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Palladium-catalyzed Regio- and Diastereoselective Allylic Alkylation in Ionic Liquids

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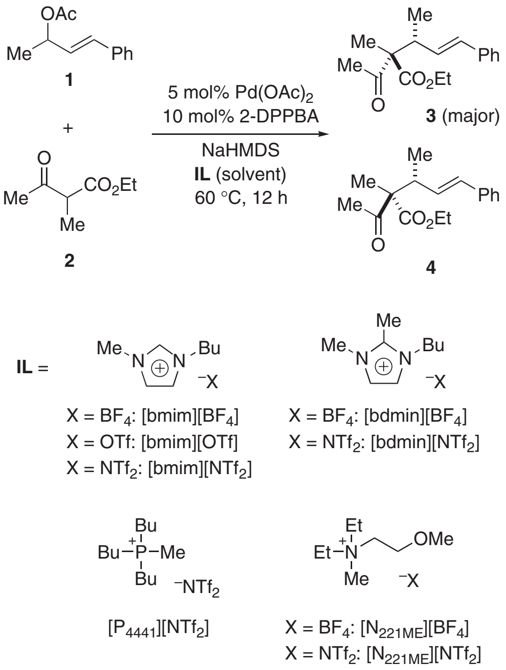
Palladium-catalyzed regio- and diastereoselective allylic alkylations using ionic liquids (ILs) as a solvent were demonstrated. The reaction using diethyl(2-methoxyethyl)methylammonium bis(trifluoromethanesulfonyl)amide ($[N_{221ME}][NTf_2]$) or ethylhexyldimethylammonium bis(trifluoromethanesulfonyl)amide ($[N_{6211}][NTf_2]$) as solvent realized the recyclable use of the palladium catalyst while maintaining excellent regioselectivity and diastereoselectivity.

Palladium-catalyzed allylic alkylation is one of the most widely and frequently used carbon–carbon bond formation reactions, and stereocontrolled reactions have been developed by several groups.[1] We also reported the palladium-catalyzed regio- and diastereoselective allylic alkylation of allylic acetates with dimethyl methylmalonate anion using 2-(diphenylphosphino)benzoic acid (2-DPPBA) as a ligand;[2] it was found that use of NaHMDS as a base was an essential factor in attaining high regio- and diastereoselectivities in the reaction. On the other hand, in recent years, ionic liquids (ILs) have been widely recognized as greener solvents, suitable for use in organic reactions including transition-metal-catalyzed reaction, catalyst immobilization and recycling.[3] We have been interested in the use of ILs in organic synthesis in both chemical and biochemical reactions, and have shown successful examples of the recyclable use of enzymes or iron salt catalysts using these liquids as reaction media.[4] Previously, ILs had been considered inappropriate for strong base-mediated reactions. However, several examples have recently been reported showing the possibility of using ILs as reaction media for strong base-mediated reactions.[5] Although palladium-catalyzed allylic substitutions using IL as a solvent have been reported,[6] there has been no example of regio- and diastereoselective allylic alkylation of 1,3-disubstituted unsymmetrical allylic esters using an ionic liquid solvent system to date. One of the most important benefits of using ILs as reaction media for transition-metal-catalyzed reaction is that the system makes it possible to realize the recyclable use of the transition-metal catalyst. To the best of our knowledge, there is only a single example of the reuse of palladium catalyst immobilized in the IL in an allylic amination reaction, although the catalyst activity decreased significantly after three repetitions of the reaction.[6h] The reason for the difficulty in reuse of the palladium catalyst for allylic alkylation was assumed to be that the reaction demanded a strong base, while many ILs have acidic protons in the molecules. Herein, we now report the first success of recyclable use of palladium catalyst in the allylic alkylation using an IL as solvent while maintaining excellent regio- and diastereoselectivities.



Scheme 1.

Based on our previous results with the palladium-catalyzed regio- and diastereoselective allylic alkylation of 1-methyl-3-phenyl-2-propenyl acetate (**1**) with ethyl 2-methylacetoacetate (**2**) using 2-(diphenylphosphino)benzoic acid in dioxane solvent,[2a,2b] we examined the reaction with several types of ILs as a solvent (Scheme 1). Although [bmim] salts were the most popular ILs, it was anticipated that [bmim] salt might be unsuitable for the reaction because the 2-proton of the imidazolium cation was too acidic to tolerate the strong NaHMDS base. The screening revealed that the [bmim] salt ILs indeed inhibited the reaction (Table 1, Entries 1–3), and we confirmed that the reaction in the [bdmin] salt type IL gave an alkylated product (Entries 4 and 5). However, we recognized that both the chemical yield and the regioselectivity depend on the anionic part of the ILs; bis(trifluoromethanesulfonyl)amide (NTf_2) salt gave a better result than did tetrafluoroborate (BF_4) salt. To our delight, further investigation revealed that changing the IL from imidazolium salts to an ammonium salt increased the yield and/or diastereoselectivity, although the diastereoselectivity was lower than that in the dioxane solvent (Entries 6 and 7). Especially, when $[N_{221ME}][NTf_2]$ was used as a solvent, the reaction afforded the alkylated product in 80% yield with 83% diastereoselectivity.[7] On the basis of this result, we next examined the reuse of the palladium catalyst in $[N_{221ME}][NTf_2]$ as solvent (Table 2). We thus established that the catalyst was successfully recycled 9 times while maintaining excellent reactivity and regioselectivity. Unfortunately, the reaction rate suddenly dropped significantly at the 10th run, probably due to

Table 1. Palladium-catalyzed regio- and diastereoselective allylic alkylation of **1** with **2** in ionic liquids

Entry	**IL**	Yield/%[a]	**3**:**4**[b]
1	[bmim][BF$_4$]	0	
2	[bmim][OTf]	0	
3	[bmim][NTf$_2$]	0	
4	[bdmin][BF$_4$]	39	80:20
5	[bdmin][NTf$_2$]	68	79:21
6	[P$_{4441}$][NTf$_2$]	30	63:27
7	[N$_{221\mathrm{ME}}$][BF$_4$]	52	88:12
8	[N$_{221\mathrm{ME}}$][NTf$_2$]	80	83:17

[a]Isolated yield. [b]Ratio was determined by ^{1}H NMR of the crude materials.

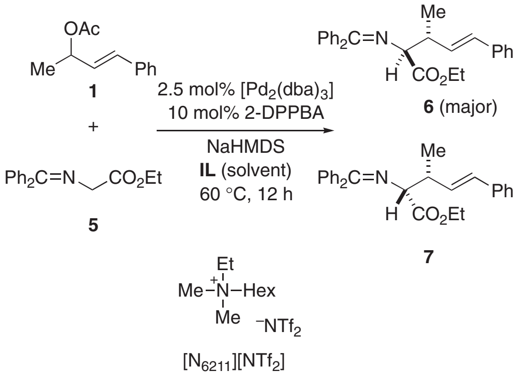
Table 2. Reuse of palladium catalyst in [N$_{221\mathrm{ME}}$][NTf$_2$] for the allylic alkylation of **1** with **2**

Cycle	Yield/%[a]	**3**:**4**[b]
1	96	82:18
2	85	81:19
3	99	80:20
4	99	81:19
5	93	80:20
6	87	80:20
7	99	81:19
8	80	84:16
9	91	82:18
10	21	86:14

[a]Isolated yield. [b]Ratio was determined by ^{1}H NMR of the crude materials.

the increased viscosity of the ionic liquid solution through the accumulation of by-products, and the product was obtained in poor yield.[8,9] However, it should be emphasized that the present system realized 9 repetitions of the reaction without any addition of the catalyst with excellent yield and good regioselectivity: [N$_{221\mathrm{ME}}$][NTf$_2$] is indeed an effective solvent and allows reuse of the palladium catalyst for the regio- and diastereoselective allylic alkylation of **1** with **2**.

We next demonstrated the regio- and diastereoselective allylic alkylation of **1** with the ethyl *N*-(diphenylmethylidene)-glycinate (**5**)[2c] in ILs (Scheme 2). As shown in Table 3, [N$_{221\mathrm{ME}}$][NTf$_2$] was this time not a suitable solvent for the reaction of **1** with **5** (Entry 3). We found however, that switching the solvent to ethylhexyldimethylammonium bis(trifluoromethanesulfonyl)amide ([N$_{6211}$][NTf$_2$]) afforded the desired product **6** in an acceptable yield (69%) with excellent regio- and diastereoselectivity (91%) (Entry 4). Based on this result, we again demonstrated the reuse of the palladium catalyst, which was immobilized in [N$_{6211}$][NTf$_2$][8] (Table 4). As expected, the desired reaction successfully proceeded without any addition of the catalyst, and the desired product **6** was obtained in acceptable yield while excellent diastereoselectivity was maintained even with repetition. However, the yield was again decreased after the 7th run, and no reaction was observed at the 10th run.



Scheme 2.

Table 3. Palladium-catalyzed regio- and diastereoselective allylic alkylation of **1** with **5** in ionic liquids

Entry	**IL**	Yield/%[a]	**6**:**7**[b]
1	[bdmin][NTf$_2$]	54	88:12
2	[P$_{4441}$][NTf$_2$]	0	—
3	[N$_{221\mathrm{ME}}$][NTf$_2$]	33	64:36
4	[N$_{6211}$][NTf$_2$]	69	91:9

[a]Isolated yield. [b]Ratio was determined by ^{1}H NMR of the crude materials.

Table 4. Reuse of palladium catalyst in [N$_{6211}$][NTf$_2$] for the allylic alkylation of **1** with **5**

Cycle	Yield/%[a]	**6**:**7**[b]
1	69	91:9
2	81	89:11
3	67	91:9
4	61	90:10
5	56	90:10
6	83	89:11
7	36	91:9
8	60	90:10
9	39	92:8
10	0	—

[a]Isolated yield. [b]Ratio was determined by ^{1}H NMR of the crude materials.

In summary, we demonstrated the first example of recyclable use of palladium catalyst in the regio- and diastereoselective allylic alkylation of **1** with ethyl 2-methylacetoacetate or the ethyl *N*-(diphenylmethylidene)glycinate using an ionic liquid as solvent. The reaction with the ammonium salt ILs effectively produced the desired alkylated product with perfect regioselectivity and high diastereoselectivity. Further investigation of the scope and limitation of this reaction will make it even more valuable.

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7 Representative procedure for the allylic alkylation of **1** with **2** in ionic liquid, and reuse of the palladium catalyst immobilized in IL. To a solution of $Pd(OAc)_2$ (5.8 mg, 0.026 mmol), 2-(diphenylphosphino)benzoic acid (**L1**) (15.9 mg, 0.052 mmol) in $[N_{221ME}][NTf_2]$ (1.0 mL) was added (*R*)-1-methyl-3-phenyl-2-propenyl acetate (**1**) (50 mg, 0.26 mmol), ethyl 2-methylacetoacetate (**2**) (56 mg, 0.39 mmol). The solution was cooled to 0 °C, then NaHMDS (0.36 mL, 1.0 M in THF) was added slowly. The resultant mixture was stirred at 60 °C for 12 h. After completion of the reaction (TLC), diethyl ether (1 mL × 10) was added for extraction. The combined ether layers were washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The regio and diastereo ratios of the product were determined by 400 MHz ^{1}H NMR of the crude material. The residue was chromatographed on silica gel (EtOAc/hexane = 1/9) to give 58 mg (80%) of **3** and **4**. The separated ionic liquid layer, which contains the palladium catalyst, was directly reused in the next reaction.

8 $[N_{221ME}][NTf_2]$ and $[N_{6211}][NTf_2]$ showed hydrophobicity, and washing by water was effective to remove by-products in the recycle experiments. However, such a process decreased the yield of alkylated products.

9 Diluted reaction conditions or addition of ILs are effective to prevent viscosity from increasing, but the reaction rate dropped and needed over 36 h to complete conversion of allylic acetate.