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Immobilization and Reuse of Pd Complexes in Ionic Liquid: Efficient Catalytic Asymmetric Fluorination and Michael Reactions with β-Ketoesters

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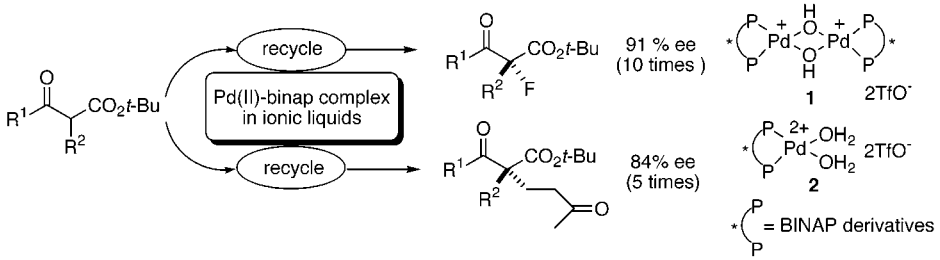
ABSTRACT



Palladium complexes (1 and 2) were immobilized in ionic liquids, and their applications to catalytic asymmetric fluorination and Michael reaction of β-ketoesters were successfully demonstrated. This immobilization enabled the reuse of the catalysts no less than 10 times in fluorination and 5 times in Michael reaction with levels of efficiency comparable to those obtained in usual organic solvents.

In the past decade, the recovery and reuse of catalysts including chiral catalysts has attracted growing interest to meet the need for environmentally friendly and cost-effective reaction processes.[1] Many attempts have been made to realize such systems.[2] Among them, immobilization of chiral catalysts on soluble or insoluble polymers and the usage of biphasic systems are representative. In most cases, however, these approaches require ligand modification, which sometimes makes the synthesis of chiral catalysts difficult. In addition, the reaction efficiency obtained under homogeneous conditions is sometimes difficult to reproduce, resulting in lower yields and ee's.[3]

Recently, organic salts which are liquid at ambient temperature [ionic liquids (IL)] have emerged as alternative solvents because they have essentially no vapor pressure and provide good solubility for a wide range of organic, inorganic, and organometallic compounds.[4] A number of reactions including hydrogenation, oxidation, and C−C bond-forming reactions have already been demonstrated in IL.[5] Surprisingly, however, investigations to develop asymmetric reactions have only recently attracted attention, and only a limited number of examples were reported until recently.[6] Furthermore, most of the reported examples showed that reaction efficiency (yield and ee) obtained in usual organic solvents was difficult to reproduce in IL, and recycling of the catalyst was less satisfactory.

(1) (a) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res*. **2002**, *35*, 686−694. (b) *Chiral Catalyst Immobilization and Recycling*; DeVos, D. E., Vankelecom, I. F. J., Jacobs, P. A., Eds.; Wiley-VHC: Weinheim, Germany, 2000.

(2) Review on the reuse of chiral catalysts: Fan, Q.-H.; Li, Y.-M.; Chan, A. S. C. *Chem. Rev*. **2002**, *102*, 3385−3466.

(3) For our attempt, see: Fujii, A.; Sodeoka, M. *Tetrahedron Lett*. **1999**, *40*, 8011−8014.

(4) (a) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev*. **2002**, *102*, 3667−3692. (b) Sheldon, R. *Chem. Commun*. **2001**, 2399−2407. (c) Wasserscheid, P.; Kein, W. *Angew. Chem., Int. Ed*. **2000**, *39*, 3772−3789. (d) Welton, T. *Chem. Rev*. **1999**, *99*, 2071−2083.

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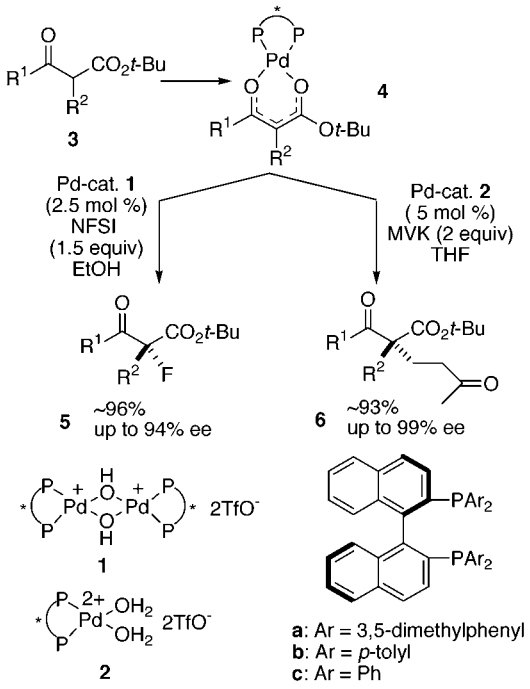
We have recently reported enantioselective Michael reaction[7] and fluorination[8] using a catalytic amount of novel chiral palladium complexes **1** and **2** (Scheme 1). In these

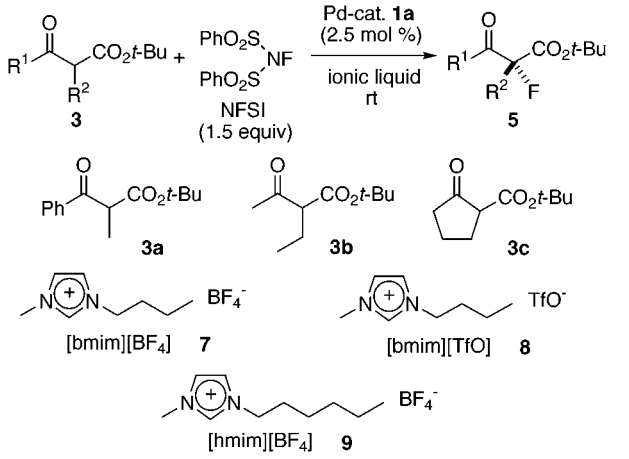
Scheme 1. Asymmetric Reactions Catalyzed by Cationic Palladium Complexes



reactions, β-ketoesters were directly activated to form a chiral palladium enolate **4**,[7] which reacted with electrophiles such as enones and *N*-fluorobenzenesulfonimide (NFSI). Both reactions proceeded in high yields, giving the products with excellent enantioselectivities of up to 99% ee in the Michael reaction and up to 94% ee in the fluorination. Since the palladium complexes are not sensitive to water, both reactions were carried out in protic solvents (alcohols, H_2O[9]). While the usage of environmentally friendly solvents is advantageous, the recovery of the palladium complexes from the reaction mixtures is not easy. To address this issue, we planed to develop an efficient catalytic system using IL, in which the palladium complexes can be repeatedly used. Thus, we envisaged that the palladium complexes **1** and **2** might be immobilized in IL due to their cationic property and that the same level of enantioselectivity would be obtained because the palladium enolate **4** may be configurationally stable even in polar ionic liquid. Herein we wish to report a successful example of the reuse of palladium complexes and its applications to two catalytic asymmetric reactions. Catalysts could be reused at least 10 times in fluorination and 5 times in the Michael reaction.

At the outset, we examined the catalytic enantioselective fluorination of the β-ketoester **3a** using three ionic liquids **7**−**9** (Table 1).[10, 11] Thus, to a solution of Pd complex **1a** in IL were added **3a** and *N*-fluorobenzenesulfonimide (1.5 equiv). The reaction mixture was stirred at ambient temperature. While the length of the side chain and the counteranion of IL seemed to have some influence on the reaction rate, excellent enantioselectivities (91−92% ee) were obtained in all three cases (entries 1−3). Using IL **9**, the desired product was obtained in 93% yield and 92% ee. Although the

Table 1. Catalytic Asymmetric Fluorination in Ionic Liquid



entry	ketoester	ionic liquid	time (h)	yield[a] (%)	ee[b] (%)
1	**3a**	**7**	60	68	91
2	**3a**	**8**	60	88	92
3	**3a**	**9**	60	93	92
4	**3b**	**7**	12	80	85
5	**3c**	**9**	6	94	91

[a] Isolated yield after ether extraction. [b] Ee's and the absolute configuration of the products were determined by chiral HPLC analysis using the conditions reported previously.[8]

(5) Recent selected examples: Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Org. Chem.* **2003**, *68*, 4281−4285. (b) Gmouh, S.; Yang, H.; Vaultier, M. *Org. Lett.* **2003**, *5*, 2219−2222. (c) Kabalka, G. W.; Dong, G.; Venkataiah, B. *Org. Lett.* **2003**, *5*, 893−895. (d) Zerth, H. M.; Leonard, N, M.; Mohan, R. S. *Org. Lett.* **2003**, *5*, 55−57. (e) Boxwell, C. V.; Dyson, P. J.; Ellis, D. J.; Welton, T. *J. Am. Chem. Soc.* **2002**, *124*, 9334−9335. (f) Dupont, J.; Fonseca, G. S.; Umpierre, A. P.; Fichtner, P. F. P.; Teixeira, S. R. *J. Am. Chem. Soc.* **2002**, *124*, 4228−4229. (g) Yao, Q. *Org. Lett.* **2002**, *4*, 2197−2199. (h) Mehnert, C. P.; Dispenziere, N. C.; Cook, R. A. *Chem. Commun.* **2002**, 1610−1611. (i) Mathews, C. J.; Smith, P. J.; Welton, T. *Chem. Commun.* **2002** 1249−1250. See also ref 4.

(6) Hydrogenation: (a) Chauvin, Y.; Mussmann, L.; Olivier, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2698−2700. (b) Monteiro, A. L.; Zinn, F. K.; de Souza, R. F.; Dupont, J. *Tetrahedron: Asymmetry* **1997**, *2*, 177−179. (c) Brown, R. A.; Pollet, P.; McKoon, E.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. *J. Am. Chem. Soc.* **2001**, *123*, 1254−1255. (d) Guernik, S.; Wolfson, A.; Herskowitz, M.; Greenspoon, N.; Geresh, S. *Chem. Commun.* **2001**, 2314−2315. Epoxidation: (e) Song, C. E.; Roh, E. J. *Chem. Commun.* **2000**, 837−838. Dihydroxylation: (f) Branco, L. C.; Afonso, C. A. M. *Chem. Commun.* **2002**, 3036−3037. (g) Song, C. E.; Jung, D.; Roh, E. J.; Lee, S.; Chi, D. Y. *Chem. Commun.* **2002**, 3038−3039. Aldol reaction: (h) Loh, T.-P.; Feng, L.-C.; Yang, H.-Y.; Yang, J.-Y. *Tetrahedron Lett.* **2002**, *43*, 8741−8743. (i) Kotrusz, P.; Kmentová, I.; Gotov, B.; Toma, S.; Solcániová, E. *Chem. Commun.* **2002**, 2510−2511. Cyclopropanation: (j) Fraile, J. M.; García, J. I.; Herrerías, C. I.; Mayoral, J. A.; Carrié, D.; Vaultier, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1891−1894. Epoxide opening reaction: (k) Song, C. E.; Oh, C. R.; Roh, E. J.; Choo, D. J. *Chem. Commun.* **2000**, 1743−1744. (l) Oh, C. R.; Choo, D. J.; Shim, W. H.; Lee, D. H.; Roh, E. J.; Lee, S.; Song, C. E. *Chem. Commun.* **2003**, 1100−1101.

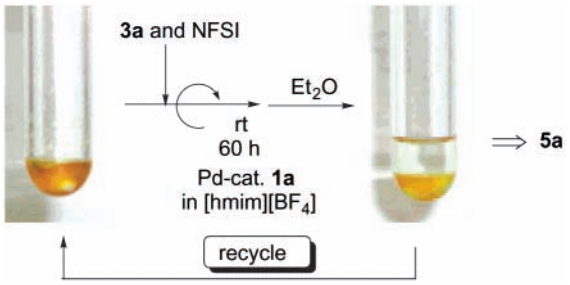
(7) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240−11241.

(8) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530−14531.

chemical yield and enantioselectivity were almost the same as those obtained in EtOH (40 h, 92%, 91% ee), a longer reaction time (60 h) was necessary for the completion of the reaction. Other β-ketoesters could be also employed for this reaction (entries 4 and 5). The reaction of **3b** afforded the desired product **5b** in 80% yield and 85% ee. The cyclic substrate **3c** was also converted to the fluorinated products with comparable selectivity (6 h, 94%, 91% ee). In contrast to the case of **3a**, substantial acceleration of the reaction rate was observed for **3b** and **3c**. For example, the reaction of **3b** was completed within 12 h, while the reaction in EtOH needed 42 h to afford a comparable yield (88%, 87% ee). [12]

After the completion of the reaction, the products were separated by simple extraction. Several organic solvents were tested, and ether was found to be the best solvent in terms of extraction efficiency. As shown in Table 2, IL **9** readily

Table 2. Recycling of Catalytic Asymmetric Fluorination



cycle	yield (%)	ee (%)	cycle	yield (%)	ee (%)
1	93	92	6	91	91
2	80	91	7	91	91
3	81	91	6	86	91
4	91	91	9	86	91
5	81	91	10	67	91
			11[a]	82	91

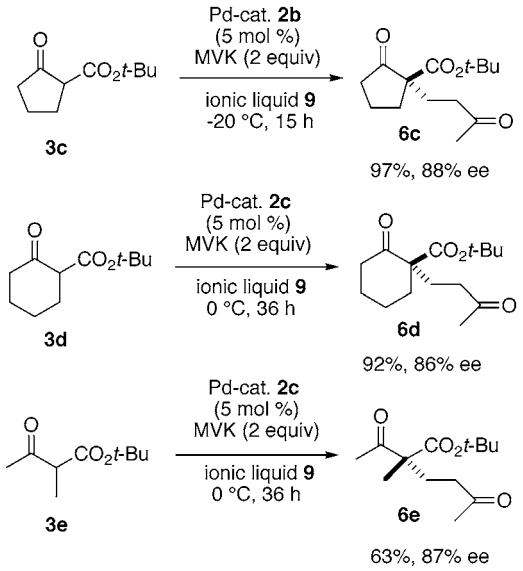
[a] 84 h.

formed a bilayer with ether. From the ether layer, the desired product **5a** was isolated in 93% yield after the purification by short column chromatography (Table 1, entry 3).[13] The yellow IL layer and colorless ether layer clearly indicated that the Pd catalyst was retained in IL. The complete reproducibility in the fluorination is a better proof for the negligible leaching of the chiral catalyst.

This result prompted us to examine the reuse of the catalyst immobilized in IL **9** (Table 2). Thus, the same amounts of starting materials were again added to the separated ionic liquid layer. The reaction reached completion after 60 h to give the desired product in 80% yield and with 91% ee (cycle 2). Further, the catalyst could be recycled no less than 10 times, maintaining the excellent enantioselectivity (91% ee). A slight decrease of the reaction rate was finally observed in the tenth reaction cycle. However, a prolonged reaction time (84 h) allowed completion of the reaction, and the fluorinated product was isolated in 82% yield and 91% ee (eleventh run). To our knowledge, this is the first time that catalytic asymmetric fluorination has been performed repeatedly in an ionic liquid.

Encouraged by this success, we turned our attention to the catalytic enantioselective Michael reaction (Scheme 2).

Scheme 2. Catalytic Asymmetric Michael Reaction in IL **9**



In the presence of a catalytic amount of Pd complex **2b** (5 mol %), the reaction of *tert*-butyl 2-oxo-cyclopentanecarboxylate **3c** with methylvinyl ketone (MVK) was conducted in IL **9** at −20 °C. The Michael adduct **6c** was obtained in 97% yield after 15 h, and the ee was determined to be 88% (92%, 92% ee in THF after 24 h). Using **2c** as a catalyst, other β-ketoesters, **3d** and **3e**, were also used for this Michael reaction. As in the case of fluorination, acceleration of the reaction was observed in IL, and the reaction reached completion after 36 h (72 h in THF).[14] The desired products were obtained in good yields and high enantioselectivities (86% ee and 87% ee, respectively; 90% ee in THF).

Similarly, we next investigated the reuse of the catalyst in the Michael reaction as well. Unfortunately, however, the

(9) Unpublished results: we recently found that the Michael reaction proceeded in water without any organic solvent. In the case of *tert*-butyl 2-oxo-1-cyclopentanecarboxylate **3c**, the reaction with MVK was completed after 24 h at 4 °C to give the product in 92% yield and 88% ee.

(10) These ionic liquids were purchased from ACROS and used directly without further purification.

(11) Recently, an enantioselective fluorination in IL was reported using a stoichiometric amount of fluorinating reagents derived from cinchona alkaloid: Baudequin, C.; Plaquevent, J.-C.; Audouard, C.; Cahard, D. *Green Chemistry*, **2002**, *4*, 584−586.

(12) Although the reason is not clear, reaction rate apparently depends on the nature of the substrates.

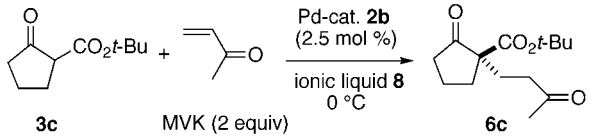
(13) **Representative Procedure for Fluorination.** To a stirred solution of Pd−cat. **1a** (15.4 mg, 7.4 μmol) in IL **9** (0.3 mL) were added **3a** (70 μL, 0.3 mmol) and NFSI (142 mg, 0.46 mmol) at room temperature. After the completion of the reaction (TLC), ether (2 mL 5 10) was added for extraction. Ether was withdrawn via a syringe, and the combined ether layers were concentrated. The resulting residue was purified by short column chromatography (hexane/ether = 10/1) to give the pure product. The absolute configuration of the product was determined to be *R* on the basis of the HPLC analysis.[8] The separated ionic liquid layer was directly reused as a catalyst solution in the next reaction.

reaction using the recovered Pd complex in IL **9** was unsuccessful due to the generation of palladium black. After several attempts, IL **8** was found to be better than IL **9**, and the initial results (82%, 84% ee after 18 h at 0 °C) were well reproduced the second time, but the third reaction cycle showed a considerable decrease of the reaction rate. We considered that fluorination might have tended to suppress the reduction of Pd complexes because formation of decomposed catalyst was not observed during the recycling experiment of fluorination (Table 2). Thus, after the reaction of **3c** with NFSI, the Michael reaction of **3c** with MVK was conducted using the recovered catalyst **2b** at 0 °C.[15] In the presence of 2.5 mol % of **2b**, the reaction proceeded more rapidly to afford the desired product in 98% yield after 8 h (84% ee). In addition, the Pd catalyst could be recycled up to 5 times, as shown in Table 3.

Using the Pd complex which was recovered from the fluorination reaction, acceleration of the reaction was clearly observed. Furthermore, decomposition of the Pd complex was significantly slower, allowing the reuse of catalyst at least 5 times. We speculate that a small amount of acidic benzenesulfonimide, a coproduct of fluorination, remained in IL, and activated the enone causing acceleration of the reaction. Also, it is likely that some unidentified effect of benzenesulfonimide played an important role in keeping the high catalyst activity.[16]

In summary, we have developed an efficient system for the recycling of Pd catalysts, **1** and **2**. These complexes were efficiently immobilized in ionic liquids, and applied to two types of catalytic asymmetric reactions. In the case of fluorination the catalyst **1** could be reused 10 times, and 5 times in the case of the Michael reaction. Both reactions gave comparable results to those obtained in usual organic solvents. These findings indicate that immobilization of transition metal complexes in ionic liquids is a powerful method for the recycling of catalysts. Our asymmetric reactions in ionic liquids have been shown to be practical from economical and environmental points of view. Further studies are under way in our laboratory.

Table 3. Consecutive Michael Reaction Using **2b** Pretreated under the Fluorination Conditions



cycle	time (h)	yield (%)	ee[a] (%)
1	8	98	83
2	8	98	84
3	8	92	83
4	8	91	84
5	15	94	84

[a] Ee's and the absolute configuration of the products were determined by chiral HPLC analysis using the conditions reported previously.[7]

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(14) In our reaction, protic acid formed during the enolate formation was reported to preferentially activate MVK to promote the Michael reaction.[7] The protonated MVK would be more polarized, and might be substantially stabilized in ionic liquid. This may be the reason the reaction proceeded more rapidly. Recently, an accelerating effect in Michael addition of acetylacetone to MVK in IL was also reported using a catalytic amount of $Ni(acac)_2$. See: Dell'Anna, M. M.; Gallo, V.; Mastrorilli, P.; Nobile, C. F.; Romanazzi, G.; Suranna, G. P. *Chem. Comm*. **2002**, 434−435.

(15) **Representative Procedure for Michael Reaction.** To a stirred ionic liquid (IL **8**, 0.2 mL) solution of Pd catalyst **2b** (8.4 mg, 0.0075 mmol) recovered from fluorination were added **3c** (55 μL, 0.3 mmol) and MVK (50 μL, 0.6 mmol) at 0 °C. After the time shown in Table 3, the product was extracted by adding ether (2 mL × 8). From the combined ether layers, **6c** was isolated by flash column chromatography (hexane/ethyl acetate = 5/1) as a colorless oil. The absolute configuration of the product was determined to be *R* on the basis of the HPLC analysis.[7]

(16) Although the exact role of benzenesulfonimde is unclear so far, the following preliminary results showed its positive role in this reaction. Thus, the control experiment was carried out with the freshly prepared **2b** in the presence of benzenesulfonimide (2 equiv to Pd) as an additive, and the comparable results were obtained after 5 cycles (96%, 86% ee, after 10 h at 0 °C). The usage of NFSI (2 equiv to Pd) instead of benzenesulfonimide gave almost the same results after 5 cycles. Therefore, the catalyst recycle in the Michael reaction may be attributed to benzenesulfonimide. The details of these experiments will be reported in due course.