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Intramolecular titanium-promoted deoxygenative cyclization to 9-substituted-1,2,3,4-tetrahydrofluorene skeleton

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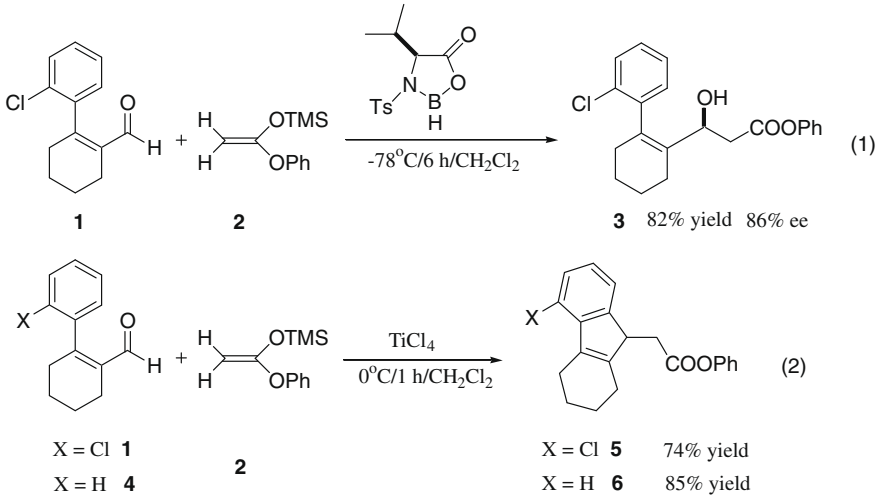
ABSTRACT

The Mukaiyama aldol reaction of 2-aryl-1-cyclohexene-1-carboxaldehydes with phenyl trimethylsilyl ketene acetal unexpectedly resulted in the formation of 9-substituted-1,2,3,4-tetrahydrofluorene derivatives via a novel intramolecular titanium-promoted deoxygenative cyclization. By successive treatment of the corresponding allyl alcohols with *n*-butyllithium and titanium tetrachloride, the cyclization products were obtained in good yields.

Tetrahydrofluorenes are ideal tricyclic precursors for the synthesis of gibberellin A diterpenoid[1] and are also recognized to be effective ligands for metallocenes.[2] However, direct synthetic routes to the substituted tetrahydrofluorenes have been limited.[3] We have recently reported the first asymmetric synthesis of anesthetic (*S*)-ketamine through 1,3-chirality transfer from an optically pure (*S*)-alcohol, prepared by enantioselective reduction with (*S*)-BINAL-H.[4] An alternative synthesis introducing the chirality to the corresponding (*S*)-alcohol by C–C bond formation has been examined using the chiral oxazaborolidinone-promoted enantioselective aldol reaction.[5] The reaction of 2-(*o*-chlorophenyl)-1-cyclohexene-1-carboxaldehyde (**1**)[6] with phenyl trimethylsilyl ketene acetal (**2**) gave the (*S*)-aldol product **3** in high enantioselectivity (Eq. 1 in Scheme 1).[7] During the process of determining the enantioselectivity of the aldol reaction, the preparation of racemic **3** led to an unexpected reaction (Eq. 2 in Scheme 1), that is, an unknown



Scheme 1.

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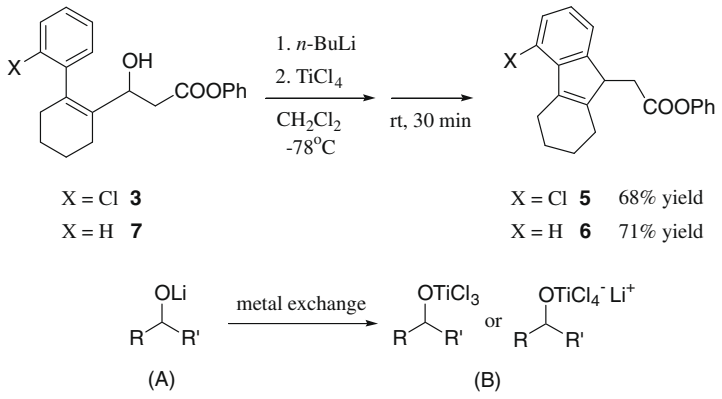


Scheme 2.

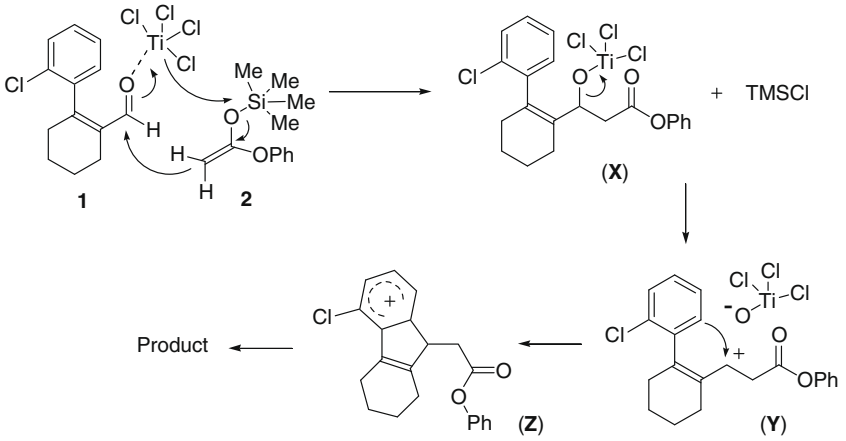
intramolecular cyclization was induced in the Mukaiyama aldol reaction. We disclose herein a novel titanium-promoted deoxygenative cyclization.

The Mukaiyama aldol reaction of **1** with **2** in the presence of stoichiometric titanium tetrachloride resulted in the formation of a large amount of an unknown compound.[8] The structure of the compound was elucidated to be 9-substituted-1,2,3,4-tetrahydrofluorene **5**, supported by comparison with the spectral data of the unsubstituted tetrahydrofluorenes.[9] The reaction of aldehyde **4** without the *ortho*-chloro substituent also smoothly produced the cyclization product **6** in an 85% yield. The cyclization is considered to have taken place via a titanium aldolate intermediate in the reaction. Apparently, the cyclization requires an unavoidable approach between the hydroxyl carbon moiety and the aryl *ortho* position, arisen from the *Z*-geometry in the titanium aldolate intermediate. If the intermediate is formed by a different method, the cyclization may be realized. Then, we envisaged generating the key intermediate by treating racemic **3** with *n*-butyllithium and titanium tetrachloride (Scheme 2). The sequence was expected to form lithium alkoxide **A**, followed by the metal exchange reaction to afford titanium alkoxide (or the corresponding ate complex) **B**. A CH_2Cl_2 solution of **3** was stirred with 1 mol equiv of *n*-butyllithium at −78 °C (low temperature was used to prevent a retro-aldol reaction), followed by the addition of one equiv of titanium tetrachloride. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. The expected **5** was obtained in a 68% yield. The reaction using the aldol **7** without the *ortho*-chloro substituent also resulted in the formation of the corresponding product **6** (71% yield), so the *ortho*-chloro substituent is not essential for the cyclization.

From a mechanistic viewpoint, an effective deoxgenative process occurs during the cyclization. The deoxygenative coupling of titanium alkoxides, derived from allyl and benzyl alcohols, has been reported only under radical conditions[10], but that is not what was shown in our case. A plausible electrophilic aromatic substitution (S_EAr) mechanism is conceivable for the deoxygenative cyclization, as shown in Scheme 3. Here, the titanium aldolate intermediate **X** is converted to allyl cationic species **Y** and then to **Z** by being assisted with steric demands.

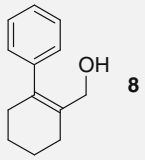
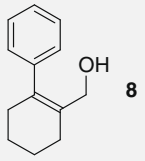
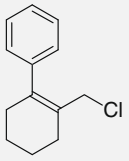
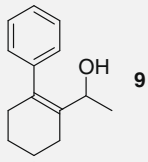
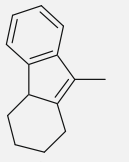
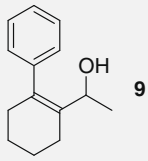
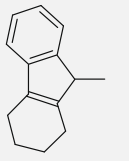
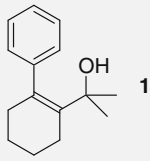
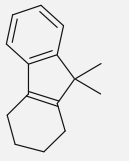
On the basis of the cyclization method (Scheme 2), we tried cyclizing allylic alcohols by the successive treatment with *n*-butyllithium and titanium tetrachloride. The results are summarized in Table 1. The reaction of primary allyl alcohol **8** at 0 °C gave complex mixtures but the reaction at −78 °C gave the corresponding chloride **11** in a moderate yield (entries 1 and 2). The chloride is presumably to have been obtained via an intramolecular chloride transfer from the titanium alkoxide intermediate.[11] Steric restriction allowing the efficient interaction between the aryl *ortho* and the hydroxyl moieties is required for the cyclization. Actually, the secondary alcohol **9** underwent the cyclization to product **12**, in which the double bond was migrated, at 0 °C (entry 3). The reaction at −78 °C gave the normal cyclization product **13** in an excellent yield (entry 4). The yield was high for tertiary alcohol **10,** probably reflecting the formation of the stable tertiary allyl cation intermediate so as to give product **14** (entry 5).

In summary, 2-aryl-1-cyclohexene-1-carboxaldehydes underwent an intramolecular titanium-promoted deoxygenative cyclization reaction to give 9-substituted-1,2,3,4-tetrahydrofluorenes. The reaction seems to have proceeded via allyl cations, followed by an intramolecular S_EAr cyclization. A novel route to such tetra-



Scheme 3. A plausible S_EAr mechanism of the intramolecular titanium-promoted deoxygenative cyclization.

Table 1
The intramolecular titanium-promoted deoxygenative cyclization reaction starting with alcohols[a]

Entry	Alcohols	Reaction temperature (°C)	Product (% yield)
1	 **8**	0	Complex mixtures
2	 **8**	−78	 **11** (57)
3	 **9**	0	 **12** (68)
4	 **9**	−78	 **13** (89)
5	 **10**	0	 **14** (95)

[a] Typical procedure is described in Ref. 12.

hydrofluorenes has been developed by successive treatment of secondary and tertiary allyl alcohols with *n*-butyllithium and titanium tetrachloride. An expanded study on the scope and limitations of the intramolecular titanium-promoted deoxygenative cyclization is currently underway.

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6. The starting aldehydes (**1** and **4**) were obtained by DIBAL-H reduction from the corresponding nitriles, according to Fleming's procedure: Fleming, F. F.; Funk, L. A.; Altundas, R.; Sharief, V. *J. Org. Chem.* **2002**, *67*, 9414.
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8. Synthesis of **5**: To a CH_2Cl_2 solution of aldehyde **1** (220 mg, 1 mmol) and $TiCl_4$ (1 mL, 1.0 M solution in CH_2Cl_2) was added a CH_2Cl_2 solution of phenyl trimethylsilyl ketene acetal **2** (250 mg, 1.2 mmol) at 0 °C. The reaction mixture was stirred for 30 min and the reaction was quenched with a satd aq solution of Na_2CO_3. The mixture was extracted with diethyl ether and dried over anhyd $MgSO_4$. The solvent was evaporated in vacuo. The crude was purified by flash column chromatography (3% ethyl acetate/*n*-hexane) to give cyclization product **5** (250 mg, 74% yield): IR 2932, 1755, 1193, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.74–1.83 (m, 4H), 2.25–2.37 (m, 2H), 2.67 (dd, J = 7.8, 16.2, 1H), 2.74–2.78 (m, 2H), 2.86 (dd, J = 4.3, 16.2, 1H), 3.69 (t, J = 4.6, 1H), 6.93–6.99 (m, 3H), 7.11–7.18 (m, 2H), 7.22–7.26 (m, 1H), 7.29–7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 22.8, 24.5, 25.3, 35.8, 47.1, 121.2, 121.4 (×2), 125.2, 125.9, 126.0, 128.6, 129.4 (×2), 136.2, 141.5, 144.9, 148.1, 150.5, 170.8.
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12. Synthesis of **13**: The *n*-BuLi (0.156 mL, 0.248 mmol) was added to the solution of alcohol **9** (50 mg, 0.248 mmol) in CH_2Cl_2 at −78 °C. After 10 min, the 1.0 M solution of $TiCl_4$ (0.25 mL) was added and the mixture was stirred for 30 min. The reaction was quenched with satd aq Na_2CO_3. The mixture was extracted with diethyl ether and dried over anhyd $MgSO_4$. The solvent was evaporated in vacuo. The crude was purified by flash column chromatography (3% ethyl acetate/*n*-hexane) to give cyclization product **13** (41 mg, 89% yield): IR 3016, 2927, 1446 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.25–1.27 (d, J = 7.8, 3H), 1.79–1.82 (m, 4H), 2.21–2.41 (m, 4H), 3.17–3.23 (q, J = 7.8, 1H), 7.11–7.18 (m, 2H), 7.22–7.26 (t, J = 7.8, 1H), 7.34–7.36 (d, J = 7.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.5, 22.0, 22.6, 23.1, 23.8, 45.5, 117.4, 122.2, 123.7, 126.2, 134.1, 144.9, 146.4, 148.6.