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Tandem five membered-ring selective Prins reaction and Friedel–Crafts reaction

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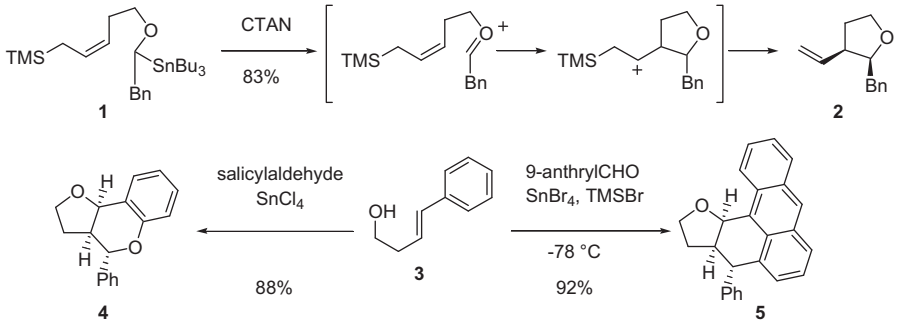
ABSTRACT

A tandem reaction consisting of five membered-ring selective Prins cyclization and subsequent Friedel–Crafts cyclization was developed. The reactions of phenyl homoallylic alcohol **3** and benzaldehyde derivatives **6** afforded tetrahydroindenofurans **7** or pentacyclic products **8**, depending upon the quantity of **6**. Also homoallylic alcohol **12** having an alkyne–cobalt moiety reacted with **6** to give rise to tetrahydroindenofurans **13** in good yields.

The Prins cyclization, which is a facile coupling of a homoallylic alcohol and an aldehyde promoted by an acid catalyst, has been applied to the stereoselective synthesis of many natural products having a tetrahydropyran ring.[1] Recently, several tandem cyclizations including the Prins cyclization have been developed, wherein annulated tetrahydropyran derivatives were obtained.[2] Reddy and Yadav et al. reported a tandem Prins/Friedel–Crafts cyclization furnishing polycyclic compounds containing a tetrahydropyran ring.[2a] The exclusive formation of tetrahydropyrans observed in many examples of the Prins reaction is attributed to the transition state taking a chair form, which is more stable than that of a tetrahydrofuran ring formation. On the contrary, reversal of the relative stability between six membered and five membered transition states makes it possible to form tetrahydrofuran derivatives exclusively. In fact, the reaction of tri-substituted alkene prefers the formation of tetrahydrofuran to tetrahydropyran derivative.[3] Although di-substituted *E*-homoallylic alcohol usually undertakes the preferential formation of tetrahydropyran, the reaction of *Z*-homoallylic alcohol has been reported to give a mixture of tetrahydropyran and tetrahydrofuran.[4] The ring-size selectivity in products has often been controlled by linking a suitable functional group stabilizing carbocation intermediates to an alkene. For example, treatment of allylsilane **1** with $Ce(NBu_4)_4(NO_3)_6$ (CTAN) resulted in the preferential formation of tetrahydrofuran **2** (Scheme 1).[5]



Scheme 1. Five membered-ring selective Prins reaction.

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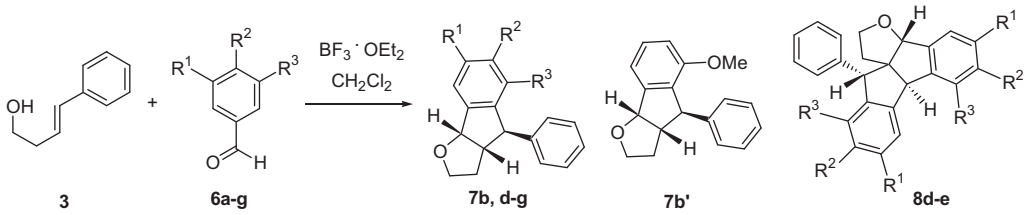
Table 1
Tandem cyclization of the phenyl homoallylic alcohol **3** and benzaldehyde **6**



Entry	Aldehyde	Equiv	Time	Temp.	Product (yield)		
1	**6a** ($R^1 = R^2 = R^3 = H$)	1.3	15 min	0 °C	Complex mixture		
2	**6b** ($R^1 = OMe$, $R^2 = R^3 = H$)	1.3	1 h	0 °C	**7b** (87%)	**7b′** (6%)	
3	**6c** ($R^2 = OMe$, $R^1 = R^3 = H$)	1.3	15 min	0 °C	Complex mixture		
4	**6d** ($R^1 = R^2 = OMe$, $R^3 = H$)	1.3	3 h	0 °C	**7d** (82%)		**8d** (7%)
5	**6e** ($R^1 = R^2 = OEt$, $R^3 = H$)	1.3	2 h	0 °C	**7e** (82%)		**8e** (5%)
6	**6f** ($R^1 = R^3 = OMe$, $R^2 = H$)	1.3	15 min	0 °C	**7f** (92%)		
7	**6g** ($R^1 = R^2 = R^3 = OMe$)	1.3	15 min	0 °C	**7g** (90%)		
8	**6d** ($R^1 = R^2 = OMe$, $R^3 = H$)	3	85 h	rt			**8d** (86%)
9	**6e** ($R^1 = R^2 = OEt$, $R^3 = H$)	3	65 h	rt			**8e** (84%)

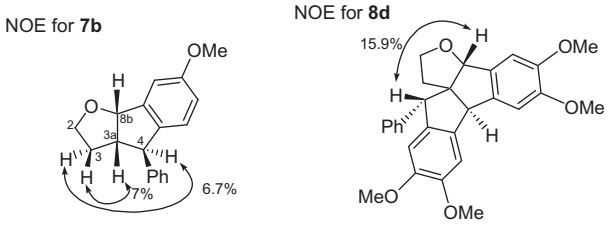
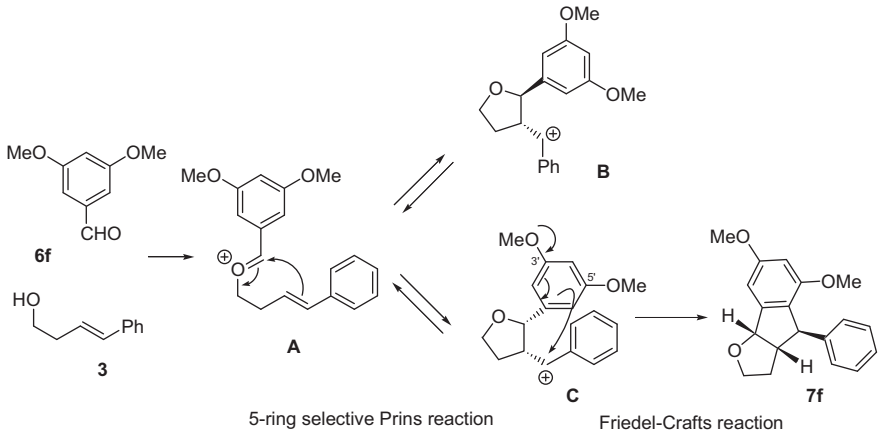


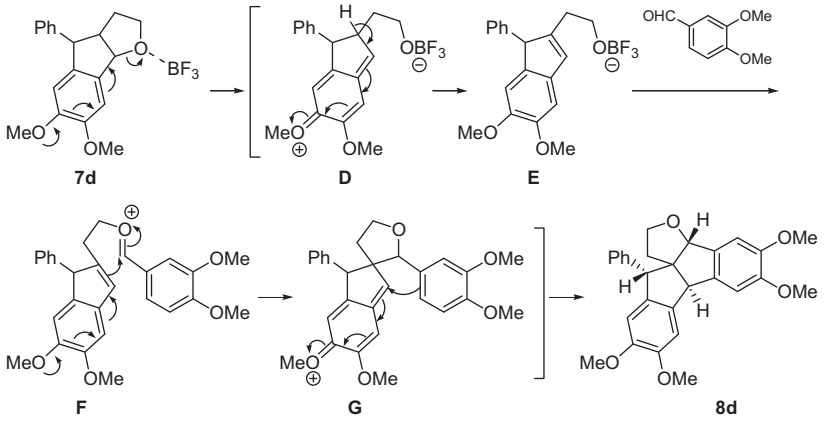
Figure 1. NOE correlations of **7b** and **8d**.

We were interested in a phenyl group and an alkyne–dicobalt complex as an alternative functional group stabilizing five membered-ring transition state of the Prins reaction. Furthermore, if the cation intermediate formed by five membered-ring formation has a nucleophilic functional group at the other site, the second cyclization may occur to give a polycyclic system. Just when we started our project based on such concept, Spivey et al. reported the polycyclization of phenyl homoallyl alcohol **3** and 9-anthraldehyde or salicylaldehyde.[6] We wish to report herein a tandem five-membered Prins/five-membered Friedel–Crafts cyclization of homoallylic alcohols linked to a phenyl group or an alkyne–dicobalt complex and various benzaldehyde derivatives.

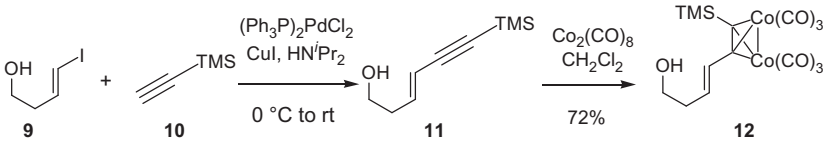
Table 1 summarizes the tandem cyclizations of the phenyl homoallylic alcohol **3**[7] and various benzaldehyde derivatives. At first, we carried out the reaction of **3** (1 equiv) with **6** (1.3 equiv) in the presence of $BF_3{\cdot}OEt_2$ (3 equiv)[8] in CH_2Cl_2 at 0 °C (entries 1–7).[9] Thus, *m*-methoxybenzaldehyde **6b** reacted with **3** smoothly to afford a regioisomeric mixture of tetrahydroindenofurans **7b**[10] (87%) and **7b′**[10] (6%) (entry 2). On the other hand, treatment of benzaldehyde **6a** or *p*-methoxybenzaldehyde **6c** under the same conditions resulted in a complex mixture (entries 1 and 3). Therefore, the presence of an electron donating group at the C3′ position is essential for the formation of tetrahydroindenofuran. Similarly, benzaldehydes **6d–g** (1.3 equiv) bearing a *m*-methoxy group reacted with **3** to give rise to tetrahydroindenofurans **7d–g**[10] (entries 4–7) in high yields. Notably, the reactions of **6f** and **6g** having two methoxy groups at both the C3′ and C5′ positions were very fast. The configuration of a phenyl group was found to be β by NOE correlations between H3a-$H3_\beta$ (7%) and $H3_\alpha$-H4 (6.7%) as shown in Figure 1. The reaction mechanism of the present tandem cyclization is shown in Scheme 2. At first, the Prins cyclization of **3** and **6** occurred via a five-membered transition state to form *trans*-cation **B** and *cis*-cation **C**, which were stabilized by a phenyl group, respectively. Since the 5-5 bicyclo rings are hard to take *trans* juncture, only the cation **C** in the equilibriums between **B** and **C** can undergo subsequent Friedel–Crafts reaction to form the



Scheme 2. Mechanism for the formation of **7**.



Scheme 3. Mechanism for the formation of **8**.



Scheme 4. Preparation of the homoallylic alcohol **12** linked to alkyne dicobalt complex.

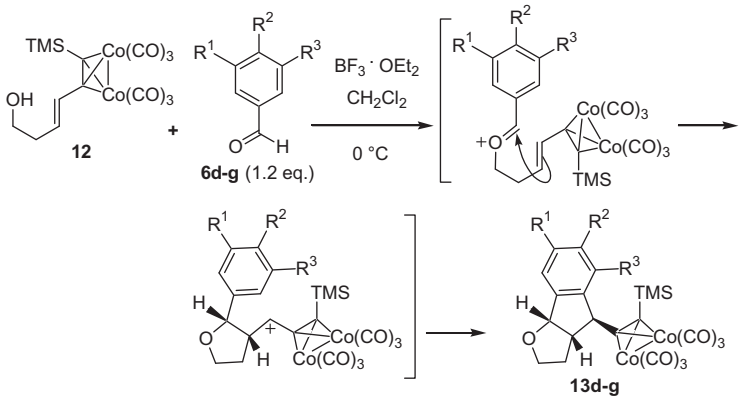
corresponding tetrahydroindenofurans **7**. The two methoxy groups at the C3′ and C5′ positions in **C** have remarkable accelerating effect on the subsequent Friedel–Crafts cyclization.

Interestingly, a small amount of pentacyclic compounds **8d**–**e**[10] were also obtained in the reactions of benzaldehydes bearing a methoxy group at the C4′ position (entries 4 and 5). We confirmed that indenofuran **7d** reacted with **6d** very slowly in the presence of $BF_3{\cdot}OEt_2$ to furnish **8d**. On the contrary, the reaction of **7b** with **6b** did not occur at all. Based on these results, we investigated the tandem cyclization of **3** with three equivalents of **6d**–**e** in the presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at room temperature (entries 8 and 9). In both cases, pentacyclic compounds **8d**–**e** were obtainable in good yields as we expected. The stereochemistry of **8d** was unambiguously determined by NOE measurements as shown in Figure 1.

Scheme 3 shows the tentative mechanism for the conversion of **7d** into **8d**. The reaction started by coordination of BF_3 to the oxygen atom on the furan ring of **7d**. The methoxy group at the C6 position in **7d** might accelerate fragmentation of the C–O bond leading to **D**, which was further transformed into **E** by deprotonation concomitant with aromatization. The intermediate **E**, which is a kind of homoallylic alcohol linked to an aryl group, was further converted into **8d** by the sequential Prins and Friedel–Crafts cyclization through intermediates **F** and **G**.

Complexation of an alkyne with dicobalt hexacarbonyl $Co_2(CO)_6$ has been known to remarkably stabilize cations of α-carbon atom adjacent to an alkyne moiety. The Nicholas reaction, a coupling reaction of $Co_2(CO)_6$ stabilized cations and nucleophiles, has been widely used in organic synthesis.[11] The alkyne–cobalt complex

Table 2
Tandem cyclization of the homoallylic alcohol **12** and benzaldehyde **6**



Entry	Aldehyde	Time (h)	Product (yield)
1	**6d** ($R^1 = R^2 = OMe$, $R^3 = H$)	6	**13d** (83%)
2	**6e** ($R^1 = R^2 = OEt$, $R^3 = H$)	2	**13e** (76%)
3	**6f** ($R^1 = R^3 = OMe$, $R^2 = H$)	4	**13f** (66%)
4	**6g** ($R^1 = R^2 = R^3 = OMe$)	4	**13g** (89%)

was also known to increase the reactivity at the β position of the neighboring alkene.[12] We thus tried the tandem cyclization of homoallylic alcohol **12**[10] linked to an alkyne dicobalt complex with benzaldehyde derivatives. Compound **12** was easily accessible by treatment of eneyne **11**, which was prepared according to the Stoltz method,[13] with $Co_2(CO)_8$ in CH_2Cl_2 (Scheme 4). As we expected, **12** reacted with aldehydes **6d–g** in the presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 to form tetrahydroindenofurans **13d–g**[10] having an alkyne dicobalt moiety in good yields (Table 2). On the other hand, when **11** was treated with **6f** under the same conditions, aldehyde **6f** was recovered and **11** was decomposed. Thus, an alkyne–dicobalt complex was also found to serve as an efficient functional group for the tandem Prins and Friedel–Crafs cyclization.

In conclusion, we have developed the novel tandem cyclizations of homoallylic alcohols linked to a phenyl group or an alkyne–dicobalt complex with various benzaldehydes. The tandem cyclization of **3** with benzaldehyde **6** (1.3 equiv) afforded the tetrahydroindenofurans **7** as the major product. On the other hand, the reaction of **3** with an excess amount of **6** gave rise to pentacyclic compounds **8** containing a furan ring by repeating the sequential five membered-ring selective Prins and Friedel–Crafts cyclization twice. Also, the tandem reaction of **12** with benzaldehydes proceeded smoothly to afford tetrahydroindenofurans **13** having an alkyne dicobalt moiety. Further synthetic application of the present tandem reaction is now in progress.

References and notes

1. Review on Prins cyclization, see: Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413.
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7. Compound **3** was prepared by reduction of *trans*-styrylacetic acid (Aldrich) with $LiAlH_4$.
8. Two equivalents or less of $BF_3{\cdot}Et_2O$ was not enough to complete the tandem cyclization of **3** and **6b**.
9. Typical procedure of the tandem cyclization is as follows. To a solution of **3** (0.6 mmol) and **6** (1.3 or 3 equiv) in CH_2Cl_2 (3 ml) was added $BF_3{\cdot}OEt_2$ (3 equiv) at 0 °C or room temperature. The mixture was further stirred for hours or minutes shown in Table, quenched with sat $NaHCO_3$ aq, extracted with AcOEt, and washed with sat NaCl aq. The organic layer was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give **7** or **8**. If polarities of product and **6** are close, the crude was subjected to column chromatography on silica gel after treatment with $NaBH_4$ in MeOH.
10. All newly synthesized compounds gave spectroscopic data in agreement with the assigned structures. Representative data are shown below. Compound **7b**: IR (film) 2941, 2864, 1609, 1491, 1254 cm^{-1}; HRMS calcd for $C_{18}H_{18}O_2$ (M^+) 266.1307, found 266.1287; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.29 (m, 2H), 7.21 (m, 1H), 7.08 (m, 2H), 7.00 (d, J = 2.0 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.83 (dd, J = 8.0, 2.0 Hz, 1H), 5.57 (d, J = 6.8 Hz, 1H), 4.16 (d, J = 3.6 Hz, 1H), 3.94 (m, 1H), 3.82 (s, 3H), 3.78 (dt, J = 8.0, 6.4 Hz, 1H), 3.08 (m, 1H), 2.24 (m, 1H), 1.94 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.61 (4°), 145.95 (4°), 143.44 (4°), 138.18 (4°), 128.58 (3°, 2C), 127.51 (3°, 2C), 126.35 (3°), 126.08 (3°), 116.55 (3°), 109.05 (3°), 86.64 (3°), 67.64 (2°), 56.73 (3°), 55.34 (1°), 53.55 (3°), 33.82 (2°). Compound **8d**: IR (KBr) 2932, 2882, 2832, 1501 cm^{-1}; HRMS calcd for $C_{28}H_{28}O_5$ (M^+) 444.1937, found 444.1927; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33 (m, 2H), 7.26 (m, 1H), 7.09 (br m, 2H), 6.94 (s, 1H), 6.91 (s, 1H), 6.87 (s, 1H), 6.51 (s, 1H), 5.31 (s, 1H), 4.55 (s, 1H), 4.51 (s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.87 (m, 1H), 3.72 (s, 3H), 3.66 (dt, J = 8.24, 6.4 Hz, 1H), 1.72 (ddd, J = 12.8, 6.4, 4.6 Hz, 1H), 1.58 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.24 (4°), 149.35 (4°), 149.18 (4°), 148.99 (4°), 142.95 (4°), 136.80 (4°), 136.66 (4°), 136.11 (4°), 133.31 (4°), 128.94 (3°), 128.51 (3°, 2C), 126.71 (3°, 2C), 108.37 (3°), 108.04 (3°), 106.60 (3°), 106.57 (3°), 93.86 (3°), 68.66 (4°), 68.22 (2°), 60.52 (3°), 58.03 (3°), 56.19 (1°), 56.06 (1°), 55.92 (1°, 2C), 35.06 (2°).
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