

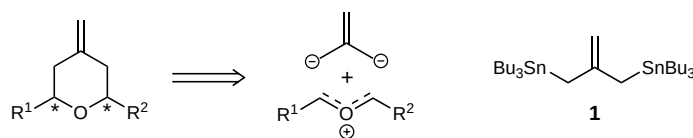
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Sequential Catalytic Asymmetric Allylic Transfer Reaction: Enantioselective and Diastereoselective Construction of Tetrahydropyran Units**

Chan-Mo Yu,* Jae-Young Lee, Byungrun So, and Junghyun Hong

There is considerable interest in the enhancement of catalysts for Lewis acid promoted reactions so that practical and useful levels of asymmetric synthesis can be achieved.^[1] Other research groups have used a ligand-accelerated strategy^[2] to activate the chiral Lewis acid through the internal regulation of the chiral catalyst by a modification of the ligand, thus leading to impressive advances in carbonyl addition reactions.^[3] In previous studies we demonstrated

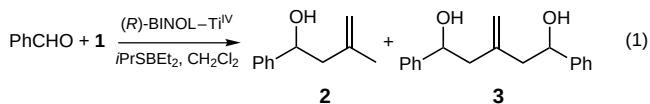
that the use of molecular synergistic reagents in catalytic asymmetric allylic transfer reactions resulted in a significant increased catalytic ability as the chiral catalyst could be regenerated expediently. Our strategy involves the use of BINOL–Ti^{IV} complex (BINOL = 2,2'-binaphthol) as a chiral promoter along with *i*PrSBET₂ or *i*PrSSiMe₃ as an accelerating synergistic reagent. Recently, this approach provided highly catalytic versions of enantioselective allylic transfer reactions of achiral aldehydes, for example, allylation,^[4] propargylation,^[5] allenylation,^[6] and dienylation.^[7] The efficiency of this protocol in terms of enantioselectivity and catalytic ability has encouraged us to apply the extension of this method to more versatile systems, which would expand the scope and utility of allylic transfer reactions. Described herein is an extension of our strategy aimed at finding new reagents and realizing practical ways to advance new levels of asymmetric synthesis. In this study we focus on the sequential addition of a bifunctional reagent to two aldehydes to form an asymmetric tetrahydropyran system (Scheme 1). An efficient method for



Scheme 1. General protocol for the synthesis of a tetrahydropyran by means of sequential allylic transfer reactions.

this reaction would be useful in the synthesis of biologically active substances that contain a tetrahydropyran unit.^[8] Several crucial points emerged from this investigation, including the development of a new catalyst and reagents for the sequential allylic transfer reaction, the introduction of highly efficient promoters for the formation of the tetrahydropyran ring, and the highly stereoselective synthesis of four different tetrahydropyran systems that contain an exocyclic double bond.

Our initial studies began with bis-stannane **1** as a dianion equivalent which was prepared from Bu₃SnLi (two equivalents) and methallyl dichloride at –78 °C in THF. Initial attempts to add **1** to benzaldehyde in the presence of BINOL–Ti^{IV} [a 2:1 mixture of BINOL and Ti(O*i*Pr)₄]^[9] were not successful. The reactivity was improved by introducing a synergistic reagent.^[4–7] Treatment of **1** with benzaldehyde in the presence of the catalyst (10 mol %), followed by the dropwise addition of *i*PrSBET₂ at –20 °C for 20 h in CH₂Cl₂ afforded undesired **3** and **2** in a combined yield of 44 % (2:1) [Eq. (1)]. The formation of alcohol **2** was attributed to a

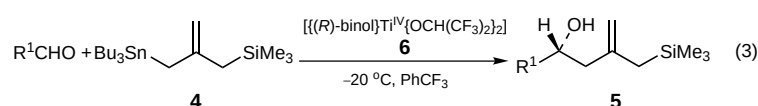
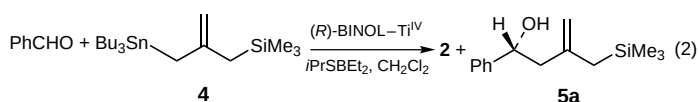


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group in **1**. As a consequence, the bifunctional reagent **4** was considered for this study [Eq. (2)].^[10]

Initial experiments on the allylic transfer reaction of **4** with benzaldehyde promoted by (*R*)-BINOL–Ti^{IV} (10 mol %) with *i*PrSBET₂ under similar conditions (–20 °C for 18–24 h in CH₂Cl₂) led to encouraging but marginal results. Although alcohol **3** was not produced during the reaction, the formation of **2** (≈15 %) and the low yield of the desired **5a** (35 to 41 %) remained to be solved.^[11] After exploring various conditions, we were delighted to find that the use of alcohol-free [(*R*)-binol]Ti^{IV}{OCH(CF₃)₂}₂ (**6**) as a chiral promoter in PhCF₃ always led to the best results in terms of yields and enantioselectivities. Furthermore, when **6** was used alone without any synergistic reagent, the new catalytic process was usually complete within 12 h at –20 °C.



The allylic transfer reaction was conducted by the dropwise addition of **4** in PhCF₃ at –20 °C to a mixture of **6** (5 mol %) and benzaldehyde in PhCF₃. After 12 h at –20 °C, the mixture was quenched by the addition of saturated aqueous NaHCO₃. Workup and chromatography on triethylamine-treated silica gel gave **5a** [Eq. (3)], R¹ = Ph, 89 %, 96 % *ee*). The reliability of the catalytic reaction was further examined with a variety of aldehydes, including aldehydes that contain a second carbonyl group (Table 1). After the conversion of **5** into **2** under acidic conditions, the absolute configuration of the predominating enantiomer of the adducts **5** was unambiguously established by comparison of their specific rotations with those of known alcohols.^[4]

The second challenge in this study was the development of synthetic routes from **5** to a variety of tetrahydropyran units (Scheme 2). It was envisaged that this could be accomplished by the formation of an oxocarbenium ion from **5** or **7** with an aldehyde, with a subsequent allylic transfer reaction.^[12] Nonetheless, each of the published approaches suffers from major disadvantages, such as low conversions and diastereoselectivities, and often partial isomerization of the exocyclic double bond to the endocyclic form. For example, treatment of **7a** with hydrocinnamaldehyde in the presence of TMSOTf (10 mol %; Tf = trifluoromethanesulfonyl) gave **8a** in only 24 % yield and with a 7:1 diastereoselectivity (after chromatography), together with several unidentified products. A survey of several Lewis acids, for example, TiCl₄, TiCl₂(OiPr)₂, SnCl₄, BF₃·OEt₂, and EtAlCl₂, provided no significant advantages and even gave poorer results. However, when TMSNTf₂^[13] was employed as a promoter, the cyclization process was greatly improved in terms of yield and diastereoselectivity (**7a**, PhCH₂CH₂CHO, TMSNTf₂

Table 1. Allylic transfer reaction from **4** to achiral aldehydes.^[a]

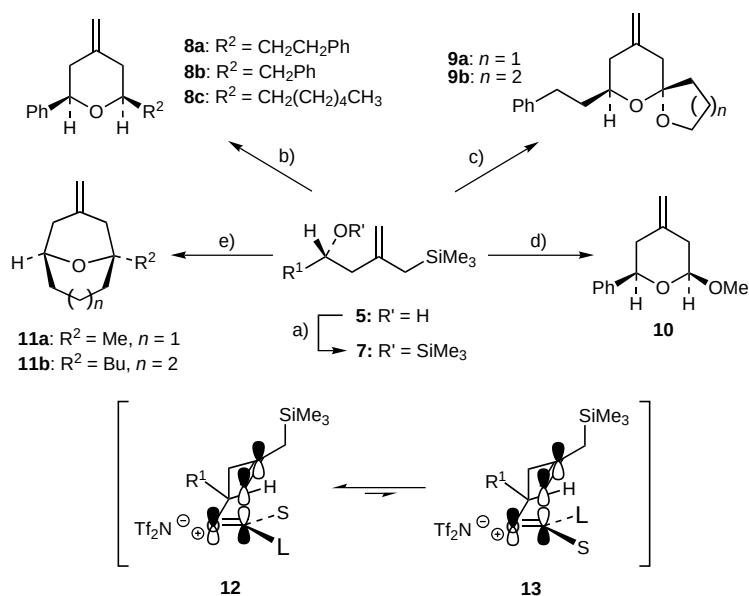
Entry	R ¹ CHO	5	<i>t</i> [h]	yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	Ph	a	12	89	96
2	PhCH ₂ CH ₂	b	12	74	91
3	<i>n</i> C ₆ H ₁₃	c	12	69	97
4	PhCH=CH	d	17	54	93
5	EtO ₂ CCH ₂ CH ₂ CH ₂	e	14	71	91
6	CH ₃ COCH ₂ CH ₂ CH ₂	f	14	94	90
7	BuCOCH ₂ (CH ₂) ₂ CH ₂	g	16	87	92
8	BuCOCH ₂ CH ₂ CH ₂	h	16	87	95

[a] The reaction was run at –20 °C in PhCF₃ with **6** (5 mol %). [b] Yields of isolated and purified products. [c] Enantiomeric excesses were determined by preparation of (+)-MTPA ester derivatives, analysis by 500-MHz ¹H NMR spectroscopic analysis (all entries), and by HPLC analysis on a chiral column (Chiracel OD-H, 3–5 % *i*PrOH in hexane, entries 1, 2, 4, and 6).

(10 mol %), CH₂Cl₂, –78 °C, 1 h; **8a**, 78 %, d.r. 17:1). This Lewis acid was superior to others for the conversion of **5** or **7** into **8**, **9**, and **10** and was chosen for systematic studies (Scheme 2).^[14] An improved synthetic route from alcohol **5a** (R¹ = Ph) gave **8a–c** in high yields and diastereoselectivities. As expected, the reaction of **7b** with 2,2-dimethoxytetrahydrofuran or pyran in the presence TMSNTf₂ gave **9a** and **9b**, respectively.

We were unable to detect the alternate diastereomers by 500-MHz ¹H and ¹³C NMR spectroscopic analysis of the crude products, and the relative stereochemistry was confirmed by NOE experiments. In close analogy, treatment of **7a** with orthoformate under the same conditions afforded **10** in 83 % yield (d.r. 11:1).

The internal chirality transfer during the cyclization is probably a result of the geometrical preference for **12** rather



Scheme 2. Reagents and conditions: a) TMSCl, Et₃N, 0 °C, 2 h, CH₂Cl₂, 86–97 %; b) 1. **5a**, R²CHCl(OMe), *i*PrNEt₂, 0–23 °C, 12 h, CH₂Cl₂; 2. TMSNTf₂ (10 mol %), –78 °C, 1 h, CH₂Cl₂ (**8a**, 91 %, d.r. 55:1; **8b**, 84 %, d.r. 37:1; **8c**, 87 %, d.r. 33:1); c) **7b**, 2,2-dimethoxytetrahydrofuran or -pyran, TMSNTf₂ (10 mol %), –78 °C, 1 h, CH₂Cl₂ (**9a**, 81 %; **9b**, 76 %); d) **7a**, CH(OMe)₃, TMSNTf₂ (10 mol %), –78 °C, 1 h, CH₂Cl₂ (83 %, d.r. 11:1); e) **7f** or **7h**, Sn(OTf)₂ (10 mol %), Me₃SiPh (2 mol %), 0–23 °C, 2 h, CH₂Cl₂ (**11a**, 78 %; **11b**, 82 %).

than for **13**: a small pseudoaxial group minimizes allylic strain with the existing stereogenic center (Scheme 2). Thus, this allylic transfer reaction led to the formation of a *cis* tetrahydropyran with high diastereoselectivity through the stereochemical model **12**.

Having been successful in forming bridged pyran ring **11**, we tried to extend this approach to intramolecular allylic transfer reactions.^[15] We were surprised that **7 f** and **7 h** did not cyclize on treatment with a variety of Lewis acids and modified substrates. After surveying numerous reaction conditions, we were gratified to find that the use of Sn(OTf)₂ and Me₃SiSPh in the intramolecular allylic transfer reaction led to the formation of **11** as the sole product (Scheme 2, e). The use of catalytic amounts of TMSSPh was crucial, presumably as a result of the formation of a thioketal intermediate, which formed a oxocarbenium ion under mediation of the tin catalyst.

In summary, we have described herein a new synthetic strategy for the stereoselective synthesis of tetrahydropyrans with an exocyclic double bond by means of a catalytic asymmetric sequential allylic transfer reaction in a very general and efficient way, which promises to be widely applicable. We believe that the products can serve as synthetic intermediates for useful substances.

Experimental Section

6:^[16] (*R*)-BINOL and Ti(OiPr)₄ (1:1) in the presence of 4-Å molecular sieves at 45 °C in PhCF₃ for 2 h afforded (*R*)-BINOL–Ti^{IV} complex. 1,1,1,3,3,3-Hexafluoro-2-propanol (2 equiv) was added to the resulting mixture. The solution was stirred at 45 °C for an additional 2 h and the volatile materials were evaporated under high vacuum (≈0.5 mmHg) in a Schlenk tube. Freshly distilled PhCF₃ was added.

Typical procedure (Table 1, entry 1): A flame-dried Schlenk flask that contained (*R*)-BINOL (57.3 mg, 0.2 mmol) and activated powdered 4-Å molecular sieves (1.0 g) was evacuated, carefully purged with nitrogen three times, and then charged with dry PhCF₃ (2 mL) followed by freshly distilled Ti(OiPr)₄ (freshly prepared, 0.5 M in PhCF₃, 0.4 mL, 0.2 mmol). The mixture was allowed to proceed at 45 °C for 2 h. After cooling to 23 °C, 1,1,1,3,3,3-hexafluoro-2-propanol (68 mg, 0.4 mmol) was added. The resulting solution was warmed to 45 °C and heated for 2 h. The solution was cooled to 23 °C and concentrated under vacuum (≈0.5 mmHg) in a Schlenk tube. The vacuum line was equipped with a drying tube (CaSO₄). Freshly distilled PhCF₃ (3 mL) was added, the homogeneous solution of **6** was cooled to –20 °C in a dry ice/CCl₄ bath, and treated with benzaldehyde (R¹ = Ph, 0.44 g, 4.0 mmol) in PhCF₃ (1 mL). The temperature was kept below –20 °C, while **4** (1.67 g, 4.0 mmol) in PhCF₃ (2 mL) was added dropwise through a gas-tight syringe to this mixture over 20 min along the wall of the flask by using a syringe pump. After stirring for 12 h at –20 °C, aqueous NaHCO₃ (5 mL) was added to the reaction mixture, which was then diluted with CH₂Cl₂ (20 mL). The molecular sieves were removed by filtration, and the aqueous layer was extracted with CH₂Cl₂ (≈20 mL). After the combined organic solution was dried over anhydrous Na₂SO₄, the solvents were removed under reduced pressure. Column chromatography (15% EtOAc in hexanes) afforded **5 a** (R¹ = Ph, 0.835 g, 3.56 mmol, 89%) as a colorless liquid. *R*_f = 0.26 (15:1 hexane/EtOAc); [α]_D²⁰ = +27.08 (c = 1.230, CHCl₃); 96% *ee* determined by means of HPLC on a Daicel OD-H column [hexane/iPrOH 97:3; *t*_r(major) = 12.4 min, *t*_r(minor) = 14.2 min]; FTIR (neat): $\tilde{\nu}$ = 3404.7 (br), 3069.9, 2953.6, 1631.7, 1250.0, 848.3 cm^{–1}; ¹H NMR (500 MHz, CDCl₃): δ = 0.03 (s, 9H; Si(CH₃)₃), 1.59 (ddd, *J* = 0.92, 13.42, 13.42 Hz, 1H; (CH₃)₃SiCHH), 1.63 (ddd, *J* = 0.92, 13.42, 13.42 Hz, 1H; (CH₃)₃SiCHH), 2.29 (d, *J* = 1.83 Hz, 1H; OH), 2.34 (dd, *J* = 9.46, 13.73 Hz, 1H; HOCHCHHC = C), 2.37 (ddd, *J* = 0.92, 3.97, 13.73 Hz, 1H; HOCHCHHC = C), 4.75 (d, *J* = 0.91 Hz, 1H; C = CHH), 4.78 (d, *J* = 0.91 Hz, 1H; C = CHH), 4.80 (dd, *J* = 0.92, 3.97 Hz, 1H; HOCH), 7.33–7.39 (m, 5H; Ph); ¹³C NMR (125 MHz, CDCl₃): δ = –0.95, 26.93,

49.48, 71.57, 111.49, 126.16, 127.80, 128.80, 144.44, 144.82; calcd for C₁₄H₂₂OSi: C 71.73, H 9.46; found: C 71.33, H 9.55.

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