaHCO_3 solution, and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution (2 $\times$), brine (1 $\times$), dried over MgSO_4 , and concentrated. The resulting residue was purified by flash chromatography on silica gel using different gradients of hexanes and ethyl acetate to afford the pure products.

General Procedure for $\text{BF}_3\cdot\text{OEt}_2$ -Promoted Oxa-Michael Additions

The cycloalkenyl alcohol 3 (1.0 equiv) was diluted in dry CH_2Cl_2 (0.10 M) at -40°C . Boron trifluoride diethyl etherate (1.3 equiv) was then added dropwise. The reaction was carried out at the indicated temperature and time. After completion of the reaction, the mixture was diluted with ethyl acetate, quenched with saturated NaHCO_3 solution, and extracted with ethyl acetate (3 $\times$). The combined organic layers were washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution (2 $\times$), brine (1 $\times$), dried over MgSO_4 , and concentrated. The resulting residue was purified by flash chromatography on silica gel using different gradients of hexanes and ethyl acetate to afford the pure products.

General Procedure for AuCl_3 -Catalyzed Oxa-Michael Additions

The cycloalkenyl alcohol 3 (1.0 equiv) was diluted in dry CH_2Cl_2 (0.10 M). AuCl_3 (10 mol %) was added at 0°C , and the reaction was allowed to warm to rt. After completion of the reaction by TLC, the reaction mixture was purified by flash chromatography on silica gel using different gradients of hexanes and ethyl acetate to afford the pure products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Impact of R^3 on the Oxa-Michael Addition.

Scheme 1. $\text{BF}_3 \cdot \text{OEt}_2$ -Promoted Cyclization Cascade

Table 1

-Iodoallenolate Cyclization using $\text{BF}_3 \cdot \text{OEt}_2$ ^[a]

Entry	1	R ¹	R ²	R ³	Product (Yield)
1	1a	Me	Me	H	4a; ^[b] 77%
2	1b	Me	Ph	H	3b; 85%
3	1c	Me	<i>p</i> -methoxyphenyl	H	4c; ^{[b]/[c]} 74%
4	1d	Me	<i>t</i> -Bu	H	3d; 85%
5	1e	H	Me	H	4e; ^{[d]/[e]} 60%
6	1f	H	Ph	H	3f; 77%
7	1g	H	<i>p</i> -nitrophenyl	H	3g; 86%
8	1h	H	<i>p</i> -methoxyphenyl	H	3h; 86%
9	1i	H	Me	Me	3i; 50%
10	1j	Me	-(CH ₂) ₄ -		3j; 88%

^[a] Reaction conditions: Alkynone (1.0 equiv), $\text{BF}_3 \cdot \text{OEt}_2$ (1.3 equiv), and *n*-Bu₄NI (1.0 equiv) in CH_2Cl_2 (0.10 M) at -40°C for 1-3 h.

^[b] Reaction warmed to 0°C .

^[c] Oxadecalin was obtained as a mixture of diastereoisomers (3.2:1 dr).

^[d] Reaction warmed to rt for 39 h.

^[e] Oxadecalin was isolated as a single diastereoisomer.

Table 2

6-*endo-trig* Oxa-Michael Additions with $\text{BF}_3 \cdot \text{OEt}_2$ (1.3 equiv) vs. AuCl_3 (10 mol%).

entry	substrate	$\text{BF}_3 \cdot \text{OEt}_2$ ^[a] temp time, yield	AuCl_3 ^[b] temp time, yield	tetrahydropyranone
1	3a	−40 to 0 °C 3 h 93% ^[c]	0 °C to rt 30 min 92%	4a
2	3e	−40 to rt 39 h 88% ^[d]	0 °C to rt 1 h 88%	4e
3	3m	−40 to rt 4.5 h 89% ^[d]	0 °C to rt 30 min 89%	4m
4	3l	60 °C ^[e] 12 h 36% ^[f]	0 °C to rt 30 min 77%	4l
5	3b	.. ^[g]	0 °C 3 h 40%	4b
6	3n	.. ^[g]	0 °C to rt 6 h ^[h] 55%	4n

entry	substrate	BF ₃ ·OEt ₂ ^[a] temp time, yield	AuCl ₃ ^[b] temp time, yield	tetrahydropyranone
7	3o	<i>[g]</i>	<i>[g]</i>	4o
8	3p	−40 °C 2 h 20%	0 °C 30 min 50%	4p

^[a]Reaction conditions: Substrate (0.3 mmol), BF₃·OEt₂ (1.3 equiv), *n*-Bu₄NI (1.0 equiv) in CH₂Cl₂ (0.10 M).

^[b]Reaction conditions: Substrate (0.06 mmol), AuCl₃ (10 mol%), CH₂Cl₂ (0.10 M) at 0 °C to rt.

^[c]When the reaction run was with BF₃·OEt₂ (10 mol %), **4a** was obtained in 87% yield for 3 h (−40 °C to 0 °C); 93% conversion

^[d]Estimated yield of oxa-Michael addition step, based on individual results from the -iodoallenolate aldol step and the Scheme 1 cascade.

^[e]Reaction run in 1,2-dichloroethane.

^[f]87% conversion.

^[g]No cyclization occurred. In most cases, a complex mixture of undesired products was obtained.

^[h]Reaction run with 20 mol% of AuCl₃.