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Stereocontrolled Synthesis of Linear 22*R*-Homoallylic Sterols via a Triflic Acid-Catalyzed 2-Oxonia Cope Rearrangement

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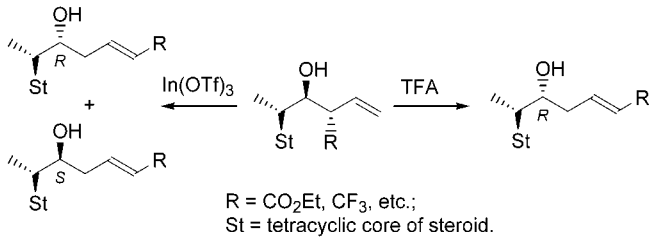
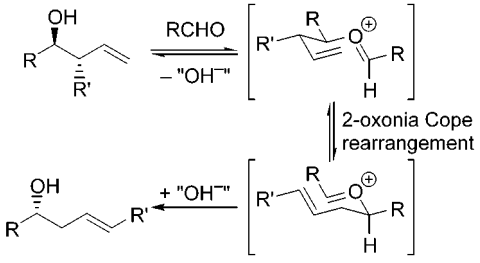
ABSTRACT



Poor stereoselectivity caused by the involvement of side reaction pathways was observed in the $In(OTf)_3$-catalyzed allyl-transfer reaction (R = electron-withdrawing group). Subsequently, it was found that the employment of triflic acid (TFA) as catalyst could successfully suppress the side reaction pathways and, hence, achieve high stereoselectivity.

The stereocontrolled synthesis of various functional molecules is one of the most essential tasks in contemporary organic synthesis.[1] Extensive efforts have been focused on the development of various asymmetric synthetic methods including the use of highly efficient chiral auxiliaries or catalysts.[2] However, such strategies sometimes failed to reach their full potential, due to the involvement of unpredictable side reaction pathways, which will generate undesired stereoisomers and undermine the stereoselectivity.[3] Therefore, the prevention of side reaction pathways plays an equally important role in achieving high stereoselectivity. Recently, the allyl-transfer reaction based on 2-oxonia Cope rearrangement[4] has attracted much interest in organic synthesis due to the great versatility of the obtained linear homoallylic alcohols[5] and the potential of its concerted mechanism for highly stereocontrolled chirality transfer (Scheme 1). On the basis of this reaction, the enantioselective

Scheme 1. Allyl-Transfer Reaction Based on 2-Oxonia Cope Rearrangement



synthesis of linear homoallylic alcohols has also been realized when R′ = Me or R′ = Ph.[3,4d,6,7] As for substrates possessing R′ = CO_2Et, relatively poor yields were obtained,[4b] and no

(1) Ojima, I. In *Catalytic Asymmetric Synthesis*; Wiley-VCH: New York, 2000.
(2) For reviews, see: (a) Corey, E. J.; Lee, T. W. *Chem. Commun.* **2001**, 1321. (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1987.
(3) For a recent example, see: Loh, T.-P.; Hu, Q.-Y.; Chok, Y.-K.; Tan, K.-T. *Tetrahedron Lett.* **2001**, *42*, 9277.

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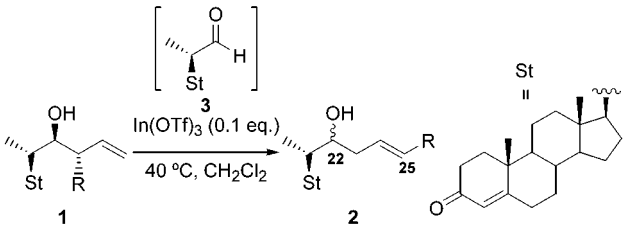
stereochemical studies were described. This substantially limited the applicability of this novel C−C bond formation method. Herein, we present an unexpected poor stereoselectivity observed in the exploration of $In(OTf)_3$-catalyzed allyl-transfer reaction (R′ = CO_2Et or CF_3) and a new protocol for highly stereocontrolled allyl-transfer reactions.

Continuing with our previous work toward the synthesis of 22-oxygenated steroids,[8] we attempted to utilize the allyl-transfer reaction to synthesize various linear 22*R*-homoallylic sterols. Initially, the $In(OTf)_3$-catalyzed allyl-transfer reaction condition[4d] was examined with substrates bearing a CO_2Et or CF_3 group (**1a** and **1b**, Table 1).[9] It was found that linear

Table 1. Unexpected Stereochemical outcome in the $In(OTf)_3$-Catalyzed Allyl-Transfer Reactions



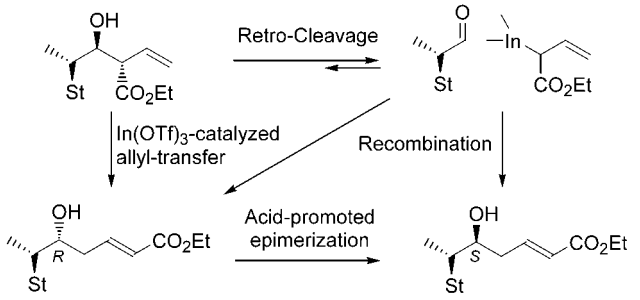
entry	SM	R	3 (mol %)	time (h)	$\Delta^{24,25}$ (*E*/*Z*)[a]	yield (%) (**2**) (22*R*/22*S*)[b]
1	**1a**	CO_2Et	10	48	*E*	**2a**; 53 (60:40)
2	**1a**	CO_2Et	0	48	*E*	**2a**; 47 (60:40)
3	**1b**	CF_3	10	48	*E*	**2b**; 57 (50:50)
4	**1b**	CF_3	0	48	*E*	**2b**; <10 (50:50)

[a] Determined through *J* value and NOE NMR analysis. [b] Determined by ^1H NMR.

22-homoallylic sterols were obtained in moderate yields when the reactions were carried out in the presence of a catalytic amount of parent aldehyde **3** (Table 1). However, the reactions exhibited almost no stereoselectivities, which greatly contrasts with the mechanistic prediction (Scheme 1).

The unexpected stereochemical outcome suggested the involvement of side reaction pathways, which led to the competitive generation of other stereoisomers. To account for this observation, two possible side reaction pathways were postulated (Scheme 2). First, the homoallylic alcohol can

Scheme 2. Postulated Side Reaction Pathways toward 22*S* Stereoisomer



undergo a Lewis acid-catalyzed retro-cleavage to the parent aldehyde and allylic anion. The presence of an electron-withdrawing group will probably enhance this retro-process via a reversible Reformatsky-type reaction pathway.[10] Subsequently, the addition of the resulting allylic anion of the parent aldehyde will preferably afford linear 22*S* homoallylic sterol. On the other hand, the Lewis acid-promoted epimerization of alcohol might be an alternative pathway to the generation of undesired stereoisomer. With this postulation, our efforts were directed to suppress these possible side reaction pathways and explore a highly stereoselective protocol.

To suppress the possible side reaction pathways, three approaches were investigated, namely decreasing the reaction temperature, employing stronger or more acid catalyst to accelerate the desired 2-oxonia Cope rearrangement, and eliminating the presence of the parent aldehyde or allylic anion. Substrate **1a** was selected in our investigation. Initially, a relatively low-temperature condition was examined (entry 1, Table 2). However, only a trace amount of product was obtained after 2 days. Subsequently, 40 mol % of $In(OTf)_3$ catalyst was employed in the reaction. Interestingly, the product was obtained in 68% yield with a much better stereoselectivity in a ratio of 89:11 (22*R*/22*S*). Encouraged by this, a series of acid catalysts were screened (entries 3−7, Table 2). As shown in Table 2, none of the Lewis acids examined is effective for this reaction (entries 3−5). As for protic acid catalysts, it is interesting to observe that triflic acid (TFA) gave the best result, affording the desired product in 72% yield and a ratio of 98:2 (22*R*/22*S*).

With the establishment of the improved protocol, various substrates were examined (Table 2). The new protocol gave satisfactory results not only for reactive substrates (e.g., **1c**, **1d**) but also for substrates with ester, CF_3, or di-Me substituents (e.g., **1a**, **1b**, **1e**), which used to be considered

(4) (a) Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S. I. *J. Am. Chem. Soc.* **1998**, *120*, 6609. (b) Sumida, S. I.; Ohga, M.; Mitani, J.; Nokami, J. *J. Am. Chem. Soc.* **2000**, *122*, 1310. (c) Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T. *J. Am. Chem. Soc.* **2001**, *123*, 2450. (d) Loh, T.-P.; Tan, K.-T.; Hu, Q.-Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2921. (e) Samoshin, V. V.; Smoliakova, I. P.; Han, M.; Gross, P. H. *Mendeleev Commun.* **1999**, *9*, 219. (f) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815. (g) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577.

(5) For reviews, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.

(6) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168.

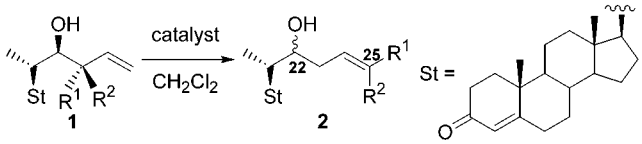
(7) Loh, T.-P.; Tan, K.-T.; Hu, Q.-Y. *Tetrahedron Lett.* **2001**, *42*, 8705.

(8) (a) Loh, T.-P.; Hu, Q.-Y.; Vittal, J. J. *Synlett* **2000**, 523. (b) Loh, T.-P.; Xu, J.; Hu, Q.-Y.; Vittal, J. J. *Tetrahedron*: *Asymmetry* **2000**, *11*, 1565.

(9) **1a** was prepared by adopting the literature method as described in ref. 8a. Compound **1b** was prepared by the method as described in: Loh, T.-P.; Li, X.-R. *Eur. J. Org. Chem.* **1999**, *8*, 1893.

(10) For a review, see: (a) Fürstner, A. *Synthesis-Stuttgart* **1989**, 571. For some examples of indium-mediated Reformatsky reactions, see: (b) Araki, S.; Ito, H.; Butsugan, Y. *Synth. Commun.* **1988**, *18*, 453. (c) Johar, P. S.; Araki, S.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 711.

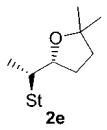
Table 2. Allyl-Transfer Method for the Synthesis of Various Linear 22-Homoallylic Sterols



a: $R^1 = CO_2Et$, $R^2 = H$; **b**: $R^1 = CF_3$, $R^2 = H$; **c**: $R^1 = CH_3$, $R^2 = H$; **d**: $R^1 = Ph$, $R^2 = H$; **e**: $R^1 = R^2 = CH_3$; **f**: $R^1 = H$, $R^2 = CO_2Et$.

entry	SM (1)	catalyst/ (mol %)	*T* (°C)	time (h)	$\Delta^{24,25}$ (*E*/*Z*)[a]	yield (%) (**2**) (22*R*/22S)[b]
1	a	$In(OTf)_3$/(10)	25	48	*E*	<5
2	a	$In(OTf)_3$/(40)	25	16	*E*	68 (89:11)
3	a	$Sn(OTf)_2$/(40)	25	48	*E*	no reaction
4	a	$Cu(OTf)_2$/(40)	25	48	*E*	no reaction
5	a	$Sc(OTf)_3$/(40)	25	48	*E*	no reaction
6	a	*p*-TsOH/(40)	25	48	*E*	no reaction
7	a	TFA/(20)	25	16	*E*	72 (98:2)
8	f	TFA/(20)	25	24		no reaction
9	b	$In(OTf)_3$/(40)	25	16	*E*	<5
10	b	TFA/(20)	25	16	*E*	76 (98:2)
11	c	TFA/(20)	25	8	*E*	74 (98:2)
12	d	TFA/(20)	25	8	*E*	71 (98:2)
13	e	TFA/(20)	25	24		82 (98:2)[c]

[a] Determined through *J* values and NOE NMR analysis. [b] Determined by ^1H NMR. [c] **2e** was isolated as a tetrahydrofuran structure. [d] All reactions were carried out in the absence of the parent aldehyde.



as unreactive substrates for 2-oxonia Cope rearrangement.[4b] In addition, TFA exhibited relatively higher catalytic efficiency than $In(OTf)_3$ (Table 2, entries 9 and 10). Unfortunately, this protocol is not effective for the allyl-transfer reaction of syn substrate (e.g., **1f**, Table 2, entry 8). All products were assigned by comprehensive spectroscopic studies, and a single-crystal X-ray diffraction analysis of **2c** was also carried out (Figure 1).[11]

In view that all the cases employing strong protic acid TFA gave high stereoselectivity, it is unlikely that the acid-promoted epimerization is the side reaction involved. Therefore, a reversible Reformatsky-type reaction pathway was tentatively adopted as an explanation. This postulate is supported by the fact that only substrates with an electron-withdrawing substituent (e.g., CO_2Et, CF_3) gave the undesired 22*S* stereoisomers. In addition, the prevention of allylic anion by acidic proton and the high catalytic efficiency of TFA toward 2-oxonia Cope rearrangement might be two possible reasons for the high selectivity obtained.

In summary, our exploration of the $In(OTf)_3$-catalyzed allyl-transfer reaction of substrates with electron-withdrawing group (e.g., CO_2Et, CF_3) led to the observation of unexpected poor stereoselectivity, which was caused by the involvement of side reaction pathways. Subsequently, it was found that the employment of triflic acid (TFA) as catalyst could successfully suppress the side reaction pathways and, hence, achieve high stereoselectivity. This finding extended the applicability of the allyl-transfer reaction and has been demonstrated in the highly stereocontrolled synthesis of various 22*R*-homoallylic sterols.

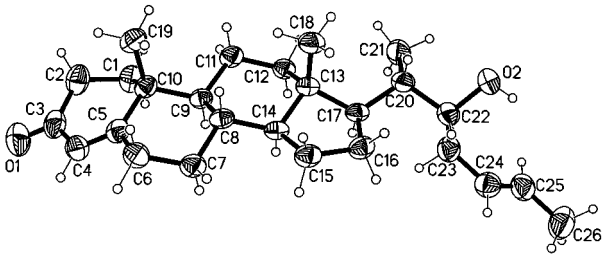


Figure 1. Single-crystal X-ray diffraction analysis of **2c**.

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Supporting Information Available: Complete experimental details, including characterization data for all new compounds; X-ray crystal data for **2c** (CIF format). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) X-ray data for **2c**: $C_{26}H_{40}O_2$; fw = 384.58; orthorhombic; space group $P2_12_12_1$; a = 7.1993(3) Å, b = 10.0365(4) Å, c = 31.1705(13) Å; V = 2252.25(16) Å^3; Z = 4; R1 = 0.0346, wR2 = 0.0747, GOF = 1.058 for 3954 observations with $I > 2\sigma(I)$.