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The role of neat substrates in phase-vanishing and tandem phase-vanishing reactions

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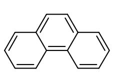
ABSTRACT

Phase-vanishing reactions are triphasic reactions, which involve a reagent, a liquid perfluoroalkane as a phase screen and a substrate. Aromatization, isomerization and halogenation of neat substrates under phase-vanishing conditions gave the expected products in good to excellent yields. In tandem single-phase–phase-vanishing reaction, two reactants, placed in the top phase, afforded the intermediate, which in a subsequent phase-vanishing reaction reacted with the reagent from the bottom phase to give the final product. The reaction worked well under solvent-free conditions on liquid substrates and intermediates. With solids, results were better if an additional solvent was employed.

Phase-vanishing reactions, introduced by Ryu, Curran and Verkade,[1–4] are triphasic reactions, which involve a reagent, a liquid perfluoroalkane and a substrate. The perfluoroalkane, which is in the layer between the two, does not dissolve either of the reactants and is used to separate them. As the reagent in the bottom layer diffuses through the perfluoroalkane layer, it reaches the top layer and reacts with it. Thus, the reaction proceeds at a moderate rate, instead of a vigorous and often violent reaction if the two reactants were mixed without a solvent. In the course of the reaction, the reagent disappears ('vanishes'). Phase-vanishing (PV) reaction allows for reactions that otherwise would be too vigorous without a solvent to be done on neat reagents.[5] This considerably simplifies the work up and makes the reactions environmentally friendly. We used FC-72 (perfluorohexane, C_6F_{14}) as a phase screen and examined phase-vanishing isomerization and addition reactions that involve halogen reagents as well as a combination of traditional single-phase (SP) reactions with phase-vanishing reactions into tandem single-phase–phase-vanishing (SP–PV) reactions.

Phase-vanishing aromatization and isomerization reactions involving halogens and hydrogen halides worked well on neat liquid substrates. Thus, reaction of dimethyl 4,5-dimethyl-1,4-cyclohexadien-1,2-dicarboxylate (**1**) gave the aromatized product **2** cleanly and in a good yield (Table 1, entry 1). Reaction of tetralin **3** with bromine required irradiation with a projector lamp or a 40 W incandescent light bulb and gave a mixture of naphthalene (**4**), 1-bromonaphthalene (**5**) and 1,4-dibromonaphthalene (**6**) (Table 1, entry 2). These results are similar to bromination of tetralin in carbon tetrachloride.[6] *cis*-Stilbene (**7**) was cleanly isomerized into *trans*-stilbene (**8**) when treated either with a catalytic amount of iodine in FC-72 or upon treatment with gaseous hydrogen bromide delivered through a tube immersed in FC-72 (Table 1, entries 3 and 4). Phenanthrene (**9**) and dimerization products, such as **10**, that often accompany iodine-catalyzed isomerization in benzene[7] were not observed. Advantage of a phase-vanishing isomerization with HBr is that delivery tube, immersed into FC-72, was not plugged with the solid product as was the case when HBr was bubbled directly into a neat *cis*-stilbene. Iodine-catalyzed isomerization of dimethyl maleate (**11**) under phase-vanishing conditions, upon exposure to a visible light (40 W light bulb), gave a mixture of dimethyl maleate (**11**) and dimethyl fumarate (**12**) (Table 1, entry 5). Reproducibility of this isomerization was poor, and extended reaction times did not change the ratio of the isomers in any consistent manner.

Iodine, as a catalyst, is not consumed in the course of the reaction and HBr reactions involved bubbling of a gas, the reagent phase did not 'vanish' and, therefore, some of the procedures were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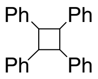

10

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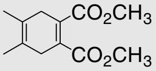
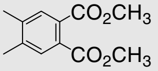
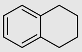
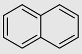
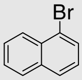
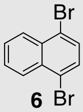
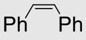
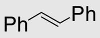
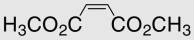
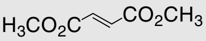
Table 1
Phase-vanishing aromatization and isomerization

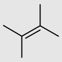
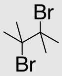
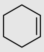
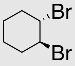
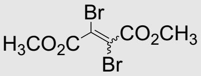
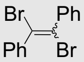
Entry	Substrate	Conditions	Product (yield %)
1	 **1**	Br$_2$ (1.1 equiv), 1 h	 **2** (88)
2	 **3**	Br$_2$ (1.1 equiv), 40 min	 **4**  **5**  **6**
3[b]	 **7**	I$_2$ (0.1 equiv), 1 h	 **8** (94)
4	**7**	HBr (g) (1.0 equiv), 1 h	**8** (91)
5	 **11**	I$_2$ (0.1 equiv), 3 h	**11** +  **12**

not strict phase-vanishing reactions. Common to all the procedures was that the substrate was in a separate phase and that the reagent was delivered through the FC-72 phase.

Phase-vanishing halogenation of neat liquid alkenes worked very well and at a high reaction rate, but not as well on neat solid substrates. Thus, bromination of neat 2,3-dimethyl-2-butene (**13**) (Table 2, entry 1) was very fast (<5 min). PV reaction was vigorous, with formation of some tri- and tetra-bromo derivatives, and 2,3-dibromo-2,3-dimethylbutene (**14**) was isolated in a modest yield. This reaction should be done with a reasonably vigorous stirring to prevent the solid product from forming a barrier between the two layers. Alternatively, if the barrier does form, it can be broken up with a glass rod. Cyclohexene (**15**) reacted slowly in the dark to give the expected product, *trans*-1,2-dibromocyclohexane (**16**) (Table 2, entry 3). In the presence of even a weak light source, allylic bromination became an important side reaction. Dimethyl acetylenedicarboxylate (**17**) (Table 2, entry 4) reacted at a high rate to give a mixture of *cis* and *trans* isomers (**18**). Reaction of neat diphenylacetylene (**19**) with bromine under phase-vanishing conditions was exceptionally vigorous and fast for a solid substrate. Product was a mixture of *cis*- and *trans*-1,2-dibromo-1,2-diphenylethenes (**20**) (Table 2, entry 5). Reaction was accompanied by formation of a tribromo compound (~7%, GC), and the corresponding amount of the starting diphenylacetylene (**19**) (~8%) was recovered. Halogenation of neat solid *trans*-stilbene (**8**) did not give good results. A large amount of the starting material was recovered and two isomeric dibromostilbenes were obtained in various ratios. That was the case even though *trans*-stilbene was finely powdered. In the course of bromination of *cis*-stilbene (**7**) (Table 2, entry 6), there was a competing isomerization into the solid *trans*-stilbene. Isomerization reaction appears to be considerably faster than bromination, and the product appears to be mainly a result of bromination of *trans*-stilbene. Besides the bromination products, a relatively large amount of *trans*-stilbene was isolated.

Reaction times can be controlled by the amount of FC-72, with a larger depth of FC-72 resulting in a slower reaction, and the rate of stirring. A reaction can be done without any stirring, or the reaction rate can be increased by slow stirring. Fast stirring is not

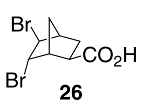
Table 2
Phase-vanishing halogenation of alkenes and alkynes

Entry	Substrate	Conditions	Product (yield %)
1	 **13**	Br$_2$ (1.1 equiv), 5 min	 **14** (72)
2	 **15**	Br$_2$ (1.1 equiv), dark, 2 h	 **16** (78)
3[b]	$H_3CO_2C{\equiv}CO_2CH_3$ **17**	Br$_2$ (1.1 equiv), 10 min	 **18** (94)
4	$Ph{\equiv}Ph$ **19**	Br$_2$ (1.1 equiv), 1 min	 **20** (81)
5	**8**	Br$_2$ (1.1 equiv), 1 h	(±)-Dibromostilbene (4–28%) *meso*-dibromostilbene (35–69%)
6	**8**	ICl (2.2 equiv), 3 h	(±)-Chlorostilbene (5–39%) *meso*-chlorostilbene (28–52%)
7	**7**	Br$_2$ (1.1 equiv), 1 h	(±)-Dibromostilbene (21–41%) *meso*-dibromostilbene (21–35%)
8	**7**	ICl (2.2 equiv), 3 h	(±)-Chlorostilbene (11%) *meso*-chlorostilbene (23%)

recommended as it may lead to mixing of the top and bottom phases and a reaction running out of control. Usually, solubility of the reaction products in FC-72 is negligible, and it can be reused. However, that is not always the case particularly when the products are polyhalogenated compounds.

Further development of phase-vanishing procedure was integration of a traditional single-phase reaction with a phase-vanishing reaction into a tandem single-phase–phase-vanishing (SP–PV) reaction. We selected Diels–Alder reaction as a single-phase reaction, and reaction of the resulting Diels–Alder adduct with a halogen as a phase-vanishing reaction. Although Diels–Alder reactions under solvent-free conditions (SFCs) have received relatively little attention,[8–10] we found them suitable for SP–PV process as long as the resulting Diels–Alder adduct was a liquid.

A halogen reagent was placed at the bottom of the reaction vessel, a phase screen (FC-72) was added and Diels–Alder reactants (a diene and a dienophile) were placed on the top of the phase screen. Thus, a relatively fast, SFC Diels–Alder reaction occurred first in the top phase, and was followed by a slower phase-vanishing reaction between the resulting Diels–Alder adduct and the halogen reagent. Reaction outcome of an SP–PV was similar to a separate SP followed by a VP reaction. Thus, reaction between cyclopentadiene (**21**) and dimethyl fumarate (**12**) followed by reaction with iodine monochloride (Table 3, entry 1) gave the resulting iodolactone **22** in 92% yield compared to 94% for separate reactions.[5] Interestingly, in one run reaction temperature of SP–PV reaction inadvertently went out of control (stirring was set too high and iodine monochloride and Diels–Alder adduct came into a direct contact). The temperature was so high that all of the FC-72 evaporated. Still, iodolactone **22** was isolated in 96% yield (>95% pure according to ^{1}H NMR). Even though dienes are highly reactive toward the halogens, with a sufficient depth of the FC-72 phase screen and in the absence of stirring there was little or no reaction between the halogen and either starting diene or dienophile. Thus, less than 2% of the bromination products of the original staring materials were observed in the GC–MS of the crude product. SP–PV reaction of cyclopentadiene (**21**) and acrylic acid (**24**) followed by treatment with bromine also gave essentially the same results as separate SP and PV reactions.[5] The major product was bromolactone **25** that was isolated in a modest yield (Table 3, entry 3), and it was accompanied by the four dibromo derivatives **26**–**29**. A reaction between a less reactive diene and a dienophile under SFC takes considerably longer, frequently days, to go to completion. Such reaction can be adapted to SP–PV conditions provided that the halogen reagent is added upon the completion of SP reaction. Thus, 2,3-dimethyl-1,3-butadiene (**30**), dimethyl acetylenedicarboxylate (**17**) and FC-72 were combined in a vial. Diels–Alder reaction took 3 d. Next, bromine was added to the bottom of the vial and the aromatized product, dimethyl 4,5-dimethylphthalate (**2**), was obtained after 1 h (Table 3, entry 4).



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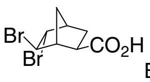

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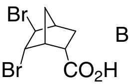

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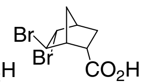

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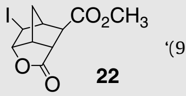
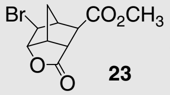
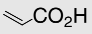
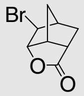
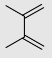
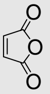
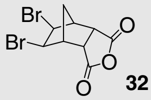
Table 3
Tandem SP–PV reactions

Entry	Substrates	Conditions	Product	
1	 + **12** **21**	ICl, SP 12 min, VP 24 h	 **22**	(92)
2	**21** + **12**	Br_2, SP 12 min, VP 12 h	 **23**	(94)
3[b]	**21** +  **24**	Br_2, SP 8 min, VP 1 h	 **25**	(45)
4	 + **17** **30**	Br_2, SP 3 d, VP 1 h	**2**	(90)
5	**21** +  **31**	Br_2, SP 10 min, VP 2 h	 **32**	(63)

While this short study proves the concept, the procedure in its present form has some limitations. Reactions that proceeded through liquid Diels–Alder adducts worked well, but with some scale limitations. SFC Diels–Alder reactions are exothermic, and the reaction temperature should be maintained below the boiling point of FC-72 (58–60 °C) by selecting reaction vessel of the appropriate size (as large as possible to allow heat dissipation) and doing the reaction on the appropriate scale. For example, Diels–Alder reactions of cyclopentadiene (**21**) and some unsaturated esters, such as dimethyl maleate and fumarate, on a very small scale (<10 mmol) do not generate much heat, are very slow (take days), and often do not go to completion. With an increase in scale, such reactions release considerably more heat and usually go to completion in 1 h or less, which makes them suitable for SP–PV reactions. Further increase in scale results in an out of control runaway reaction that is not practical. In addition, size and shape of the reaction vessel affects the reaction temperature. Thus, a reaction on a smaller scale should be done in as small vessel as possible in order to retain the heat and to ensure that reaction proceeds at a reasonable rate and goes to completion, while a reaction on a larger scale should be done in much larger vessels to allow dissipation of excess heat. A detailed study of SFC Diels–Alder reactions will be published elsewhere. Diels–Alder reactions that gave solid products did not give good results under SFC. The product would form either clumps or a single solid piece, which did not react very well with the reagent. Such reactions can be done if an additional solvent, such as ethyl acetate, is employed to dissolve the intermediate Diels–Alder adduct (Table 3, entry 5). Work on optimization and expanding the scope of SP–PV reactions is in progress.

In a typical procedure, to a 40 mL (28 × 95 mm) vial equipped with a stirring bar, 5.50 mL (55 mmol) of ICl and 10 mL of FC-72 were added. Cyclopentadiene (**21**) (4.15 mL, 50 mmol) and dimethyl fumarate (**12**) (7.20 g, 50 mmol) were carefully added to the top of FC-72 layer. SP reaction was allowed to proceed without stirring for 12 min. After the exothermic Diels–Alder reaction was completed, VP reaction was continued with stirring for another 24 h.

In conclusion, both PV and tandem SP–PV reactions avoided use of any solvent, and the work up consisted of mechanical separation of the product from the phase screen. SP–VP Diels–Alder-halogenation reactions work well on a moderate (multi-gram) scale on liquid Diels–Alder intermediates, and compare favorably to running separate SP and VP reactions.

Acknowledgment

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