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Cyclopropanation of Alkenes with CH_2I_2/Et_3Al by the Phase-Vanishing Method Based on Fluorous Phase Screen

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This paper is dedicated to Professor Dennis P. Curran for his great contribution to fluorous chemistry.

Abstract
Phase-vanishing (PV) method using perfluorohexanes as a screen phase was applied to cyclopropanation reactions with CH_2I_2/Et_2Zn and CH_2I_2/Et_3Al. When Et_3Al was used as a carbenoid generator, the reaction proceeded smoothly and desired cyclopropane derivatives were obtained in high yield. The PV cyclopropanation took two or three days to complete, however, reduction of reaction time by a factor of 2 – 3 was also achieved by vigorous stirring after the bottom CH_2I_2 layer disappeared.

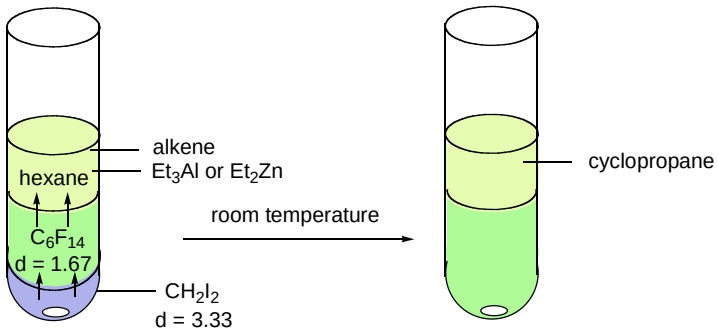
Key words: fluorous solvent; phase-vanishing; Simmons-Smith cyclopropanation; diiodomethane; triethylaluminum

1. Introduction

Fluorous phase chemistry has opened up a new fresh ground in the way of organic synthesis and separation process [1]. Perfluorinated compounds are generally immiscible with most organic solvents and are denser than typical organic molecules. By utilizing the unique properties of fluorous solvents inherent to perfluoroalkyl moieties, we recently reported a synthetically convenient triphasic system [2]: a phase vanishing (PV) method, in which fluorous solvents, such as FC-72 (perfluorohexanes) and Garden HT-135 (polyperfluoroalkyl ethers), act as a screen phase to connect two separated layers. The PV method is demonstrated to be useful in a variety of situations including: for the bromination of alkenes [3] or at benzylic positions [4] with Br_2, demethylation of methyl ethers [3] with BBr_3, bromination of alcohols [5] with $SOBr_2$ or PBr_3, and Friedel-Crafts acylation of aromatic compounds [6] with $SnCl_4$ under mild conditions. The PV method has other variations for example using: chlorine gas [7], lighter reagents [5] than fluorous solvents, and solid reagents [8]. We also introduced a “quadraphasic PV” method [9], in which an aqueous phase was

added to the orginal triphasic PV method to remove acidic by-products.

Diiodomethane (CH_2I_2), a denser liquid (d = 3.33) than FC-72 (perfluorohexanes: d = 1.67), has been used for the Simmons-Smith cyclopropanation reactions as the methylene source [10-12]. The Furukawa variant [11] uses the combination of diethylzinc and CH_2I_2 to give cyclopropane derivatives usually in improved yields as compared with the original Simmons-Smith conditions (Zn-Cu/CH_2I_2). The Maruoka/Yamamoto variant [12] uses trialkylaluminum to generate the carbenoid from CH_2I_2 to afford cyclopropanation products in good yield. In both variants, cooling of the reaction mixture by carefully controlled slow addition of CH_2I_2 is required to avoid rapid heat evolution. Herein we wish to report that a phase-vanishing method can be applied to cyclopropanation reaction of olefins using CH_2I_2/Et_3Al or CH_2I_2/Et_2Zn, which can be conducted at ambient temperature without the need for slow addition of reagents (Scheme 1).



Scheme 1. A Concept of Phase-Vanishing Cyclopropanation Using Diiodomethane

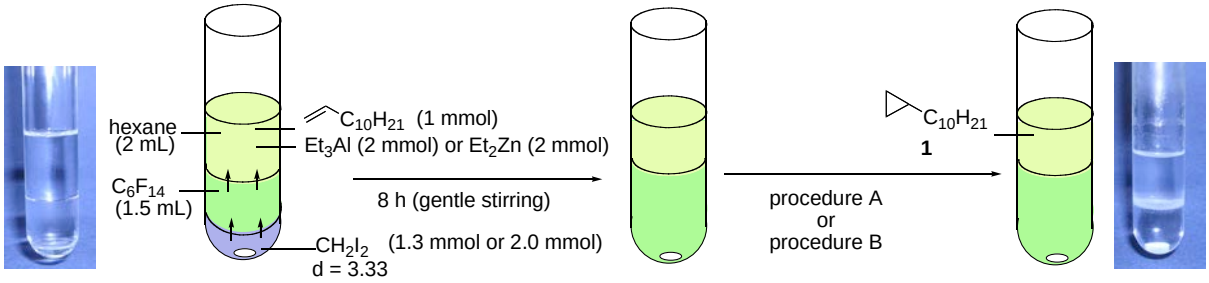
2. Results and Discussion

We examined the phase-vanishing cyclopropanation of 1-dodecene as a model; the results of this study are summarized in Table 1. Diiodomethane (d = 3.33) was overlaid by FC-72 (d = 1.67), which in turn was overlaid by a hexane solution of 1-dodecene and triethylaluminum. The bottom layer was gently stirred, taking care not to mix the three layers. The diiodomethane layer disappeared after 8 h, giving two layers, however the reaction was not complete at this stage. The reaction took almost 2 days to finish (Procedure A). The organic phase was collected and after column chromatography on silica gel decylcyclopropane was obtained in 78% yield (entry 1, Table 1). In a similar procedure, the use of 2 equivalents of diiodomethane increased the yield to 98% (entry 2, Table 1). In contrast, diethylzinc was not observed to be as effective as triethylaluminum in the PV procedure. With this reagent, while extending reaction time or increasing the molar ratio of diiodomethane did not increase the product yield (entries 4 and 5, Table 1), exposure of the reaction mixture to oxygen slightly improved the yield (entry 6, Table 1). In order to reduce

the reaction time for the reaction of Et_3Al/CH_2I_2, after the bottom layer had disappeared, the test tube was stirred vigorously for a further 4 h (Procedure B). This modification also gave a good result (entry 3, Table 1).

Table 1

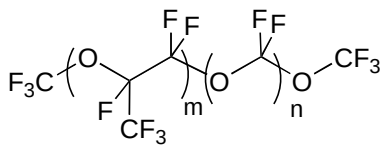
Control experiments for phase-vanishing cyclopropanation of 1-dodecene



entry	conditions	procedure[a]	isolated yield of **1** (%)
1	Et_3Al (2 mmol), CH_2I_2 (1.3 mmol)	A	78
2	Et_3Al (2 mmol), CH_2I_2 (2.0 mmol)	A	98
3	Et_3Al (2 mmol), CH_2I_2 (2.0 mmol)	B	98
4	Et_2Zn (2 mmol), CH_2I_2 (1.3 mmol)	A	20
5	Et_2Zn (2 mmol), CH_2I_2 (2.0 mmol)	A	31
6[b]	Et_2Zn (2 mmol), CH_2I_2 (2.0 mmol)	A	39

[a] Procedure A: gentle stirring, 36 h; Procedure B: vigorous stirring, 4h.
[b] Under dry air atmosphere.

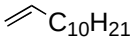
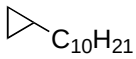
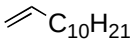
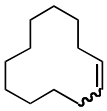
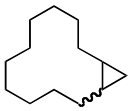
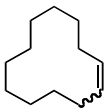
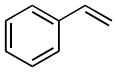
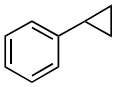
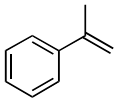
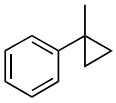
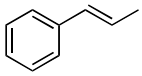
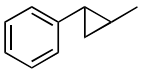
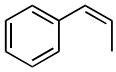
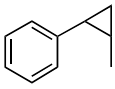
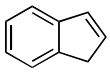
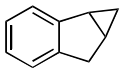
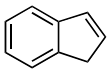
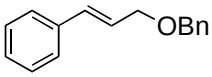
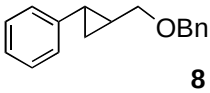
Encouraged by the excellent adaptability of the Maruoka-Yamamoto cyclopropanation reaction to the PV method, we embarked on experiments with several other alkenes. In each case 2 equiv. of CH_2I_2 and Et_3Al was used (Table 2). In all cases examined, the cyclopropanation reaction took place to give high yields of the desired cyclopropanes. Styrene derivatives required longer reaction times to complete than aliphatic alkenes (Procedure C: with extended reaction time (58 h) after the bottom phase disappeared) (entries 5-9, 11, Table 2). Coupled with the use of vigorous stirring after the bottom layer disappeared, the total reaction time was able to be shortened by a factor of 2 – 3 (entries 2 and 10, Table 2). Galden® HT-135 is a polyether-type perfluorinated solvent, commercially available as a heat transfer liquid (Solvay Solexis Inc.), bp 135 ºC, density = 1.72 g/mL at 25 ºC, average molecular weight = 610. This inexpensive polyperfluoro ether solvent was shown to function equally as well with FC-72 (entry 4).



Galden® HT-135
d = 1.72

Table 2

Phase-vanishing cyclopropanation of alkenes by Et_3Al/CH_2I_2[a]

entry	substrate	procedure	product	isolated yield (%)[b]
1		A	 **1**	98
2		B	**1**	98
3[c]		A	 **2**	98 cis/trans = 2.14/1[d]
4[c, e]		A	**2**	98 cis/trans = 2.12/1[d]
5		C	 **3**	93
6		C	 **4**	97
7		C	 **5**	99
8		C	 **6**	97
9		C	 **7**	92
10		D	**7**	92
11		C	 **8**	92

[a] General conditions: substrate (1 mmol), CH_2I_2 (2 mmol), hexane solution of Et_2Zn or Et_3Al (1M, 2 mL), FC-72 (1.5 mL) with aluminum foil protection from light, kept at room temperature with gentle stirring. Procedure A: 36 h; Procedure B: 4 h with vigorous stirring; Procedure C: 58 h; Procedure D: 16 h with vigorous stirring.

[b] Isolated yield by silica gel chromatography.

[c] Cis/trans = 2.43/1.

[d] Determined by ^{1}H-NMR.

[e] Galden HT-135 (1.5 mL) was used as a fluorous phase.

3. Conclusion

Through the use of fluorous media, such as FC-72 (perfluorohexanes) and Garden HT-135, as a phase screen, we have demonstrated that cyclopropanation of alkenes can be easily carried out conveniently without the necessity for slow addition of diiodomethane and equipment for temperature control, which are necessary for the conventional glass-flask reaction. Whereas the Furukawa reagent (Et_2Zn/CH_2I_2) did not function satisfactorily for the present test tube-based triphasic system, the Maruoka-Yamamoto reagent (Et_3Al/CH_2I_2) gave the desired cyclopropanation products in high yields. This carbenoid reagent coupled with the vigorous stirring of the resulting two layers after the bottom layer disappeared significantly reduced the reaction time.

4. Experimental

FC-72 and Galden® HT-135 were purchased from Sumitomo 3M Ltd., and Solvay Solexis Inc., respectively, and dried over molecular sieves 4Å before use. Reagents and solvents were used as received. Hexane solution of diethylzinc (1M) and triethylaluminum (1M) were purchased from Kanto Chemical Co,. Inc., and used as received. Products were purified by column chromatography on silica gel (Kanto Chemical Co., Inc., Silica Gel 60N, 70-230 mesh). ^{1}H NMR spectra were recorded with a JEOL JMN-500 (500 MHz) or a JEOL JMN-400 (400 MHz) spectrometer while ^{13}C NMR spectra were recorded with a JEOL JMN-500 (125 MHz) or a JEOL JMN-400 (100 MHz) spectrometer. Infrared spectra were obtained on a JASCO FT/IR-4100 spectrometer. Conventional and high-resolution mass spectra were recorded with a Shimazu GCMS-QP 5050A instrument and a JEOL MS-700 spectrometer, respectively.

4.1. General Procedure for Cyclopropanation of Olefins by the Phase-Vanishing Method (Table 1, Entry 2) (Procedure A).

FC-72 (1.5 mL) was placed in a pyrex test tube (13 mm ϕ x 105 mm) to which diiodomethane (2.0 mmol, 536 mg) was added slowly using a glass pipette under argon atmosphere. 1-Dodecene (1.0 mmol, 168 mg) was then added slowly, forming three layers. A hexane solution (2 mL) of triethylaluminum (1M) was added to the top layer, and the test tube was covered with aluminum foil in order to shield the reaction from light and kept it at room temperature. The diiodomethane layer was gently stirred using a magnetic stirrer, taking care not to mix the three layers. The diiodomethane layer disappeared after 8 h, the hexane layer was taken up with a pipette after 44 h. Additional hexane (3 mL x 4) was placed on the

residual FC-72 layer, then decanted off. The combined organic layer was washed with aqueous 0.5 M HCl (20 mL) and saturated brine (20 mL), dried over Na_2SO_4, and concentrated. Purification by short column chromatography on silica gel with hexane gave decylcyclopropane (**1**, 178 mg, 98%) as a colorless oil; IR (neat): ν 3000, 2955, 2925, 2850, 1465, 1375, 1040, 1015, 820, 720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ -0.12 (2H, m, CH_2 of cyclopropane), 0.38 (2H, m, CH_2 of cyclopropane), 0.88 (3H, t, J = 6.9 Hz, CH_3), 1.17 (2H, q, J = 7.4, $C\underline{H}_2$-*c*-C_3H_6), 1.26–1.42 (16H, m, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 4.35, 10.92, 29.39, 29.54, 59.59, 29.66, 29.69, 29.72, 29.75, 31.96, 33.85, 34.81; EI MS 70 eV, m/z (relative intensity): 182 $[M]^+$ (10), 168 $[M-CH_2]^+$ (13), 154 $[M-C_2H_4]^+$ (14), 140 $[M-C_3H_6]^+$ (8), 125 (19), 111 (45), 97 (93), 83 (100), 69 (88), 55 (66); HRMS (EI): m/z = $[M]^+$ calcd for $C_{13}H_{26}$: 182.2035; found: 182.2036.

All other products **2**[13], **3**[14], **4**[15], **5**[14], **6**[14], **7**[14] and **8**[16] are known compounds and were identified by spectral data with comparison of literature data.

Acknowledgements

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