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FeCl₃-Catalyzed Tandem Prins and Friedel-Crafts Cyclization: A Highly Diastereoselective Route to Polycyclic Ring Structures

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Abstract

Catalytic FeCl₃ in the presence of 4Å molecular sieves has been shown to effect highly diastereoselective tandem Prins and Friedel-Crafts cyclization of substituted (*E/Z*)-6-phenylhex-3-en-1-ol and a variety of aldehydes to provide a range of polycyclic compounds in good to excellent yields. The reaction of an enantioenriched alcohol with an aldehyde provided the cyclization product without loss of optical activity. Furthermore, a Lewis acid catalyzed ring opening resulted in functionalized tetralin derivatives with multiple chiral centers.

Keywords

FeCl₃ catalysis; Isochromene; Prins cyclization; Friedel-Crafts reaction; CBS reduction

Iron salts are inexpensive, widely abundant, and considerably less toxic than other transition-metal catalysts. In recent years, there has been significant effort towards the development of iron-based catalysts for carbon-carbon and carbon-heteroatom bond formation.^{1,2} In our continuing interest in the synthesis of substituted tetrahydropyran rings, we have recently developed Cu(OTf)₂ and bisphosphine catalyzed reactions that provided a range of tetrahydropyran derivatives through a sequential olefin migration and Prins-type cyclization.³ A number of other effective methods have also been developed for the synthesis of such functionalized tetrahydropyrans using Prins cyclizations.^{4,5} These methods have been widely employed in the synthesis of natural products and other bioactive compounds.^{6,7} Furthermore, combination of Prins and Friedel-Crafts reactions in an intermolecular sense provided convenient access to 4-aryl tetrahydropyran derivatives.^{8,9} The potential of the Prins and Friedel-Crafts cyclization in an intramolecular pathway has been reported by trapping a carbocation with an aromatic nucleophile.¹⁰ These reactions were carried out in the presence of Sc(OTf)₃ and *p*-TsOH to provide heterocyclic and polycyclic ring systems. An InBr₃-catalyzed Prins and Friedel-Crafts cyclizations have also

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Supplementary Data

Supplementary data associated with this article can be found in the online version.

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shown to afford polycyclic ring compounds.¹¹ This methodology was utilized in the synthesis of moluccanic acid methyl ester.

The availability of substituted alkenols and aldehydes makes this synthesis of polycyclic ring structures very attractive. However, current catalytic systems require both Brønsted and Lewis acids, or expensive metal triflates and high catalyst loading. In addition, shorter reaction time, high diastereoselectivity, and access to these polycyclic structures in optically active form would greatly enhance the utility of this tandem cyclization. Herein, we report a FeCl₃-catalyzed sequential Prins and Friedel-Crafts cyclization of *E/Z*-substituted alkenols with a variety of aldehydes to provide a range of *cis* and *trans*-fused tricyclic derivatives with high diastereoselectivity and good to excellent isolated yields. Reaction of an enantioenriched alkenol with an aldehyde generated the corresponding tricyclic derivative in optically active form. Furthermore, Cu(OTf)₂-catalyzed opening of the tetrahydropyran ring provided access to functionalized tetralin derivatives with three contiguous chiral centers.

For an initial survey of suitable catalysts and reaction conditions, we carried out a cascade cyclization of (*Z*)-6-phenylhex-3-enol **1-(Z)**¹² with *p*-nitrobenzaldehyde (**2a**) as shown in Scheme 1. The results are summarized in Table 1. As can be seen, both Dy(OTf)₃ and Cu(OTf)₂ in the presence of 2 equivalents of aldehyde did not provide the desired cyclization product (entries 1 and 2). However, reaction with Cu(OTf)₂ (20 mol %) in combination with commercially available (*Z*)-1,2-bis(diphenylphosphino)ethylene (20 mol %) in CH₂Cl₂ at 23 °C for 24 h furnished desired cyclization product **4a** as the only isolable product in 81% yield. Both ¹H-NMR and ¹³C-NMR of the crude product did not show the other diastereomer. In this particular reaction, after 24 h, the reaction mixture showed the presence of around 6% starting alkenol by ¹H-NMR analysis (entry 3). We then surveyed the feasibility of FeCl₃ for the Prins and Friedel-Crafts cyclization. Reaction of alkenol **1-(Z)** and 1.2 equivalents of aldehyde **2a** in the presence of 20 mol% FeCl₃ in CH₂Cl₂ provided cyclization product **4a** as the only isolable product in 68% yield. The reaction was completed within 2 h and the ¹H-NMR of the crude reaction mixture showed the presence of **4a** as the sole diastereomer (entry 4). The corresponding reaction with 10 mol% FeCl₃ provided an improved yield of **4a** (entry 5). This reaction in the presence of molecular sieves afforded **4a** in 89% yield within 1 h (entry 6). Thus, the presence of molecular sieves reduced the reaction time and slightly improved the yield. The reaction with Fe(OTf)₃, however, resulted in no product **4a** (entry 7). We then investigated the scope and utility of these catalytic conditions using both **1-(E)**- and **1-(Z)**-alkenols^{12,13} and a number of aromatic and aliphatic aldehydes.

As shown in Table 2, reaction of alkenol **1-(E)** and *p*-nitrobenzaldehyde provided 71% yield of the cyclization product **5a** as a single isomer by ¹H-NMR and ¹³C-NMR analysis. The yield of product **5a** was reduced compared to reaction with alkenol **1-(Z)**. Reactions of **1-(E/Z)** with electron-rich 4-methoxybenzaldehyde **2b** and piperonal **2c** have shown similar yields (entries 3-6). Furthermore, reaction of benzaldehyde **2d** and conjugated aldehyde **2e** proceeded well to provide the corresponding cyclization products in good to excellent yields (entries 7-10). Reactions of aliphatic aldehydes such as isovaleraldehyde **2f** and benzyloxypropionaldehyde **2g** also furnished good to excellent yields and excellent diastereoselectivity (entries 11-14). Stereochemical assignments of products were made

based upon ^1H -NMR NOESY experiments of the tricyclic products. Also, the X-ray crystal structure of **5b** supports our stereochemical assignment (Figure 1).^{14,15} While a wide range of functionalities are tolerated for these cyclization conditions, it should be noted that reactions with benzyloxyacetaldehyde or tosyloxyacetaldehyde did not provide the desired tricyclic products.

We have also investigated this FeCl_3 -based cyclization protocol using three secondary alkenols **6a-c** in combination with a variety of aldehydes. As can be seen in Table 3, both electron-poor and electron-rich aromatic aldehydes provided excellent yields with methyl, phenyl and benzyl substituted alkenols (compounds **7a-7e**). However, reaction of phenyl substituted alkenol **6c** with 4-methoxybenzaldehyde and acetaldehyde provided the cyclization products **7f** and **7g**, respectively, with substantial reduction in yields. Reaction of **6a-c** with isovaleraldehyde **2f**, piperonal **2c** and benzaldehyde **2d** provided excellent yield of cyclization products **7h-7m** with excellent diastereoselectivity. The reaction of sterically demanding 2-methoxybenzaldehyde with alkenol **6c** provided cyclization product **7n** as the only isolable product in 70% yield. Stereochemical assignment of these products were made by ^1H -NMR NOESY studies. The X-ray structure of cyclization product **7e** further corroborated our stereochemical assignment (Figure 2).^{14,16}

To further examine whether this cyclization reaction involved an oxonia-Cope rearrangement,¹⁷ we have carried out the cascade cyclization using an optically active alcohol **9**. As shown in Scheme 2, reaction of known Weinreb amide **8**¹⁸ with Grignard reagent derived from *m*-trifluoromethylphenyl bromide provided the corresponding ketone in 74% yield. The resulting ketone was subjected to Corey-Bakshi-Shibata reduction¹⁹ to provide enantioenriched alcohol **9** in 92% yield. Enantiopurity of **9** (82% *ee*) was determined by HPLC with a chiral column after forming the corresponding *p*-nitrobenzoate derivative.²⁰

The cyclization reaction of alcohol **9** with 4-methoxybenzaldehyde afforded tricyclic derivative **10** with high diastereoselectivity (*dr* = 20:1) and in 82% isolated yield. HPLC analysis using a chiral column showed that enantiopurity of compound **10** was 84% *ee*. This result indicated that the cascade cyclization may not have involved an oxonia-Cope rearrangement^{4b,c,17} which was described by Rychnovski and co-workers in the context of the racemization of Prins cyclizations.

We have investigated chemoselective acyloxycarbenium ion-mediated ring opening of the tetrahydropyran rings.²¹ Our initial attempts at ring opening of **7g** using 5 mol% $\text{Zn}(\text{OTf})_2$ proved to be inefficient as large amounts of the starting material remained after 24 h. However, reaction of **7g** with 5 mol% $\text{Cu}(\text{OTf})_2$ and 20 equivalents of Ac_2O in toluene at reflux resulted in the corresponding ring opened product within 1 h (Scheme 3). Saponification of the resulting acetate derivative then afforded alcohol **11g** in 79% isolated yield in two steps. Furthermore, we have applied these reaction conditions to tricyclic ring compound **7i** with bulky substituents. However, this ring opening required higher temperature and xylene was used as the solvent. The corresponding ring opened product was saponified to provide alcohol **11i** in moderate yield.

In conclusion, we have demonstrated an inexpensive FeCl_3 catalyzed (10 mol%) Prins-Friedel Crafts cascade cyclization of (*E*)- and (*Z*)-6-phenylhex-3-en-1-ols with a variety of aliphatic and aromatic aldehydes. This FeCl_3 -based reaction protocol provided convenient access to tricyclic substituted hexahydro-1*H*-benzo[*f*]isochromene derivatives with excellent diastereoselectivity and good to excellent isolated yields. Using an optically active alkenol, we have shown that the present cyclization pathway does not involve an oxonia-Cope process. Furthermore, treatment of the tricyclic derivatives with $\text{Cu}(\text{OTf})_2$ and acetic anhydride provided the corresponding ring opened tetralin derivatives. Application of these substituted cyclic derivatives in synthesis is ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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15. CCDC 997772 contains the supplementary crystallographic data for Compound **5b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

16. CCDC 997771 contains the supplementary crystallographic data for Compound **7e**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif
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Figure 1.
ORTEP drawing of compound **5b**

Figure 2.
ORTEP drawing of compound 7e

Scheme 1.
Prins and Friedel Crafts tandem cyclization.

Scheme 2.

Prins and Friedel-Crafts Cyclization of optically active alcohol

Scheme 3.

Chemoselective opening of tetrahydropyran rings

Table 1

Preliminary survey of catalysts and conditions.

Entry	Aldehyde	Conditions	Time (h)	Yield
1	2 equiv	Dy(OTf) ₃ (20 mol %)	24	NR ^[a]
2	2 equiv	Cu(OTf) ₂ (20 mol %)	24	NR ^[a]
3	2 equiv	Cu(OTf) ₂ (20 mol %) + L	24	81% ^[b]
4	1.2 equiv	FeCl ₃ (20 mol%)	2	68% ^[c]
5	1.2 equiv	FeCl ₃ (10 mol%)	4	87% ^[c]
6	1.2 equiv	FeCl ₃ (10 mol%) + 4Å MS	1	89% ^[c]
7	1.2 equiv	Fe(OTf) ₃ (10 mol %)	24	NR% ^[a]

^[a]No Reaction;^[b]L = (Z)-1,2-bis(diphenylphosphino)-ethylene (20 mol%), around 6% starting material remained;^[c]dr = 20:1 by crude ¹H NMR. All reactions were carried out at 23 °C

Table 2

Substrate scope and structures of cyclization products

Entry	Aldehyde	Alkene	Product ^{[a],[b]}	Yield (%)
1		1-(Z)	4a	89
2	2a	1-(E)	5a	71
3		1-(E)	5b	68
4	2b	1-(Z)	4b	86
5		1-(E)	5c	77
6	2c	1-(Z)	4c	85
7		1-(E)	5d	71
8	2d	1-(Z)	4d	73
9		1-(E)	5e	68

Entry	Aldehyde	Alkene	Product ^{[a],[b]}	Yield (%)
10	2e	1-(Z)	4e	89
11	2f	1-(E)	5f	91
12	2f	1-(Z)	4f	77
13	2g	1-(E)	5g	77
14	2g	1-(Z)	4g	76

^[a] Conditions: **1** (1 equiv), aldehyde (1.2 equiv), FeCl₃ (10 mol %), 4 Å MS, CH₂Cl₂, 23°C, 1-2 h.

^[b] Diastereomeric ratio 20:1 by ¹H-NMR analysis.

Table 3Product structures resulting from substituted alkenols^[a] ^[a] Only isolated product is shown. Diastereomeric ratio 20:1 by ^1H NMR analysis.