Lewis Acid Catalysis in Supercritical Carbon Dioxide. Use of Scandium Tris(heptadecafluorooctanesulfonate) as a Lewis Acid Catalyst in Diels-Alder and Aza Diels-Alder Reactions

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Diels-Alder reactions of carbonyl dienophiles with dienes and aza Diels-Alder reactions of imines with a diene have been successfully carried out using scandium tris(heptadecafluorooctanesulfonate) ($Sc(OSO_2C_8F_{17})_3$) as a Lewis acid catalyst in supercritical carbon dioxide ($scCO_2$). It was revealed that the length of perfluorocarbon chains of the scandium catalyst was an essential factor for the catalytic activity in $scCO_2$.

Lewis acid-catalyzed reactions are now of great interest because they proceed under mild conditions to achieve unique reactivity and selectivity.[1] While various types of Lewis acids have been employed in many synthetic processes, the reactions are usually carried out in anhydrous aprotic organic solvents such as dichloromethane. On the other hand, we have focused on use of Lewis acid catalysts in water.[2] Water is no doubt a cheap, safe, and environmentally friendly solvent. While most Lewis acids are believed to be decomposed or deactivated in the presence of even a small amount of water, we have recently found that rare earth compounds[3] and some other metal salts[4] are stable and work as Lewis acid catalysts in water. In these reactions, although water works as a Lewis base to coordinate to the Lewis acid, the coordination occurs under equilibrium conditions and Lewis acid catalysis has been performed efficiently in such media. Similarly, it was expected that such Lewis acids would work well in supercritical carbon dioxide ($scCO_2$), which has also been regarded as a desirable substitute for some toxic organic solvents to accomplish benign chemical reactions.[5] In this paper, we report our preliminary results on Lewis acid catalysis in $scCO_2$, especially focused on Diels-Alder reactions and aza Diels-Alder reactions using scandium tris(heptadecafluorooctanesulfonate) as a Lewis acid catalyst.[6]

Diels-Alder reactions provide one of the most useful methods for the preparation of cyclic compounds with high stereoselectivities.[7] Recently, although these reactions in $scCO_2$ have been investigated, major interest has been directed to the stereoselectivity, and synthetic applications are limited because the reactions proceed sluggishly in $scCO_2$ in many cases.[8] In order to overcome the low reactivity in $scCO_2$, we decided to examine use of Lewis acids in Diels-Alder reactions in $scCO_2$. It was also anticipated that stereoselectivities would be improved by using Lewis acids. We first examined the Diels-Alder reaction between methylvinylketone (MVK) and isoprene as a model and using rare earth salts as Lewis acids. One problem incurred in using Lewis acids in $scCO_2$ was the low solubility of most Lewis acids. Since the use of perfluoroalkylated groups was known to increase solubility, we decided to employ scandium perfluoroalkanesulfonates. In our first experiments, MVK and isoprene were introduced by the Feed Line method described by Danheiser et al.[8a] The effect of perfluoroalkyl substituents of scandium catalysts is shown in Table 1. Among the scandium compounds we tested,[9] $Sc(OSO_2C_8F_{17})_3$[10] gave the best result. These results showed that the scandium catalysts having longer perfluoroalkyl chains gave high activity and catalyzed the Diels-Alder reaction more efficiently.[11] It was observed that $Sc(OSO_2C_8F_{17})_3$ was dissolved in $scCO_2$ to form a homogeneous solution, while $Sc(OTf)_3$ was not completely soluble under the same conditions.[12] In addition, it is noted that the

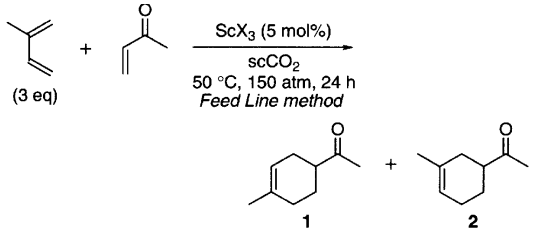
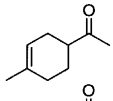
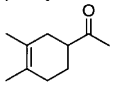
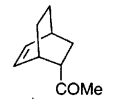
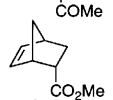
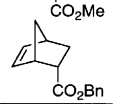


Table 1. Effect of Perfluoroalkyl Chains of ScX_3 in the Diels-Alder Reaction

Entry	ScX_3	Yield/%[a]	**1/2**[a]
1	none	4	80/20
2	$Sc(OTf)_3$	41	93/7
3	$Sc(OSO_2C_4F_9)_3$	64	94/6
4	$Sc(OSO_2C_8F_{17})_3$	74	94/6

[a]Determined by GC analyses using an internal standard (GC-IS).

Table 2. $Sc(OSO_2C_8F_{17})_3$-catalyzed Diels-Alder reactions in $scCO_2$[a]

Entry	Dienophile	Diene	Major Product	Yield/%[b]
1				80[c]
2				>99 (>99)[d]
3				97[e]
4[f]				95[g]
5[f]				>99[h]

[a]Reaction conditions; $Sc(OSO_2C_8F_{17})_3$ (5 mol%), Dienophile (1 eq), Diene (3 eq), 50 °C, 150 atm, 24 h by the modified Ampoule method.[8a] [b]Isomer ratios and yields were determined by GC-IS except for entries 4 and 5, in which they were determined by ^{1}H-NMR. [c]**1/2** = 95/5. [d]One mol% of the catalyst was used. [e]*Endo*/*exo* = 90/10. [f]The reaction time was 3 h. [g]*Endo*/*exo* = 76/24. [h]*Endo*/*exo* = 92/8.

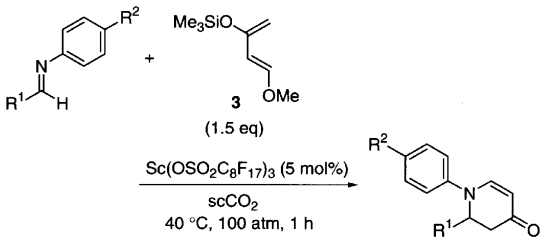


Table 3. $Sc(OSO_2C_8F_{17})_3$-catalyzed aza Diels-Alder reactions in $scCO_2$[a]

Entry	R^1	R^2	Yield/%[b]
1	Ph	H	72 (>99)[c] (81)[d]
2	Ph	OMe	86
3	Ph	Cl	73
4	2-pyridyl	H	68
5	*c*-C_6H_{11}	H	60[c]

[a]Imines and **3** were introduced by the modified Ampoule method.[8a] [b]Determined by ^{1}H-NMR using an internal standard. [c]Diene (2 eq) was used. [d]Diene (2 eq) and the catalyst (0.5 mol%) were used.

regioselectivity (**1/2**) has been improved by using Lewis acid catalysts.[13]

Several examples of the Diels-Alder reactions using $Sc(OSO_2C_8F_{17})_3$ as a catalyst are shown in Table 2. In all cases, the reactions proceeded smoothly to afford the desired adducts in high yields with high selectivities. Even when 1 mol% of $Sc(OSO_2C_8F_{17})_3$ was used, the Lewis acid catalysis was successfully carried out in $scCO_2$ to give the cycloaddition product in high yield (entry 2), and these results indicate the synthetic utility of the present Diels-Alder reactions in $scCO_2$ using $Sc(OSO_2C_8F_{17})_3$ as a catalyst.

Moreover, it was revealed that aza Diels-Alder reactions of imines with Danishefsky's diene (**3**)[14] proceeded cleanly in $scCO_2$ using $Sc(OSO_2C_8F_{17})_3$.[12,15] Not only the imine derived from benzaldehyde but also the imines derived from 2-pyridinecarboxaldehyde and cyclohexanecarboxaldehyde reacted with **3** to afford the corresponding piperidone derivatives in good to excellent yields (Table 3). It is noted that 81% yield of the adduct was obtained even when 0.5 mol% of the catalyst was employed.

A typical experimental procedure is described for the reaction of MVK with isoprene (Table 1, entry 4): Under an argon atmosphere, $Sc(OSO_2C_8F_{17})_3$ (138 mg, 0.089 mmol) was placed in a 10-mL reactor along with a magnetic bar, and pre-cooled low-pressure CO_2 was introduced to the sealed reactor at room temperature. After a mixture of MVK (131 mg, 1.87 mmol) and isoprene (0.56 mL, 5.60 mmol) was added through the Feed Line, the reactor was pressurized to 150 atm at 50 °C. After 24 h, the pressure in the reactor was slowly released, the reactor was opened under 0 °C, and H_2O (10 mL) was added to the residue. The mixture was extracted with Et_2O, and the chemical yield (74%) and the stereoselectivity (**1/2** = 94/6) were determined by GC using an internal standard.

In summary, we have developed Diels-Alder reactions of carbonyl dienophiles with dienes and aza Diels-Alder reactions of imines with a diene using $Sc(OSO_2C_8F_{17})_3$ as a Lewis acid catalyst in $scCO_2$. The synthetic utility of these reactions has been demonstrated, and effective Lewis acids and catalysis in $scCO_2$ have been proposed. Use of the water-stable scandium catalyst as well as $scCO_2$ as a solvent is expected to lead to benign chemical processes. We are currently investigating other Lewis acid-catalyzed reactions in $scCO_2$.

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