LETTER

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Aza-Diels–Alder reaction catalyzed by perfluorinated metal salts in fluorous phase†

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In this paper, we describe the aza-Diels–Alder reaction of Danishefsky's diene with arylaldehydes and aromatic amines in a fluorous phase. With perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture) as the fluorous solvent and a perfluorinated rare earth metal salt [$Sc(OSO_2C_8F_{17})_3$] (2.0 mol %) as a catalyst, this aza-Diels–Alder reaction can be performed many times without reloading the catalyst.

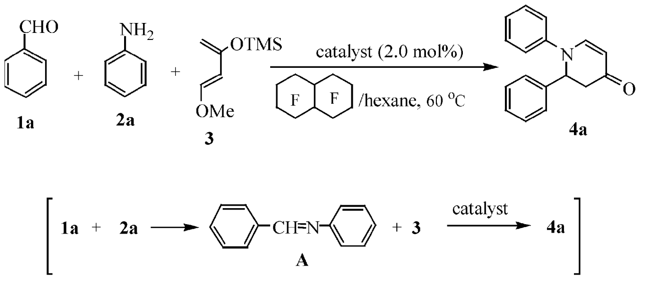
Aza-Diels–Alder reactions provide a powerful methodology for the construction of nitrogen-containing six-membered ring compounds,[1] which constitute a broad spectrum of natural products, biologically active compounds, and other functional materials. Recently, significant progress has been made in a number of Lewis acid catalyzed aza-Diels–Alder reactions of Danishefsky's diene with imines in organic solvents,[2] as well as its asymmetric versions using chiral Lewis acid catalysts.[3] In addition, several reports disclosed that the one-pot "three-component" synthesis of dihydro-4-pyridones from the aza-Diels–Alder reaction of Danishefsky's diene with aldehydes and amines also proceeded smoothly under mild conditions.[2c, 2e, 4]

On the other hand, perfluorocarbon fluids, especially perfluoroalkanes, have some unique properties that make them attractive alternatives for conventional organic solvents.[5] They have limited miscibility with conventional organic solvents. Compounds functionalized with perfluorinated groups often dissolve preferentially in fluorous solvents. This character can be used to extract fluorous components from reaction mixtures.[6] The "Fluorous Biphase System" (FBS) technique was first reported by Horvath and Rabai.[6a] This allows the catalysis to be performed in a two-phase reaction mixture consisting of a perfluorinated solvent and an organic solvent. Therefore, by introducing a perfluorinated catalyst in a catalytic reaction system, the catalyst is solubilized and simultaneously immobilized in the fluorous phase. By elevating the temperature the biphasic system forms a homogenous solution and the catalytic process can take place. Cooling down the reaction mixture leads to the reformation of two separate phases. Afterwards, easy product isolation and the recovery of the perfluoro-tagged metal catalyst can be achieved by simple phase separation.[7] The isolation and recovery of perfluorinated components can be accomplished not only by a phase separation of immiscible liquid layers but also by solid–liquid extraction using a perfluorinated nonpolar stationary phase.[6a]

Based on this concept, we attempted the application of fluorous phase separation techniques to the one-pot "three-component" aza-Diels–Alder reaction of Danishefsky's diene with arylaldehydes and aromatic amines using perfluorinated rare earth metal salts or other metal salts as catalysts. By this technology, the efficiency of the synthetic process of this aza-Diels–Alder reaction can be increased because the recovery of perfluorinated rare earth metal salt or other metal salt catalysts from the reaction solution can be avoided.

In order to perform this aza-Diels–Alder reaction in fluorous phase, we prepared several perfluorinated rare earth metal salts [$Ln(OSO_2CF_3)_3$ and $Ln(OSO_2C_8F_{17})_3$, Ln = Yb, Sc][8] and perfluorinated alkali metal salts [$M(OSO_2CF_3)$ and $M(OSO_2C_8F_{17})$, M = Li, Na, K][9] and used them as catalysts in the one-pot "three-component" aza-Diels–Alder reaction of Danishefsky's diene **3** with benzaldehyde **1a** and aniline **2a** in hexane[10] and perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture) (Scheme 1). The results are summarized in Table 1 and as can be seen, $Ln(OSO_2C_8F_{17})_3$ Lewis acid catalysts are more effective than $Ln(OSO_2CF_3)_3$ (*cf.* entries 3, 4 and 5, 6) while perfluorinated alkali metal salts (entries 7–10) are inefficient in this FBS catalytic reaction system. It should be emphasized here that no reaction occurred in the absence of catalyst. In addition, the Brønsted acids $HOSO_2CF_3$ and $HOSO_2C_8F_{17}$ themselves can catalyze this reaction as well, with $HOSO_2C_8F_{17}$ being more effective than $HOSO_2CF_3$ under identical conditions (entries 1 and 2). These results suggest that a long perfluorinated alkyl chain, a so-called "pony tail", could indeed allow more efficient transfer of the the catalyst into the fluorous phase. Overall, $Sc(OSO_2C_8F_{17})_3$ is the most active catalyst in this reaction. This is the first time that the aza-Diel-Alder reaction of benzaldehyde and aniline with Danishefsky's diene is carried out in a fluorous phase.

On the basis of previous investigations, this reaction proceeds *via* an imine intermediate **A** derived from an arylaldehyde **1** with an aromatic amine **2**. The aza-Diels–Alder reaction of imine intermediate **A** with Danishefsky's diene **3** in the



Scheme 1

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† Electronic supplementary information (ESI) available: full experimental and characterization data of the products; reaction profile of the reaction to give **4a**. See http://www.rsc.org/suppdata/nj/b4/b406878e/

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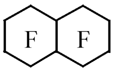
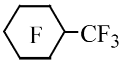
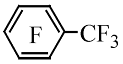
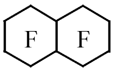
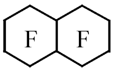
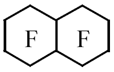
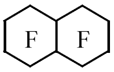
Table 1 Yield of **4a** from the aza-Diels–Alder reaction of **1a**, **2a** and **3** with different catalysts in fluorous phase[a] (Scheme 1)

Entry	Catalyst[b]	% Yield[c]
1	$HOSO_2CF_3$	52
2	$HOSO_2C_8F_{17}$	64
3	$Yb(OSO_2CF_3)_3$	59
4	$Yb(OSO_2C_8F_{17})_3$	70
5	$Sc(OSO_2CF_3)_3$	64
6	$Sc(OSO_2C_8F_{17})_3$	82
7	$Na(OSO_2C_8F_{17})_3$	16
8	$Na(OSO_2CF_3)_3$	13
9	$K(OSO_2C_8F_{17})_3$	15
10	$Li(OSO_2C_8F_{17})_3$	36

[a] Conditions: catalyst, 2.0 mol %; fluorous solvent/hexane; 60 °C; 2 h. [b] No reaction occurred in the absence of catalyst. [c] Isolated yields.

Table 2 Yield of **4a** from the aza-Diels–Alder reaction of **1a**, **2a** and **3** in different fluorous solvents[a] (Scheme 1)

Entry	Fluorous phase	% Yield[b]
1		82
2		60
3		43
4	$CF_3(CF_2)_4CF_3$	52
5[c]		71
6[c]		74
7[c]		72
8[c]		72

[a] Conditions: catalyst $Sc(OSO_2C_8F_{17})_3$, 2.0 mol %; fluorous solvent/hexane; 60 °C; 2 h. [b] Isolated yields. [c] The catalyst in fluorous phase reused.

presence of a Lewis acid produced the [4 + 2] cycloaddition product. The rate-determining step is the formation of this imine intermediate **A** because the aza-Diels–Alder reaction proceeds quickly in the presence of Lewis acids such as perfluorinated rare earth metal salts.[11] One control experiment was carried out by use of the imine, prepared according to the previous literature,[12] with Danishefsky's diene in the presence of $Sc(OSO_2C_8F_{17})_3$ under the same conditions (Scheme 2). The corresponding aza-Diels–Alder adduct **4a** was isolated in similar yield (70%). No other product can be found in this reaction. The reaction profile showing the appearance-disappearance of starting materials and intermediate as well as the appearance of product clearly supported above results (see Electronic supplementary information).

Next, we screened several other fluorous solvents, such as perfluorotoluene (C_7F_8), perfluoro(methylcyclohexane) (C_7F_{14}) and perfluorohexane (C_6F_{14}) in this FBS catalytic system. The results are summarized in Table 2. We found that during the aza-Diels–Alder reaction proceess, the loss of fluorous solvent is very serious at 60 °C when using C_7F_8, C_7F_{14} and C_6F_{14} as solvents because they are volatile (bp 58–76 °C). Perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture) is the best fluorous solvent for this reaction (Table 2, entries 1–4). This new fluorous phase is not volatile because it has a higher boiling point (bp 142 °C). Based on the ^{19}F NMR spectroscopic data and GC-MS, no loss of catalyst or perfluorodecalin to the organic and water phase during workup can be detected.

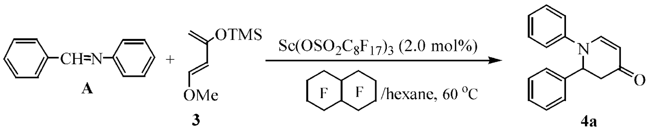
The perfluorodecalin fluorous phase containing $Sc(OSO_2C_8F_{17})_3$ catalyst can be easily isolated by simple separation of the fluorous phase. This catalytic phase can be reused four times to give similar results without reloading fluorous solvent and the catalyst (Table 2, entries 5–8).

Using $Sc(OSO_2C_8F_{17})_3$ as a catalyst and perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture) as the fluorous solvent in a biphasic way, the aza-Diels–Alder reaction of Danishefsky's diene with other arylaldehydes and aromatic amines were examined as well (Scheme 3). The results are shown in Table 3. These aza-Diels–Alder reactions proceeded smoothly at 60 °C to give the corresponding adducts in good yields (Table 3, entries 1–5). No reaction occurred when using aliphatic aldehydes as substrates with aromatic amines in this reaction under the same conditions. This is because the corresponding imines formed *in situ* are not stable in the presence of Lewis acids. In these cases, the reactions gave no other by-products. The starting materials could be recovered during the purification of the adducts by column chromatography. Thus, a novel FBS catalytic process of aza-Diels–Alder reaction has been explored.

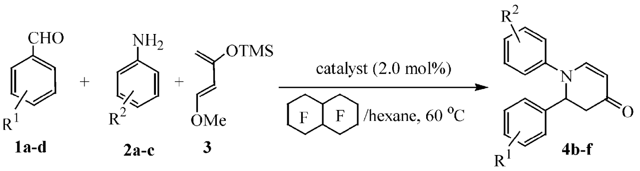
In summary, we reported in this paper a new way to carry out the aza-Diels–Alder reaction of Danishefsky's diene with arylaldehydes and aromatic amines in fluorous phase. Using perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture) as a fluorous solvent and $Sc(OSO_2C_8F_{17})_3$ as a catalyst, this aza-Diels–Alder reactions can be repeated many times without reloading the fluorous solvent and the catalyst. By the conventional Lewis acid catalyzed reaction, the water-stable Lewis acids, $Sc(OTf)_3$ or $Sc(OPf)_3$, could be recovered from the water phase after the usual workup. Obviously the water must be evaporated and this will consume a lot of energy. By this technology, the catalytic phase can be easily recovered and can be reused for the next reaction without any treatment. Further investigations to develop other types of reactions in fluorous phase with perfluorinated metal salts as the catalyst are now in progress.

Experimental

For the preparation of the perfluorinated rare earth metal catalysts [$Ln(OSO_2C_8F_{17})_3$, Ln = Yb, Sc],[8] the reaction procedure was the following. An excess amount of a lanthanide(III) oxide (99.9% purity) was added to an aqueous solution of $C_8F_{17}SO_3H$ (50% v/v) and this was heated at boiling temperature for 30–60 min. The mixture was filtered to remove the unreacted oxide. The water was then removed from the filtrate under reduced pressure. The resulting hydrate was dried by heating under vacuum at 180–200 °C for 48 h



Scheme 2



Scheme 3

Table 3 Yield of **4** from the aza-Diels–Alder reaction of **1**, **2** and **3** in fluorous phase[a] (Scheme 3)

R^1	R^2	Product	% Yield[b]
1b, R^1 = *p*-Cl	**2a**, R^2 = H	**4b**	73
1c, R^1 = *p*-NO_2	**2a**, R^2 = H	**4c**	82
1d, R^1 = *p*-OMe	**2a**, R^2 = H	**4d**	77
1a, R^1 = H	**2b**, R^2 = *p*-F	**4e**	84
1a, R^1 = H	**2c**, R^2 = *o*-CF_3	**4f**	68

[a] Conditions: catalyst $Sc(OSO_2C_8F_{17})_3$, 2.0 mol %; fluorous solvent/hexane; 60 °C; 2 h. [b] Isolated yields.

For the preparation of the perfluorinated alkali metal salt catalysts [$M(OSO_2C_8F_{17})$, M = Li, Na, K],[9] the following reaction procedure was used. Trifluoromethanesulfonic or heptadecafluorooctanesulfonic acid was added dropwise to a solution of the carbonate salt in methanol at 0 °C. The reaction mixture was stirred at room temperature for 30 min, then it was refluxed for 30–60 min. The clear solution was concentrated under reduced pressure. The resulting white cake was dried at 125 °C for 2 h. The obtained product was recrystallized from methanol or ethanol–diethyl ether

The typical reaction procedure for the aza-Diels–Alder reaction in fluorous phase was as follows. To a solution of $Sc(OPf)_3$ (10 mg, 0.006 mmol) in perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture; fluorous solvent, 1.0 mL) was added a solution of aniline (27 μL, 0.3 mmol) and benzaldehyde (30 μL, 0.3 mmol) in hexane (organic solvent, 1.0 mL). Danishefsky's diene (90 μL, 0.45 mmol) was added to the reaction mixture with stirring. The reaction mixture was stirred at 60 °C for 2 h. Then, the fluorous layer was separated for the next reaction. The reaction mixture (organic layer) was washed with water (5 mL) and extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 5 v/v) to give the product as a colorless solid (62 mg, yield 82%)

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