The First $In(OTf)_3$-Catalyzed Conversion of Kinetically Formed Homoallylic Alcohols into the Thermodynamically Preferred Regioisomers: Application to the Synthesis of 22α-Sterols**

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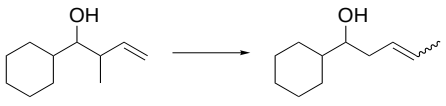
Processes which convert readily available kinetic products to their less readily accessible thermodynamic isomers are of synthetic value and mechanistic interest in organic synthesis.[1] In this respect, homoallylic alcohols are versatile building blocks for the synthesis of many biologically active molecules, and the allylation of carbonyl compounds and the carbonyl ene reaction offer ready access to this class of compounds.[2] Nevertheless, almost all current methods produce predominantly γ adducts, except in a few special cases, and hence access to the α adducts is restricted.[3] Coincidentally, our recent studies on the synthesis of various steroids with 22-oxygenated side chains required an efficient access to linear homoallylic 22-sterols,[4] for which the thermodynamically controlled conversion of the γ adduct to the corresponding α adduct appeared to be an appealing approach.[5] Here we describe the first $In(OTf)_3$-catalyzed conversion of branched homoallylic alcohols to the thermodynamically preferred linear regioisomers.

Given our interest in indium chemistry,[6] we explored this thermodynamic conversion on the basis of indium reagents.[7] In our initial study, 1-cyclohexyl-2-methylbut-3-en-1-ol (**1a**) was subjected to a series of experiments to evaluate the merits of various indium reagents [Eq. (1), Table 1]. Among them, $In(OTf)_3$ exhibited excellent efficiency in the conversion of **1a** to its linear isomer **2a** (Table 1, entry 4).[8]

Table 1. Evaluation of various indium reagents for the thermodynamic conversion (1).



(1)

1a **2a**

Entry	Indium reagent	Yield [%]
1	In, allyl bromide, HMPA[a]	no reaction
2	InF_3[b]	no reaction
3	$InCl_3$[b]	no reaction
4	$In(OTf)_3$[b]	78%

[a] The reaction was performed with the branched isomer (0.5 mmol), In (1.0 mmol), bromide (1.5 mmol) and hexamethylphosphoramide (HMPA, 7.5 mmol) in THF (5 mL). [b] Reactions were performed with the branched isomer (0.5 mmol) and the Lewis acid (0.05 mmol) in CH_2Cl_2 (4 mL).

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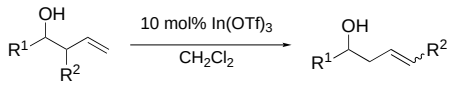
We then extended this method to a variety of substrates [Eq. (2), Table 2]. In most cases, the reactions afforded the linear isomers in moderate to good yields (except for entries 4 and 6). In addition, there appears to be a correlation between the relative stereochemistry of the substrate and the geometry at the double bond of the product (*syn* $\rightarrow Z$ and *anti* $\rightarrow E$; entries 7 and 8).

Table 2. $In(OTf)_3$-catalyzed thermodynamic conversion of homoallylic alcohols **1** [Eq. (2)].[a]



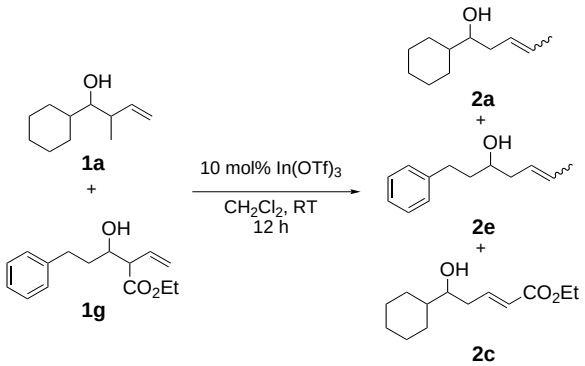
(2)

1 **2**

Entry	**1**	R^1	R^2	*anti*/*syn* of **1**[c]	*T* [°C]	Yield of **2** [%][b] (*E*/*Z*)
1	**1a**	*c*-C_6H_{11}	Me	80/20	25	78 (68/32)
2	**1b**	*c*-C_6H_{11}	Ph	98/2	25	81 (*E*)[d]
3	**1c**	*c*-C_6H_{11}	CO_2Et	85/15	40	69 (85/15)[e]
4	**1d**	Ph	CO_2Et	86/14	40	19 (*E*)
5	**1e**	$PhCH_2CH_2$	Me	50/50	25	72 (55/45)
6	**1f**	$PhCH_2CH_2$	Ph	70/30	25	36 (>99/1)[f]
7	**1g**	$PhCH_2CH_2$	CO_2Et	80/20	40	74 (84/16)[e]
8	**1g**	$PhCH_2CH_2$	CO_2Et	>99/1	40	78 (*E*)
9	**1h**	$CH_3(CH_2)_4$	Me	55/45	25	53 (65/35)
10	**1i**	$CH_3(CH_2)_4$	Ph	90/10	25	76 (97/3)[g]
11	**1j**	$CH_3(CH_2)_4$	CO_2Et	70/30	40	73 (80/20)[e]

[a] All reactions were performed with the branched isomer (0.5 mmol) and $In(OTf)_3$ (0.05 mmol) in CH_2Cl_2 (4 mL). [b] Yields of isolated products. [c] Determined by ^1H NMR (300 MHz). [d] 9% of **1b** was recovered (*syn* only). [e] *Z* isomer was obtained as lactenone. [f] 36% of **1f** was recovered (*anti*/*syn* 1/3). [g] 13% of **1i** was recovered (*syn* only).

A weak signal for an aldehydic proton at $\delta = 9.61$ was observed in the ^1H NMR spectrum of the crude reaction mixture when **1a** was treated with $In(OTf)_3$, which suggested the involvement of a retro-process that generates the free aldehyde in situ. To verify this, a crossover experiment was conducted (Scheme 1). A mixture of **1a** and **1g** was subjected to the reaction conditions, and the reaction was quenched after 12 h. Column chromatography gave **2a** (67%) and recovered **1g** (62%), together with 5% **2e** and **2c**. This proved that the conversion involves a retro-process that generate the parent aldehyde in situ.



Scheme 1. Crossover exchange experiment.

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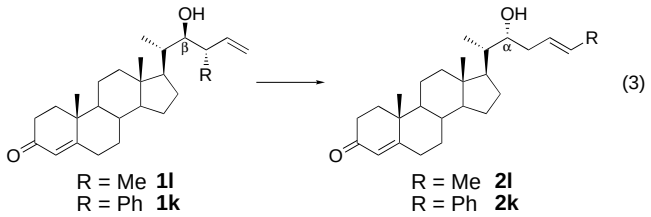
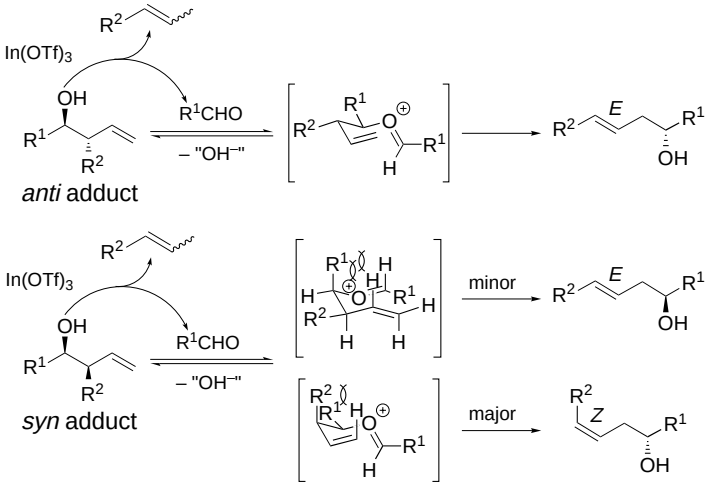
Afterwards the $In(OTf)_3$-catalyzed thermodynamic conversion was applied to the construction of steroidal side chains. The optically pure branched homoallylic sterols **1l** and **1k**[4] were subjected to the conversion procedure. A solution of **1l** or **1k** (1.0 equiv) in CH_2Cl_2 was added dropwise to a suspension of $In(OTf)_3$ (0.1 equiv) in CH_2Cl_2, and the mixture was heated to reflux for 48 h. The optically pure isomers **2l** and **2k** were obtained in good yield (71 and 73%, respectively) [Eq. (3)]. Interestingly, the stereochemistry at C-22



(3)

was assigned as 22α. In other words, the allyl fragment attaches to the steroid in an anti-Cram manner,[9] which excludes the possibility of re-addition of the allyl anion to the aldehyde. Therefore, a pericyclic pathway was invoked to account for this stereochemical outcome, for which the 2-oxonia [3,3]-sigmatropic rearrangement proposed by Nokami et al.[10] was adopted. The overall postulated reaction pathway for the $In(OTf)_3$-catalyzed thermodynamic conversion is shown in Scheme 2. Lewis acid catalyzed retro-ene[11] cleavage of the carbon–carbon bond releases the parent aldehyde, which subsequently promotes a 2-oxonia [3,3]-sigmatropic rearrangement to afford the stereochemically inverted homoallylic alcohol.



Scheme 2. Postulated reaction pathway for the conversion of branched to linear homoallylic alcohols.

In conclusion, an $In(OTf)_3$-catalyzed conversion of branched homoallylic alcohols to the thermodynamically preferred linear regioisomers has been developed. This method can be utilized for the construction of steroidal side chains with anti-Cram stereoselectivity. Hence, efficient access to 22α-oxygenated steroidal side chains, such as those in ecdysone derivatives,[9] is facilitated. As opposed to the previously proposed mechanisms involving transfer of allyl anions or concerted rearrangement for the equilibration of branched and linear homoallylic alcohols, our study of this thermodynamic conversion suggests that both retro-cleavage to generate the parent aldehyde in situ and a concerted rearrangement are involved, plausibly a retro-ene reaction followed by a 2-oxonia [3,3]-sigmatropic rearrangement in this case. This indicates the possibility of the concurrent involvement of both mechanisms for the generation of the thermodynamically preferred linear adducts in other allylation reactions. Further studies to verify this postulate are in progress.

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