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Report

Enantioselective, Chromium-catalyzed, Natural Product, Prins cyclization, Tetrahydropyran

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Enantioselective Synthesis of *cis*-2,6-Disubstituted-4-methylene Tetrahydropyrans via Chromium Catalysis

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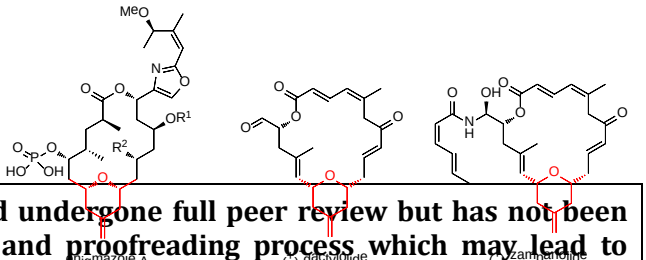
Summary of main observation and conclusion. Enantioenriched 2,6-disubstituted 4-methylene tetrahydropyrans have been obtained via a two-step sequence consisting of a highly enantioselective chromium-catalyzed carbonyl 2-(trimethylsilyl methyl)allylation and Prins cyclization. Commercially available (2-(chloromethyl)allyl)trimethylsilane serves as the bifunctional linchpin to combine two aldehydes to assemble the 2,6-disubstituted pyrans. A variety of functional groups are compatible under the mild reaction conditions. The synthetic utility of this methodology was demonstrated by the asymmetric synthesis of 16 examples of homoallylic alcohol and 8 examples of 2,6-disubstituted 4-methylene tetrahydropyrans, including an advanced intermediate which could be transformed to natural product centrolobine via a known procedure.

Background and Originality Content

As functionalized heterocycles are widely present in bioactive natural products and medicinally relevant molecules, efficient, practical and stereoselective synthetic methods for heterocycles are critical to both medicinal and synthetic organic chemistry. Especially, chiral pyrans represent a ubiquitous class of heterocyclic compounds. Within them, 2,6-disubstituted 4-methylene tetrahydropyrans attract historically prolonged research interests as this moiety are observed as cores in a number of macrolactone natural products, such as enigmazole A and zampanolide, which exhibit potent and special anti-cancer bioactivities (**Scheme 1**).[1] Several elegant synthetic strategies have been developed to construct this segment, including Smith's Petasis–Ferrier union/rearrangement strategy[2a] and the intramolecular ene reaction.[2b] Very recently, Trost et al. reported an elegant synthesis of bryostatin 3, notably, a metal-catalyzed enyne cyclization cascade was used to construct the 4-methylene tetrahydropyran ring.[3a] Song et al. completed an expedient synthesis of bryostatin 8 via a organosilane intermediate.[3b] Within those preparation, carbonyl allylation - Prins cyclization[4] in the presence of chiral agent holds the promise for a convergent synthetic approach. To date, a variety of allylic organometallic reagents utilizing boron,[5] silicon,[6] tin,[7] zinc,[8] nickel,[9] indium,[10] and ruthenium[11] have been successfully applied to the carbonyl addition, however mainly in stoichiometric and racemic versions. Asymmetric catalysis have limited success using tin reagent.[7b,7c] Given the wide occurrence of this type of molecular skeleton, new catalytic systems for asymmetric preparation of 2,6-disubstituted 4-methylene tetrahydropyrans under mild reaction conditions with tolerance of broad and sensitive functionalities are highly desired.

To this end, we turned our attention to enantioselective chromium-catalyzed addition of functionalized carbohalides to aldehyde, well-known as the Nozaki-Hiyama-Kishi reaction when catalytic amount of Ni salt was employed.[12a-f] The discovery of this catalytic system, as well as the chiral ligands, led to a number of elegant synthesis of complex natural product.[12g-i] On the other hand, utilization of the commercially available 2-(chloromethyl)allyl)trimethylsilane in 2,6-disubstituted 4-methylene tetrahydropyrans synthesis has been only briefly investigated in chromium and indium catalysis in an symmetric version.[13] The asymmetric version, however, remains an unrealized challenge. In line with our interests in developing efficient asymmetric chromium catalyst,[14] we expect a suitable chiral catalytic system should impart enantioselectivity in this important transformation. Herein, we wish to report a highly enantioselective 2-(trimethylsilyl methyl)allylation reaction highlighted by a chromium catalysis system. The resulting homoallylic alcohols were treated with TMSOTf in the presence of aldehydes, providing synthetically useful enantioenriched 2,6-disubstituted 4-methylene tetrahydropyrans as single diastereomers. To our delight, this reaction exhibits broad functional group compatibility and mild reaction conditions.

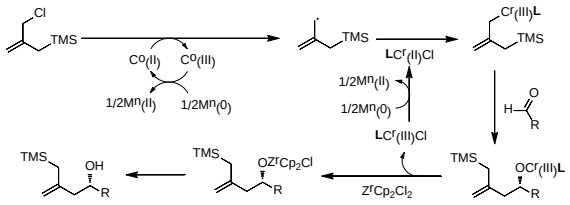
Scheme 1 Representative Natural Products.



Results and Discussion

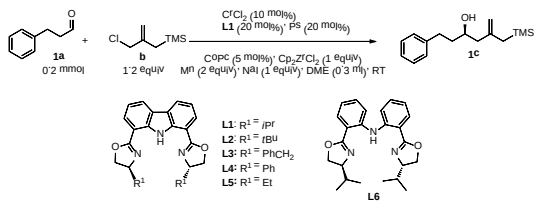
Based on our previous research experiences and many others',[14,15] a general experimental procedure for organochromium allylation was designed as follows to initiate our research (**Scheme 2**) : (1) chromium chiral catalyst could be formed in-situ through complexation step in which $CrCl_2$ was treated with chiral ligand and bases, preferred proton sponge for easily handing; (2) allylic radical species could be generated via treatment of allylic chloride with radical initiator, such as CoPc, and subsequently transformed to allylic chromium(III) utilizing chromium chiral catalyst; (3) The resulting chiral allylic chromium (III) would be subject to addition of the aldehyde, followed by Zr or Si dissociation of O-Cr bond, to yield the desired enantioenriched homoallylic alcohol. During this process, Mn was selected as a reducing reagent.[17a]

Scheme 2 proposed reaction mechanism



To practice our proposal and encouraged by previous success with carbazole-based bisoxazolines (Nakada ligands),[15f] a number of representative chiral ligands (was selected in our preliminary model study utilizing (2-(chloromethyl)allyl)trimethylsilane (**1a**) and 3-phenylpropanal (**1b**) (**Table 1**).

Table 1 Evaluation of Chiral Ligands and Other Reaction Parameters

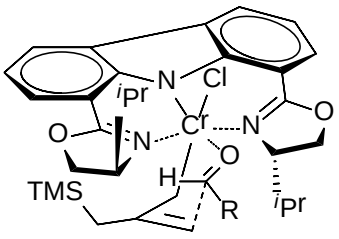


entry[a]	ligand and deviation from the standard	yield (%)[b]	ee (%)[c]
1	None	88	87
2	**L2**	57	81
3	**L3**	60	77
4	**L4**	34	70
5	**L5**	69	80
6	**L6**	35	86
7	$CrCl_2$ 5 mol %, **L1** 10 mol %	60	85
8	Without CoPc	18	--
9	$NiCl_2$ instead of CoPc	75	75
10	THF instead of DME	81	83
11	CH_3CN instead of DME	trace	--
12	Without $CrCl_2$	--	--
13	Without NaI	30	--
14	Without PS	<5%	--
15	CsI instead of NaI	trace	--
16	LiI instead of NaI	36	84
17	Allyl iodide instead of chloride	83	85
18	1 mmol of aldehyde	87	87

[a]The reactions were carried out at 0.2 mmol scale unless noted otherwise. [b]Isolated yield. [c]Determined by chiral HPLC analysis, absolute configuration was assigned by comparison of the specific rotation to literature value (see the Supporting Information). [d] without NaI. PS = proton sponge.

In addition to ligand screening, the impact of various deviations from the standard reaction conditions was also evaluated. Lower catalyst loading ($CrCl_2$ 5 mol %, **L1** 10 mol %) resulted in decreased yield and ee (60% yield, 85% ee, Table 1, entry 7). The presence of CoPc and NaI proved critical to the efficiency of the coupling reaction, as the yield of **1c** decreased under conditions with absence of either of two components (Table 1, entry 8 and 13). CoPc were reported to significantly increase the rate of Cr-catalyzed process; [16] NaI have similar functions to increase the rate of transmetallation to the chiral chromium complex and likely facilitate the reduction of allyl halide through Cl/I exchange, notably, the reaction of allyl iodide provided similar result. The screening of solvents revealed that DME was optimal among those tested (entry 10 and 11). Both TMSCl [17] and $ZrCp_2Cl_2$ [18] worked well as dissociating agent of chromium-alkoxides. In this case, $ZrCp_2Cl_2$ was selected for further studies because deprotection of TMS might be problematic due to the coexistence of same functionality in the product. It's worthy to point out, no allylation took place in the absence of $CrCl_2$, indicating the formation of products through allylcobalt and allylzirconium species are less likely (Table 1, entry 12).

Scheme 3 Proposed transition state



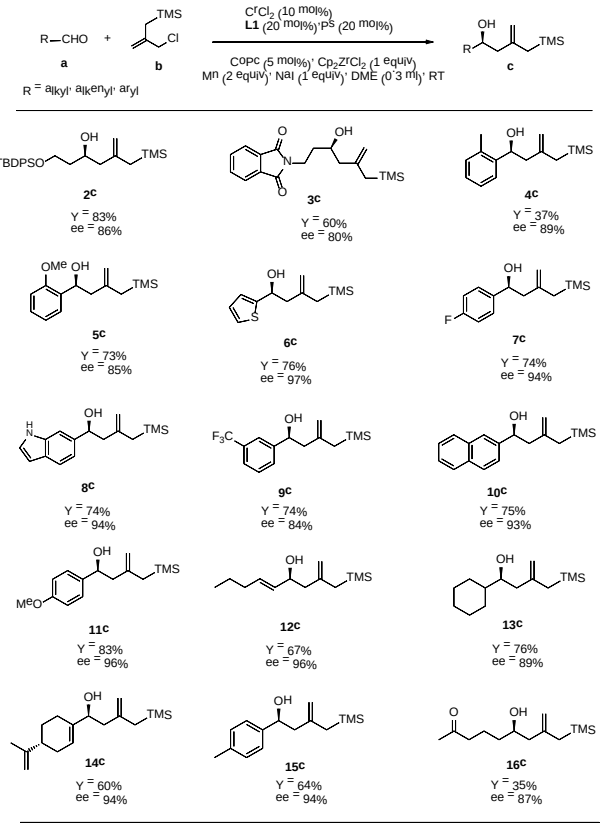
Si attack (R = aryl or alkenyl groups)

Notably, the reaction scale could be increased to 1 mmol with maintenance of the efficiency (Table 1, entry 18). All those experimental results are consistent with our proposed mechanism (Scheme 3). A transition state was also proposed to account for the preferential formation of the (*S*)- enantiomer of product (Scheme 3).

Utilizing our optimized conditions found in the model study, this highly enantioselective synthesis of **1c** could also be expanded to reactions with a broad range of aldehydes to yield desired products with high enantioselectivity (80 – 97% ee, **Scheme 4**). In addition, the versatility of this reaction was also proved through the efficient allyl additions to most of the 16 highly representative aldehydes with aliphatic (alkyl, alkenyl), aromatic and heterocyclic functional groups. Notably, the low yield of **4c** is possibly due to the steric hindrance. The ketone in **16c** interfered with the nucleophilic addition resulting in low yield.

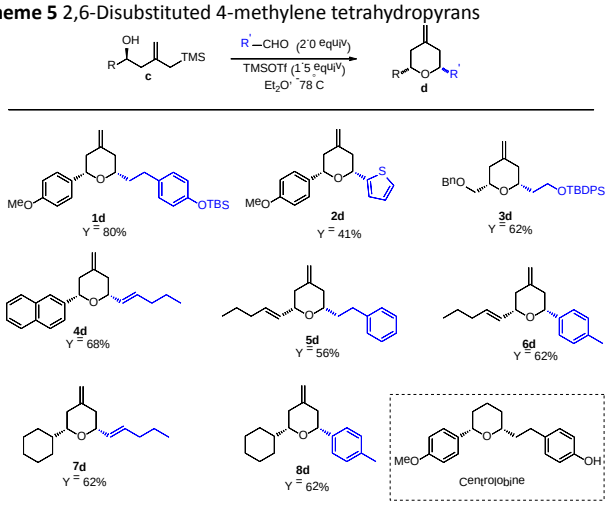
With the enantioenriched homoallylic alcohols in hand, our attention turned to the synthesis of 2,6-disubstituted 4-methylene tetrahydropyrans through Prins cyclization. After a brief condition screening, we found that 1.5 equivalents of TMSOTf appeared to be the most efficient reagent to combine the homoallylic alcohol with the aldehyde to yield the desired product as a single diastereomer. In order to demonstrate the synthetic potential of our methodology, 8 diversified 2,6-disubstituted 4-methylene tetrahydropyrans (R' = alkyl, alkenyl and aryl) was synthesized with perfect diastereomer ratio (**Scheme 5**) which is in accordance with literature reports.[7b,7c] Within the products, it is worthy to mention that compound **1d** comprised the whole carbon skeleton and all stereocenters of natural product centrolobine, and could be transformed to the natural product with a known procedure.[10a]

Scheme 4 Substrate Scope Studies with aldehyde [a,b]



[a]Reaction conditions: $CrCl_2$ (10 mol%), **L1** (20 mol%), Ps (20 mol%), CoPc (5 mol%), Cp_2ZrCl_2 (1 equiv), Mn (2 equiv), NaI (1 equiv), DME (0.3 ml), RT. [b]Isolate yields.

Scheme 5 2,6-Disubstituted 4-methylene tetrahydropyrans



Conclusions

In summary, a highly enantioselective synthesis of 2,6-disubstituted 4-methylene tetrahydropyrans has been achieved through a two-step cascade including a novel chromium-catalyzed asymmetric carbonyl allylation followed by a Prins cyclization. As an overall picture of the whole cascade, the commercially available 2-(chloromethyl)allyl)trimethylsilane serves as a linchpin to connect two pieces of aldehydes together to form highly functionalized pyran moiety. [19] This catalytic synthetic approach provides a powerful tools to access ubiquitous 2,6-disubstituted 4-methylene tetrahydropyrans in a highly stereocontrolled and convergent manner. Future work will focus on expanding this catalytic system to other chromium-mediated transformations and applying this protocol to the synthesis of complex molecules with biological and medicinal significance.

Experimental

Generally information

Unless stated otherwise, all reactions were carried out in flame-dried glassware under a dry nitrogen atmosphere. All solvents were purchased and without further purified and dried. All manipulations were carried out under nitrogen using 10 ml tube with a seal. All glassware was oven or flame dried prior to use. All solvents were purified and dried according to standard methods prior to use, unless stated otherwise. All reagents were obtained from commercial sources and used without further purification. Thin-layer chromatography (TLC) was performed using 60 mesh silica gel plates visualized with short-wavelength UV light (254 nm). Silica gel 60 (200 - 300 mesh) was used for column chromatography. ^{1}H NMR spectra were obtained at 400 MHz and recorded relative to the tetramethylsilane signal (0 ppm) or residual proton-solvent. ^{13}C NMR spectra were obtained at 100 MHz, and chemical shifts were recorded relative to the solvent resonance ($CDCl_3$, 77.0 ppm). Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br = broad singlet, coupling constant(s) in Hz, integration). IR spectra were recorded on a Nicolet FT-IR spectrometer and only major peaks are reported in cm-1. For EI-HR and ESI-HR spectrometer were applied.

Chemicals were purchased from commercial suppliers. Unless stated otherwise, all the substrates and solvents were purified and dried according to standard methods prior to use. Reactions requiring inert conditions were carried out in glove box.

General procedure for coupling products

General procedure for the synthesis of 1c-16c: To a mixture of anhydrous chromium(II) chloride (10 mol%), 1,8-bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-9H-carbazole (**L1**, 20 mol%) and proton sponge (20 mol%) was added DME (0.3 ml) under an nitrogen atmosphere. The mixture was stirred vigorously at room temperature for 2h before it was transferred into a vessel charged with CoPc (0.5 mol%), NaI (1.0 equiv), Zr(Cp)2Cl2 (1.0 equiv), and manganese powder (2.0 equiv). Then aldehyde (0.2 mmol, 1.0 equiv) and (2-(chloromethyl)allyl)trimethylsilane (1.5 equiv) were added. The resulting suspension was left stirred at ambient temperature for 18 hours. After the full consumption of aldehyde, the reaction mixture was diluted with undried ethyl acetate (2 ml). Then resulting suspension was filtered over a pad of silica gel using cosolvent (hexane: ethyl acetat = 5:1) as eluent. Volatiles were evaporated in vacuo. The residue was purified by basified (Et_3N) chromatography which afforded the final product.

The ee was determined by HPLC analysis with Chiralcel OD and IE et al. columns. The absolute configuration was assigned by comparing the optical rotation with that of reported analogs. [7]

(R)-1-phenyl-5-((trimethylsilyl)methyl)hex-5-en-3-ol (**1c**) (8.4 mg, 0.04 mmol) was prepared from 3-phenylpropanal (6.7 mg, 0.05 mmol) as yellow oil in 80% yield.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.16 (m, 1H), 4.70 (d, *J* = 3.7 Hz, 1H), 3.77-3.69 (m, 1H), 2.87-2.78 (m, 1H), 2.74-2.63 (m, 1H), 2.17 (dd, *J* = 13.5, 2.8 Hz, 1H), 2.05 (dd, *J* = 13.6, 9.5 Hz, 1H), 1.91 (d, *J* = 1.9 Hz, 1H), 1.79 (ddd, *J* = 11.4, 8.2, 5.2 Hz, 1H), 1.52 (dd, *J* = 31.2, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.5, 142.1, 128.4, 128.3, 125.7, 110.5, 67.8, 46.6, 38.6, 32.1, 26.6, -1.4. IR (neat) cm^{-1} ṽ: 3407. 3069. 3027. 2951. 2924. 2858, 1631, 1604, 1495, 1454, 1418, 1247, 1154, 1071, 1052, 1030, 839, 769, 745, 697, 631; HRMS (EI(+), 70 eV) : $C_{16}H_{26}OSi$ $[M-H_2O]^+$: calcd. 244.1647, found. 244.1645; $[\alpha]_D^{20}$ = +33.7 (c = 0.70, CH_2Cl_2); HPLC (Chiralcel OD-H column, hexanes:i-PrOH = 90:10, 1.0 ml/min, 210 nm), t_{minor} = 4.0 min, t_{major} = 5.3 min, 87% ee.

General procedure for the synthesis of 1d-8d: To a solution of *β*-hydroxy allylsilane (1.0 equiv) in diethyl ether (2.0 ml), aldehyde (2.0 equiv) was added, and the mixture was cooled to -78 ℃. TMSOTf (1.5 equiv) was added and the mixture was stirred for 1h at -78 ℃. Aqueous NaOH solution (1 M) was added and the mixture was brought to rt., then transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 5 ml). The organic layers were combined and washed with brine (5 ml), then dried over MgSO4. The solvents were evaporated under reduced pressure and the crude material was purified by flash chromatography to afford 2,6-cis-disubstituted 4-methylenetetrahydropyrans.

tert-butyl(4-(2-((2S,6S)-6-(4-methoxyphenyl)-4-methylenetetrahydro-2H-pyran-2-yl)ethyl)phenoxy)dimethylsilane ***(1d)*** (87 mg, 0.2 mmol) was prepared from **11c** (66.1 mg, 0.25 mmol) as colorless oil in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.33 (m, 2H), 7.08-7.04 (m, 2H), 6.94-6.90 (m, 2H), 6.79-6.74 (m, 2H), 4.79 (d, *J* = 1.5 Hz, 2H), 4.28 (dd, *J* = 11.4, 2.3 Hz, 1H), 3.82 (s, 3H), 3.47-3.37 (m, 1H), 2.84-2.63 (m, 2H), 2.47 (d, *J* = 13.2 Hz, 1H), 2.26 (t, *J* = 12.6 Hz, 2H), 2.08 (t, *J* = 12.3 Hz, 1H), 2.01–1.92 (m, 1H), 1.87-1.74 (m, 1H),1.00 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.9, 153.5, 144.8, 134.9, 134.8, 129.3, 127.1, 119.8, 113.7, 108.7, 79.5, 55.2, 42.5, 40.5, 38.0, 30.8, 25.7, 18.2, -4.4. IR (neat) cm^{-1} ṽ: 3072, 2931, 2895, 2857, 1652, 1611, 1585, 1510, 1464, 1248, 1172, 1093, 1067, 1006, 912, 825, 778, 689, 624; HRMS (EI(+), 70 eV) : $C_{27}H_{38}O_3Si$ $[M]^+$: calcd. 438.2590, found. 438.2600; $[\alpha]_D^{20}$ = -27.4 (c =3.16 , CH_2Cl_2).

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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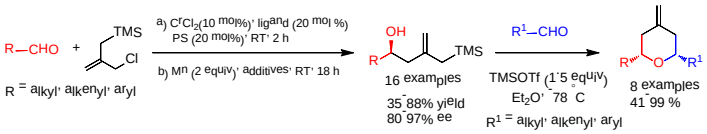
Enantioselective Synthesis of *cis*-2,6-Disubstituted-4-methylene Tetrahydropyrans via Chromium Catalysis



Enantioenriched 2,6-disubstituted 4-methylene tetrahydropyrans have been obtained via a two-step sequence consisting of a highly enantioselective chromium-catalyzed carbonyl 2-(trimethylsilyl methyl)allylation and Prins cyclization. Commercially available (2-(chloromethyl)allyl)trimethylsilane serves as the bifunctional linchpin to combine two aldehydes to assemble the 2,6-disubstituted pyrans.

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