Facile and Recyclable Method for the Prins Reaction Using Hafnium(IV) Bis(perfluorooctanesulfonyl)amides in Fluorous Biphase System

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In fluorous biphase system, $Hf[N(SO_2C_8F_{17})_2]_4$ has been found to be an efficient catalyst for the Prins reaction of α -methyl styrene with aldehydes at low catalytic loading. The reaction proceeds smoothly and affords the corresponding 1,3-dioxanes in good yields. The catalyst is selectively soluble in lower fluorous phase and can be recovered simply by phase separation. Furthermore, the recovered fluorous phase containing catalyst can be recycled 17 times with yields consistently above 80%.

The Prins reaction is a fundamental reaction for carbon-carbon bond formation and is one of the most straightforward method for the synthesis of 1,3-dioxanes, which are widely used in organic synthesis as solvents or intermediates.^{1,2} Some traditional Lewis acids (e.g., BF₃, SnCl₄) and mineral acids (e.g., H₂SO₄, H₃PO₄) can promote this transformation, but most of these methods involve the use of corrosive or toxic reagents and high reaction temperature resulting in low to moderate yield of products due to the polymerization of starting materials.³ Although some improvements have been made using 5 mol % Bi(OSO₂CF₃)₃ in acetonitrile⁴ and 10 mol % 2,6-di-tert-butylphenoxy(difluoro)borane in 1,4-dioxane,⁵ but high catalyst loading was required and no catalyst recycle was given. Recently, Yadav et al. reported 10 mol % InBr₃ catalyzed the Prins reaction of styrene with paraformaldehyde in dialkylimidazolium-based ionic liquids and have showed that the recovered ionic liquid containing catalyst can be recycled in 3 to 4 subsequent runs.⁶ On the other hand, fluorous biphase system (FBS), as a phase separation and catalyst immobilization technique, can be shown to be one of the environment-benign technical candidates.⁷

Our previous works in FBS have found that metal (e.g., Hf, Sn, Yb) complexes with bis(perfluorooctanesulfonyl)imide ponytails are excellent active and recyclable catalysts in the fluorous immobilized phase for the Baeyer–Villiger oxidation, esterification, and the Friedel–Crafts acylation, far superior to the corresponding metal trifluoromethanesulfonates.⁸

In this letter, we will describe our new approach to FBS for the Prins reaction, and industrial application possibilities of this FBS technique.

The potential of Hf[N(SO₂C₈F₁₇)₂]₄ in FBS was first studied and compared with other Hf^{IV}-based sulfonate complexes, using the Prins reaction of α -methyl styrene and paraformaldehyde under the mild condition of 35 °C for 0.5 h. A catalyst loading of 0.5 mol% turned out to be ideal. The use of a lower catalyst/ α -methyl styrene ratio led to longer reaction time or to incomplete conversion. As summarized in Table 1, no product was obtained in the absence of catalyst (Entry 4). Hf[N(SO₂C₈F₁₇)₂]₄ (Entry 1) was found to be more active than Hf(OSO₂C₈F₁₇)₄(Entry 2) or Hf(OSO₂CF₃)₄ (Entry 3) in FBS. It is reasonable to speculate that the stronger electron-withdrawing ligands of Hf[N(SO₂C₈F₁₇)₂]₄ renders it super Lewis acidi-

ties in FBS and hence shows better catalytic activity. Furthermore, $Hf[N(SO_2C_8F_{17})_2]_4$ in FBS gives significantly good recyclability than $Hf(OSO_2C_8F_{17})_4$ or $Hf(OSO_2CF_3)_4$, i.e., $Hf[N(SO_2C_8F_{17})_2]_4$ could be immobilized in the lower fluorous phase and directly reused more than 17 times, whereas $Hf(OSO_2C_8F_{17})_4$ and $Hf(OSO_2CF_3)_4$ could be reused only for 3 to 4 times owing to their distribution in the upper 1,2-dichloro-ethane phase. In addition, the use of formaldehyde aqueous solution (35 wt %) instead of paraformaldehyde thus resulted in much slow reaction rates, unlike previously reported processes in the gas phase.⁹ To the best of our knowledge, this is the first example for fluorous activity comparison of amide with sulfonate complexes.

As an approach to fragrance industrial application, the recyclable $Hf[N(SO_2C_8F_{17})_2]_4$ -catalyzed fluorous biphase Prins reaction system was used to investigate the production of 2,4,6-trimethyl-4-phenyl-1,3-dioxanes, employed for more than 20

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6	+ (HCHO) _n	Catalyst (0.	5 mol %)	
Į	1,2 GA	-dichloroetha LDEN [®] SV 1	ne 1.5 mL 35 1.5 mL	I
	1 mmol 2 mmol	35 °C, 0	0.5 h	
Entry	Catalyst	Cycle	Conversion/% ^b	Yield/% ^c
1	$Hf[N(SO_2C_8F_{17})_2]_4$	1	95	87
		2	97	87
		3	97	85
		4	96	85
		5	100	86
		6-16	94-100	81-85
		17	95	80
		18	94	73
		19	93	74
2	$Hf(OSO_2C_8F_{17})_4$	1	77	50
		2	93	77
		3	95	82
		4	89	74
		5	91	72
		6	81	65
3	Hf(OSO ₂ CF ₃) ₄	1	99	75
		2	92	84
		3	92	86
		4	85	58
4	None	1	0	0

^aParaformaldehyde (60 mg, corresponding to 2 mmol equivalents of formaldehyde) was used as formaldehyde source; GALDEN[®] SV 135 (CF₃{[O-CF(CF₃)-CF₂]_n-(O-CF₂)_m}-O-CF₃) was purchased from Solvay Solexis K.K.; The partition coefficients (1,2-dichloroethane/GALDEN[®] SV 135 solvent) is (<1)/(>99) for Hf[N(SO₂C₈F₁₇)₂]₄ and (>30)/(<70) for Hf[OSO₂CF₃)₄, which were determined by atomic emission spectrometry. ^bConversion of α -methyl styrene. ^cYields were determined by calibrated quantitative GC and GC/MS analysis using *n*-tridecane as internal standard.



Figure 1. Effect of the catalyst amount on the conversion (---) and yield (—), in the Prins reaction of α -methyl styrene with paracetaldehyde over Hf[N(SO₂C₈F₁₇)₂]₄: 1.0 mol % (\blacklozenge), 0.5 mol % (\blacksquare), 0.1 mol % (\blacklozenge), 0.05 mol % (\blacktriangle).

years as an aromatic substance and sold under the name VERTACETAL® (manufacture: Symrise GmbH & Co. KG, Holzminden).¹⁰ As summarized in Figure 1, optimized reaction conditions included the use of paracetaldehyde as the acetaldehyde source and 10 °C as the suitable reaction temperature. As can be seen, a significant increase of yield was observed when the catalyst amount was increased from 0.05 to 0.1 mol%, but further increase (over 0.1 mol%) resulted in gradual decrease. It can also be noticed that the long-time yield leveled off or increased slightly. These reasons are currently under investigation, but it is most likely related to the amount of acetaldehyde in the reaction mixture. The generally accepted mechanism of the Prins reaction is that the reaction proceeds through the initially formed monomeric acetaldehyde by the interaction of paracetaldehyde with Lewis acid catalyst, but it is a wonder that, under current reaction conditions, the reaction seems to become very slow when paracetaldehyde was almost decomposed to monomeric acetaldehyde. This was confirmed by the fact that a reaction conducted under identical conditions using acetaldehyde instead of paracetaldehyde led to much slow reaction rates. When the catalyst over 0.1 mol % was used or the prolonged reaction time was conducted, the decomposition of paracetaldehyde to monomeric acetaldehyde became faster or paracetaldehyde almost disappeared to monomeric acetaldehyde, the Prins reaction thus became very slow. In addition, the Prins reaction did not yield any product under devoid of catalyst, despite prolonged time (120 h).

The possibility of recycling $Hf[N(SO_2C_8F_{17})_2]_4$ catalyst was also investigated in the Prins reaction of α -methyl styrene and paracetaldehyde under 10 °C for 48 h. As shown in Table 2, even after $Hf[N(SO_2C_8F_{17})_2]_4$ catalyst was recycled 8 times, the GC conversion and GC yield remained at a constant level, giving after 8 cycles turnover numbers¹¹ (TONs, calculated using the yield of 2,4,6-trimethyl-4-phenyl-1,3-dioxanes) of 6220, which was a relatively high result of the use of Lewis acid as the catalyst. In addition, the product was obtained as a mixture of isomers 2,4,6-trimethyl-4-phenyl-1,3-dioxanes, which contains the isomer (2*RS*,4*SR*,6*RS*)-2,4,6-trimethyl-4-phenyl-1,3-

Table 2. Recycles of $Hf[N(SO_2C_8F_{17})_2]_4$



^aConversion of α -methyl styrene. ^bYields were determined by calibrated quantitative GC and GC/MS analysis using *n*-tridecane as internal standard. ^cCombined yields of isomers.

dioxane, (2*RS*,4*RS*,6*RS*)-2,4,6-trimethyl-4-phenyl-1,3-dioxane, (2*RS*,4*SR*,6*SR*)-2,4,6-trimethyl-4-phenyl-1,3-dioxane, and there are no considerable differences for ratio of isomers in each cycle. For example, the product obtained in the 6th reaction cycle was characterized by GC/MS, ¹H NMR, ¹³C NMR and also by comparison with authentic sample, which exhibited the following compositional distribution: 52.5% (2*RS*,4*SR*,6*RS*)-2,4,6-trimethyl-4-phenyl-1,3-dioxane, 45.9% (2*RS*,4*SR*,6*SR*)-2,4,6-trimethyl-4-phenyl-1,3-dioxane and 1.6% (2*RS*,4*SR*,6*SR*)-2,4,6-trimethyl-4-phenyl-1,3-dioxane.

In summary, a simple and practical Prins reaction has been devised on the basis of active $Hf[N(SO_2C_8F_{16})_2]_4$ catalyst and fluorous biphase system. Easy recycle and reuse of this FBS technique is expected to contribute to the development of industrial application process for the manufacture of 1,3-dioxanes.

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