Palladium-Catalyzed Benzannulation of Conjugated Enynes in Fluorous Biphasic System

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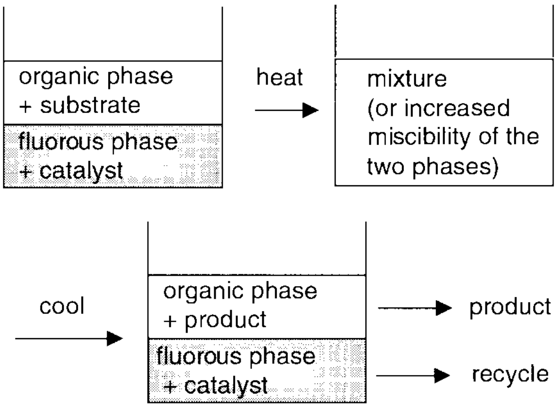
We carried out the benzannulation (cyclodimerization) of conjugated enynes in fluorous biphasic system in the presence of perfluoro-tagged palladium catalyst and succeeded in reusing the catalyst for several times.

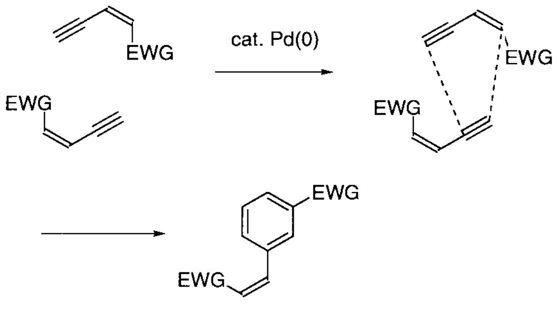
The development of recyclable catalytic system is an important issue for the improvement of catalytic processes in organic synthesis and some interesting approaches have been reported. For example, carrying out the reaction under biphasic systems such as liquid–solid or liquid–liquid phase is a well-known approach for the recovery and reuse of the catalyst. A new approach in this field is the utilization of a combination of organic solvent and fluorous solvent (fluorous biphasic system) as the reaction media.[1] In this approach, the selective solubility of the highly fluorinated catalyst in the fluorous phase was utilized to separate the product and the catalyst efficiently and easily (Scheme 1). This concept has been recently applied to many catalytic reactions.[2]

The recent vast applications of this system in many reactions led us to consider the possibility of applying this system to the palladium-catalyzed benzannulation of conjugated enynes (eq 1).[3] In this paper we report the first application of fluorous biphasic system to the palladium-catalyzed benzannulation of conjugated enynes.

The highly fluorinated palladium catalyst was prepared in situ from $Pd_2dba_3{\cdot}CHCl_3$ (**3**) and **4**[4] in a mixture of organic sol-

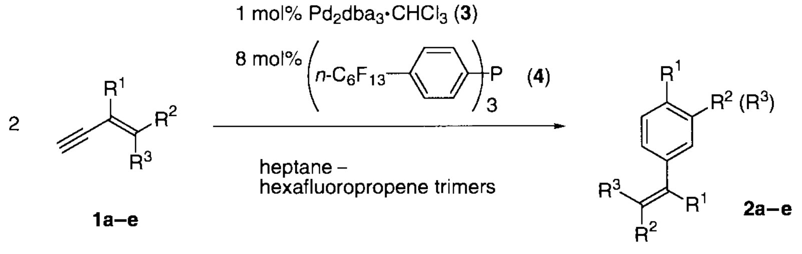
Scheme 1





(1)

Table 1. Benzannulation of enynes under fluorous biphasic condition



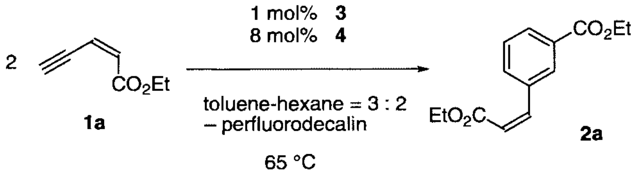
Entry	enyne	R^1	R^2	R^3	Temp./°C	Time/h	Isolated yield of **2**/%
1[a]	**1a**	H	H	CO_2Et	65	1	78
2	**1b**	H	H	CO_2*n*-C_8H_{17}	65	1	76
3	**1c**	*n*-C_6H_{13}	H	CO_2Et	80	2	74
4	**1d**	H	CO_2*n*-C_8H_{17}	H	80	3.5	43
5	**1e**	*n*-C_6H_{13}	CO_2Et	H	80	4	53

[a] The reaction was carried out in toluene : hexane = 3 : 2 / perfluorodecalin and in the presence of 8 mol% of **4**.

vent and highly fluorinated solvent such as perfluorodecalin or hexafluoropropene trimers.[5] The facile ligand exchange was confirmed by the disappearance of the purple color of **3** in the organic phase. The color of the fluorous phase turned yellow at the same time, indicating the formation of the highly fluorinated palladium catalyst. The organic layer was then removed, and the reactions were carried out by the addition of a solution of enyne to the fluorous solution.

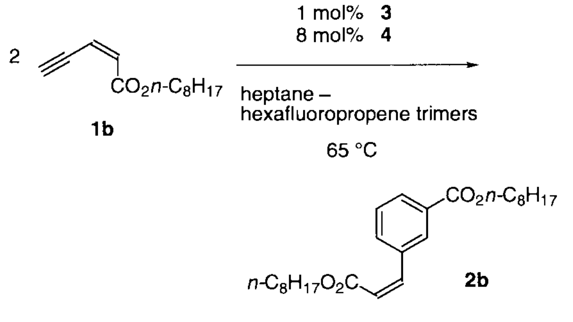
The results of the reactions are summarized in Table 1. Thus, the benzannulation of a highly reactive enyne **1a**[6] proceeded at 65 °C and the product was isolated in 78% yield (entry 1). The separation of **2a** and the catalyst was quite easy, and the organic phase which contains the product was easily separated by a syringe after cooling the reaction mixture to 0 °C.[6] We also carried out the reactions of other enynes, and the products were obtained in good to fair yields (entries 2–5). Compared to the reaction conditions required for the reaction of enynes **1a–e** in the presence of $Pd(PPh_3)_4$ in organic solvents,[7] the reactions must be carried out at elevated temperatures and for a longer periods under this fluorous biphasic system. This result may be explained in terms of the low catalytic activity of the highly fluorinated palladium catalyst.

Table 2. Benzannulation of **1a** under fluorous biphasic condition



Cycle	Time/h	Isolated yield of **2a**/%
1	1	78
2	1	76
3	1	81
4	2	79
5	14 days	13

Table 3. Benzannulation of **1b** under fluorous biphasic condition



Cycle	Time/h	Isolated yield of **2b**/%
1	1	76
2	1	71
3	1	78
4	1	74
5	1	81
6	1	71
7	7 days	41

To examine the possibility of reusing the catalyst, we carried out the benzannulation of conjugated enynes for several times in the presence of recovered fluorous catalyst, and the results are summarized in Tables 2 and 3. As shown in the tables, it is possible to recycle the catalyst which was dissolved in the fluorous phase up to four times without a significant loss of the catalytic activity. However, the reactivity of the catalyst significantly decreased when the reaction was carried out for more than five times. The decreased reactivity may be caused by the oxidation of the fluorinated ligand by the trace amount of the oxygen in the solvent and/or the loss of palladium species in the organic phase.[8] We are currently re-designing the fluorous ligand to improve the catalytic activity.

In summary, we carried out the palladium-catalyzed benzannulation using the fluorous biphasic system and succeeded in recycling the catalyst. This is the first example of the application of benzannulation reaction in fluorous biphasic system, which is a very clean and efficient method for the synthesis of substituted benzenes.

References and Notes

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5 "Hexafluoropropene trimers" is a 1:1 mixture of $(CF_3)_2CF\text{–}CF{=}C(CF_3)CF(CF_3)_2$ and $(CF_3)_2CFCF_2\text{–}C(CF_3){=}C(CF_3)_2$ which was purchased from Daikin (Japan).
6 The product was efficiently isolated by this simple operation, and only a trace amount of **2a** was present in the fluorous phase.
7 a) S. Saito, Y. Chounan, T. Nogami, T. Fukushi, N. Tsuboya, Y. Yamada, H. Kitahara, and Y. Yamamoto, *J. Org. Chem.*, **65**, 5350 (2000). b) S. Saito, N. Tsuboya, Y. Chounan, T. Nogami, and Y. Yamamoto, *Tetrahedron Lett.*, **40**, 7529 (1999).
8 In fact, our preliminary ICP atomic emission analysis of the fluorous phase indicated that the concentration of the palladium species decreased to a significant extent. The incomplete recovery of the catalyst should be a problem in this reaction.