One-Carbon Homologation of Knoevenagel Adducts: Enantioselective Access to Benzhydryl Derivatives

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One-Carbon Homologation of Knoevenagel Adducts: Enantioselective Access to Benzhydryl Derivatives

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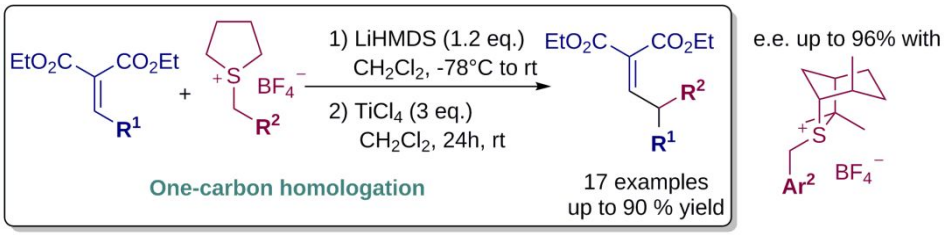
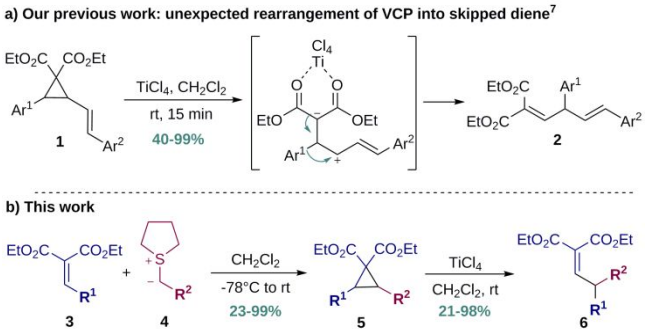


Abstract:
A one-carbon homologation of Knoevenagel adducts enabling the insertion of a CHAr fragment is reported. The strategy involves a sulfur ylide mediated cyclopropanation followed by the rearrangement of cyclopropanes and enables the synthesis of a series of benzhydryl derivatives. Mechanistic studies reveal that the cyclopropane rearrangement involves a Lewis acid-catalyzed ring-opening followed by the 1,2-migration of an aryl group. The possibility of controlling the absolute stereochemistry of the generated stereogenic allylic carbon center using a chiral sulfonium ylide is demonstrated.

The one-carbon homologation of alkenes is an important strategic transformation in organic synthesis which remains a challenge. A series of multi-step methodologies were developed to insert one CH_2-fragment: hydroboration/oxydation/Wittig olefination,[1] metathesis/allylic carbonate reduction[2] and hydrophosphination/Wittig olefination.[3] One-step homologation of small olefins (ethylene, propene, isobutene...) has been also reported using methylenation reagent[4] or metal/SiO_2-catalysis (metal = Fe, Ru, Os, Mo), in the gas phase at high temperature.[5] However, the insertion of a CHR-fragment has proved to be elusive. One example is the elegant strategy of homologation of vinylboronate developed by Mattesson and Aggarwal.[6]

In a recent study, we showed that vinylcyclopropanes **1** rearrange into skipped dienes **2** through a ring-opening/1,2-migration sequence (Scheme 1a).[7] Inspired by this work, we envisioned that, applied to Knoevenagel adducts (**3**), a similar cyclopropanation-rearrangement methodology would enable obtaining corresponding one-carbon homologation products (**6**, Scheme 1b).

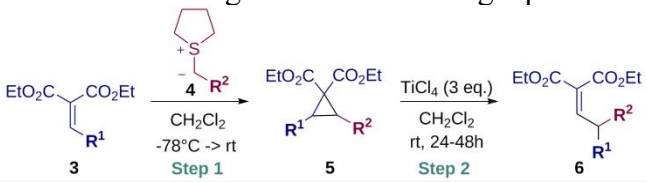
Scheme 1. Rearrangement of vinylcyclopropane into skipped diene and our one-carbon homologation of Knoevenagel adduct strategy.



Herein, we present the efficiency of the planned strategy for the one-carbon homologation of Knoevenagel adducts enabling the rapid synthesis of benzhydryl derivatives. We also show that the use of a chiral sulfonium ylide allows for an enantiocontrol of the stereogenic center in the homologated product.

We began our study by carrying out the cyclopropanation of a series of Knoevenagel adducts **3** using sulfonium ylides **4** (Table 1). Corresponding cyclopropanes **5** were obtained in moderate to excellent yields. Both electron-rich (entries 2-3, 10, 18) and electron-poor (entries 4-5) aryl substituents are tolerated on the Knoevenagel adduct, as well as alkyl groups (entries 7-9). Substitution of the benzylic sulfonium ylide is also well tolerated (entries 10-15). The diastereomeric ratio varies according to substitution but, in most cases, a mixture of the two diastereomers is obtained with the *cis* isomer as the main product.

Table 1. Homologation of Knoevenagel products



			Yield (%)[a]	
Entry	**R^1**	**R^2**	**step 1[b]**	**step 2**
1	Ph	Ph	47 (45/55)	91
2	*p*-MeC_6H_4	Ph	quant. (60/40)	68
3[c]	*p*-$MeOC_6H_4$	Ph	quant. (67/33)	88
4	*m*-$MeOC_6H_4$	Ph	78 (67/33)	60
5	*p*-$CO_2MeC_6H_4$	Ph	70 (67/33)	21
6	2-napthyl	Ph	48 (50/50)	52
7	cyclopropyl	Ph	47 (40/60)	63
8	*t*-Bu	Ph	65 (0/100)	74
9	Me	Ph	80 (60/40)	0(77)[d]

10	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	quant. (67/33)	90
11	*p*-$MeOC_6H_4$	*p*-FC_6H_4	71 (67/33)	34
12[c]	Ph	*p*-$MeOC_6H_4$	quant. (67/33)	88
13	Ph	*p*-FC_6H_4	34 (50/50)	88
14	Ph	*o*-FC_6H_4	60 (80/20)	94
15[e]	Ph	*m*-ClC_6H_4	77 (75/25)	58
16	Ph	*o*-MeC_6H_4	60 (75/25)	98
17[f]	Ph	H	63	70

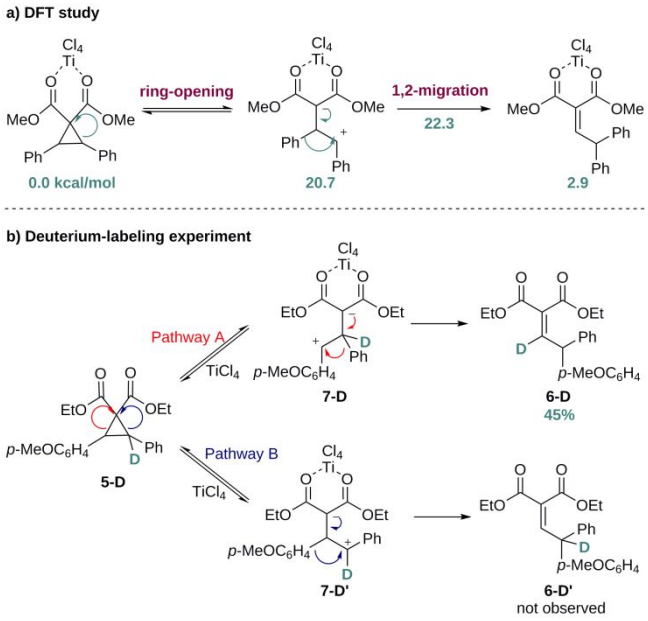
[a] Yield in pure isolated product, unless mentioned otherwise. [b] *cis/trans* ratio in brackets. [c] Rearrangement carried out using 0.4 eq. $TiCl_4$ for 2h. [d] Olefin resulting from the migration of H is obtained as the main product (yield reported in brackets). [e] Rearrangement carried out using 6 eq. $TiCl_4$. [f] Cyclopropanation carried out with trimethylsulfoxonium and rearrangement catalyzed by $FeCl_3$ (3 eq.).

Next, we investigated the second step of our strategy, the rearrangement of the cyclopropane. We found that cyclopropanes **5** rearrange efficiently under $TiCl_4$ catalysis at room temperature to yield corresponding homologated olefins **6** (see SI for full optimisation details). No limitation concerning the scope was observed excepted for cyclopropanes substituted by a poor migrating group such as *p*-$CO_2MeC_6H_4$ or Me (see entries 5 and 9). In the latter case, that is the product resulting from the competing hydrogen migration which is observed, in good yield. Interestingly, the diastereoselectivity of the cyclopropane has no noticable impact on the rearrangement outcome.

Overall, the developed two-step sequence represents a one-carbon homologation of Knoevenagel adduct enabling the insertion of a CHAr fragment.

In order to better understand the mechanism of the rearrangement, it was studied by DFT methods.[8] Obtained results indicate that, as for the previously reported rearrangement of VCP,[7] the mechanism involves the heterolytic ring-opening of the cyclopropane and a subsequent 1,2-migration of an aryl group (Scheme 2a).

Scheme 2. Mechanism of the rearrangement: a) DFT study (relative free energy in kcal/mol at the M06-2X/6-311+G**(CH_2Cl_2)//M06-2X/6-31+G*(CH_2Cl_2) level), b) deuterium-labelling experiment.



In the case of non-symmetrically substituted cyclopropanes ($R^1 \neq R^2$), there are however two possibilities: the ring-opening can occur either on the R^1 side with the 1,2-migration of R^2 or instead on the R^2 side with the R^1 group migrating (pathways A and B in Scheme 2b, respectively). These two pathways leading to the same homologated olefin, in order to differentiate them, we prepared and rearranged deuterated cyclopropane **5-D**. Indeed, depending on the pathway which is followed, the deuterium atom will end up in a different position in the homologated product.

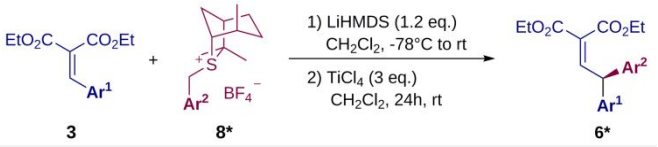
The analysis of the crude mixture by ^{1}H NMR after the rearrangement of **5-D** showed the formation of **6-D** with no trace of **6-D'**. This indicate that the cyclopropane opens preferentially on the side of the substituent which better stabilizes a carbocation (p-$MeOC_6H_5$ in **5-D**) and, consequently, that it is the other group (Ph) which migrates (pathway A in Scheme 2b). The key factor for determining the followed pathway is thus the relative stability of the zwitterionic intermediate **7** and not (or less) the relative migratory aptitude of the two substituents (p-$MeOC_6H_5$ being a better migrating group than Ph[9]).

Interestingly, our computational study indicates that the rearrangement should be stereospecific, the absolute stereochemistry of the carbon bearing the migrating group determining the stereochemistry of the homologated product (see SI for details).[10]

Accordingly, we planned to use a chiral sulfonium ylide to control the absolute stereochemistry of the cyclopropane, which will dictate the enantioselectivity of the homologated product. In the event, we found that application of our methodology to the chiral sulfonium salts **8** developed by Aggarwal[11] leads to the corresponding homologated olefins **6** with a highly variable enantiocontrol (from 48 to 96 % *e.e.*; Table 2).[12] In fact, when the two substituents (R^1 and R^2) show a strong difference in their electronic properties, such

as in entries 1-2, the enantiocontrol is very high whereas in the case of electronically similar groups the enantioselectivity drops dramatically (see entries 3-4).

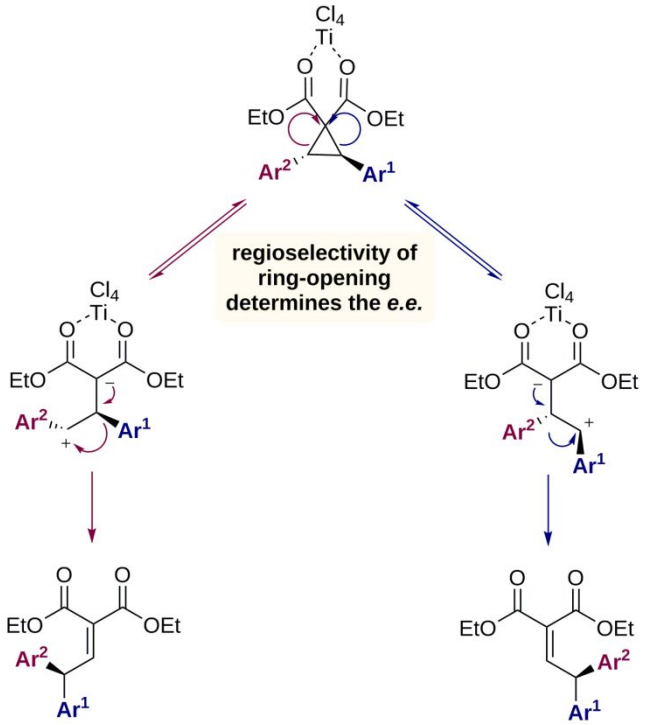
Table 2. Enantioselective version.



Entry	Ar^1	Ar^2	Yield (%)	*e.e.* (%)
1	*p*-$MeOC_6H_4$	Ph	45	96
2	*p*-$MeOC_6H_4$	*p*-FC_6H_4	57	94
3	2-napthyl	Ph	22	70
4	*p*-FC_6H_4	Ph	29	48

This decrease in the enantiocontrol when the two substituents have similar electronic properties can be accounted for by a lower regioselectivity for the ring-opening and the subsequent R^1 vs R^2 migration (Scheme 4).

Scheme 4. Rationale for the variation of enantioselectivity.



In conclusion, we have developed a new one-carbon alkene homologation strategy via a sulfonium ylide-mediated cyclopropanation and a cyclopropane rearrangement. The methodology results in a formal insertion of a CHAr fragment to provide compounds possessing a tertiary allylic stereocenter, including benzhydryl derivatives. Experimental and

DFT studies indicated that the cyclopropane rearrangement involves two elementary steps: a Lewis-mediated heterolytic ring-opening of the cyclopropane and a subsequent 1,2-migration of an aryl group. Preliminary studies demonstrated the stereospecificity of the rearrangement and the possibility of controlling the absolute stereochemistry of the generated stereogenic allylic carbon center using a chiral sulfonium ylide.

Experimental Section

See SI for full details and characterization of all compounds.

Typical procedure for cyclopropanation. In a dry round-bottomed flask, under an inert atmosphere, sulfonium salt (1.2 equiv.) is dissolved in dichloromethane (1 mL/20 mg of sulfonium salt). LiHMDS (1.0 M in THF, 1.2 equiv.) is added dropwise at -78 °C. The olefin is then added dropwise. The mixture is stirred at -78°C for 1 h and 1 h at room temperature. Water is added to stop the reaction. An aqueous solution of hydrochloric acid (1 M) is added. The two layers are separated and the aqueous one is extracted two times with dichloromethane. The combined organic layers are washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The cyclopropane is then purified by flash column chromatography to yield a mixture of *trans* and *cis* isomers.

Characterization of 5a ($R^1 = R^2 = Ph$; EWG = CO_2Et). white solid, yield 47%, d.r (*cis/trans*) = 3/4; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.07 (m, 20H), 4.30 (q, J = 7.1 Hz, 2H), 3.95 (q, J = 7.1 Hz, 4H), 3.93 (q, J = 7.1 Hz, 2H), 3.83 (s, 2H), 3.31 (s, 2H), 1.30 (t, J = 7.1 Hz, 6H), 0.95 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 166.6, 165.8, 134.7 132.9, 130.7, 126.8, 62.2, 61.4, 61.0, 45.4, 41.1, 35.5, 34.5, 14.1, 13.8, 13.6; HRMS (APCI) calculated for $C_{21}H_{22}O_4$: 339.15909. Measured: 339.15935.

Typical procedure for the rearrangement. Cyclopropane (1 eq.) and dry dichloromethane (1 mL/10 mg of cyclopropane) are introduced in a dry round-bottom flask under argon atmosphere. Then, 3 equivalents of $FeCl_3$ are added and the mixture is stirred at room temperature for 24 h. Water is added to stop the reaction. An aqueous solution of hydrochloric acid (1 M) is added. The two layers are separated and the aqueous one is extracted twice with dichloromethane. The combined organic layers are washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure.

Characterization of 6a ($R^1 = R^2 = Ph$; EWG = CO_2Et). Brown oil, yield: 91%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (d, J = 10.9 Hz, 1H), 7.29 (m, 10H), 5.18 (d, J = 11.0 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 4.24 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 182.9, 148.4, 141.2, 128.7, 128.4, 128.2, 127.0, 61.5, 61.4, 50.1, 14.1; HRMS (APCI): Calculated for $C_{21}H_{22}O_4$: 339.15909, found: 339.15900.

Computational methods. Calculations were carried out using the Jaguar 8.5 program package.[8] Geometry optimisations were performed at the M06-2X/6-31+G(d) level of theory. The basis set was used for every atom except for Ti for which LACV3P was used. Solvent effects were modelled by using the polarizable continuum-Poisson method as incorporated in Jaguar, using the parameters for dichloromethane.

The stationary points were characterized by full calculation of vibrational frequencies at the M06-2X/6-31+G(d)(CH_2Cl_2) level using ultrafine grids. These frequency calculations provided also thermal and entropic contributions to free energy. In Jaguar, the translational partition function is computed for ideal gas standard conditions, corresponding to a pressure of 1 atm at 298.15 K. For solution reactions, the standard condition is instead 1 mol/L. Accordingly, the free energy value computed in Jaguar was corrected by a concentration term, equal to RT ln (V_mol_1M/V_mol_gas_1 atm), i.e. 1.89 kcal/mol at 298.15 K.

Gas phase electronic energies were obtained after corresponding fully analytical single point calculations, at the M06-2X/6-311+G(d,p) level of theory.
We have made a systematic attempt to locate all possible local minima (at the M06-2X/6-31+G(d) level), with the data presented referring to the lowest energy form.

Associated content

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data and copies of NMR spectra for all new compounds, computational details and Cartesian coordinates for all computed structures (PDF)

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Note

The authors declare no competing financial interest.

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