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Palladium-catalyzed allylation of malonic acid derivatives in heterogeneous systems containing ionic liquids

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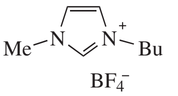
Palladium-catalyzed potassium carbonate-assisted reaction between diethyl malonate and allyl acetate in the presence of 1,3-dialkyl-imidazolium ionic liquids (ILs) as solvents or phase transfer catalysts affords major monoallylation product, whereas in the presence of 1,2,3-trialkylimidazolium or quaternary ammonium/phosphonium ILs diallylation product is preferably formed. These procedures are extended to some other CH-acids and allylic acetates.

Ionic liquids (ILs), the low-melting (< 100 °C) salts comprising organic cations, have been recognized in the last decade as perspective green media for chemical reactions due to their recoverability, negligible volatility and special solvation effects.[1] Certain usually ineffective in conventional organic solvents reactions have been successfully accomplished in IL media.[2,3] Among variety of reactions performed in ILs, transition metal-catalyzed processes attract considerable attention. In distinction to the Suzuki–Miyaura, Heck and Sonogashira C–C cross-coupling,[4] the Tsuji–Trost reaction[5] (TTR, a palladium-catalyzed reaction between nucleophiles and allylic alcohol derivatives), is far less explored in IL media. In cases of 1-butyl-3-methylimidazolium tetrafluoroborates or hexafluorophosphates ([bmim][BF_4], [bmim][PF_6]), the palladium source and phosphine ligand were preliminarily heated in these ILs to supposedly furnish N-heterocyclic carbene (NHC) which acted as the additional ligand,[6] the further cross-coupling having been performed at room temperature. The stoichiometric amounts of 1,3-disubstituted imidazolium derivatives were used to purposefully prepare Pd–NHC complexes, followed by coupling in a usual manner.[7] Microwave irradiation in a water–1-ethyl-3-methylimidazolium tetrafluoroborate ([emim][BF_4]) mixture on using water-soluble trisodium salt of tris(3-sulfophenyl)phosphine as the ligand effected the complete coupling within several minutes for a large scope of reactants.[8] These data limited mostly to coupling between highly active 1,3-diphenylprop-2-enyl or cinnamyl acetates and typical CH acids do not clarify which type of ligands, NHC or phosphine, can be preferable in the TTR.

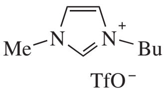
Note that our recent studies on TTR under phase transfer conditions[9] allowed us to replace traditional expensive and/or flammable BSA–AcOH and NaH by cheap and convenient in handling potassium carbonate and phosphate. However, the application of such a procedure was limited by a substrate type. Taking these results into account, we pioneered in performing the TTR in supercritical carbon dioxide.[10]

The purpose of the present study was to thoroughly examine effect of the IL nature on the outcome of the TTR. Ionic liquids **IL1–11** differing in both cation and anion structure were tested, with their subdivision into 1,3-dialkylimidazolium **IL1–4**, 1,2,3-trialkylimidazolium **IL5**,**6**, pyrrolidinium **IL7–10** and tetraalkylphosphonium **IL11** chemotypes. Reactions were performed in IL media as well as in ordinary solvents with the use of ILs as phase transfer catalysts (PTC). The model coupling between diethyl malonate **1** and allyl acetate **2a** leading generally to mono- (**3a**) and diallylation (**4a**) products (Scheme 1) was carried out on using potassium carbonate. We anticipated that similarly to other types of reactions ILs would promote better deprotonation of the CH acids and stabilization of their carbanions[1,4] and influence the Pd-mediated catalytic cycle.



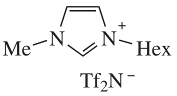
[bmim][BF_4]

IL1



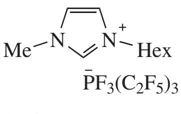
[bmim][OTf]

IL2



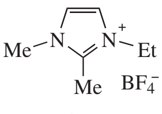
[bmim][NTf_2]

IL3



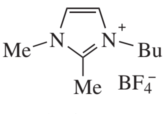
[hmim][$PF_3(C_2F_5)_3$]

IL4



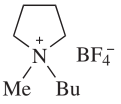
[memim][BF_4]

IL5

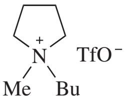


[mbmim][BF_4]

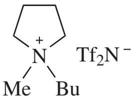
IL6



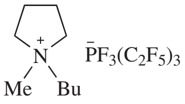
IL7



IL8



IL9

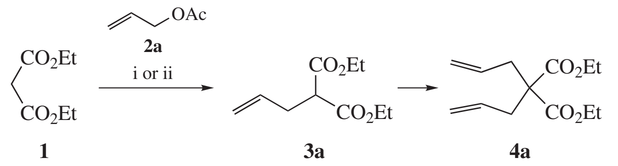


IL10

$Hex_3\overset{+}{P}C_{14}H_{29}\ \overset{-}{P}F_3(C_2F_5)_3$

IL11

The coupling **1** + **2a** in the essence of 1,3-dialkylimidazolium salts **IL1–4** (see Scheme 1, conditions i)[†] never brought about full diallylation (Table 1, entries 1–4) and usually monoallyl derivative **3a** was obtained. In cases of quaternary ammonium **IL8–10** and phosphonium **IL11** salts diallylated compound **4a** was the sole product (entries 5–8). Apparently, imidazolium salts **IL1–4** on the action of the base form the corresponding NHCs



Scheme 1 *Reagents and conditions*: i, AllOAc (2.4 equiv.), Pd(dba)$_2$ (2 mol%), PPh_3 (8 mol%), K_2CO_3 (2.5 equiv.), IL, 20 °C, 18–24 h; ii, AllOAc (2.4 equiv.), Pd(dba)$_2$ (2 mol%), PR_3 (8 mol%), K_2CO_3 (2.5 equiv.), IL (~13 mol%), CH_2Cl_2, 20 °C, 18–24 h.

Table 1 Coupling between diethyl malonate **1** and allyl acetate **2a** in IL media.[a]

Entry	Ionic liquid	Product composition (GC) (%)		
		3a	**4a**	unreacted **1**
1	**IL1**	49	51	0
2	**IL2**	85	0	15
3	**IL3**	69	31	0
4	**IL4**	78	22	0
5	**IL8**	0	100	0
6	**IL9**	0	100	0
7	**IL10**	0	100	0
8	**IL11**	0	100	0

[a] *Conditions*: AllOAc (2.4 equiv.), Pd(dba)$_2$ (2 mol%), PPh$_3$ (8 mol%), K$_2$CO$_3$ (2.5 equiv.), IL (2 g mmol^{-1}), 20 °C, 18–24 h.

which would coordinate on palladium thus giving less active catalytic system. Nature of the IL anion was in whole less crucial.

Then, we studied reactions of diethyl malonate **1** with allyl acetate **2a** in dichloromethane using ILs as PTCs since they contained bulky lipophilic cations (Scheme 1, conditions ii, Table 2).[‡] On using 1,3-dialkylimidazolium salts **IL1–4** and PPh$_3$ as the ligand (entries 1, 2, 4, 6), monoallylated product **3a** at incomplete conversion of the starting compound **1** was mostly formed, analogously to the phenomenon observed when such ILs were used as reaction media (see Table 1, entries 1–4). When PBu$_3$ was used instead of PPh$_3$ the yield was significantly dropped (Table 2, entries 3, 5, 7); most probably, this stronger ligand in combination with the corresponding NHCs afforded the Pd complexes less suitable for TTR. On moving to 1,2,3-trisubstituted imidazolium salts **IL5**,**6** (entries 8, 9, 11, 12), which cannot form carbenes under the action of bases, the yield of diallylated product **4a** was 100% regardless PPh$_3$ or PBu$_3$ having been applied. However, in the case of tricyclohexylphosphine (entry 10), the yield of monoallylation product **3a** was negligible, apparently, due to bulkiness of this electron-rich phosphine which completely covers the palladium atom thus retarding formation of π-allylic complexes. The close results were obtained with pyrrolidinium **IL7–10** (entries 13–17), phosphonium **IL11** (entries 18, 19) and tetrabutylammonium (entry 20) salts. Control experiment without

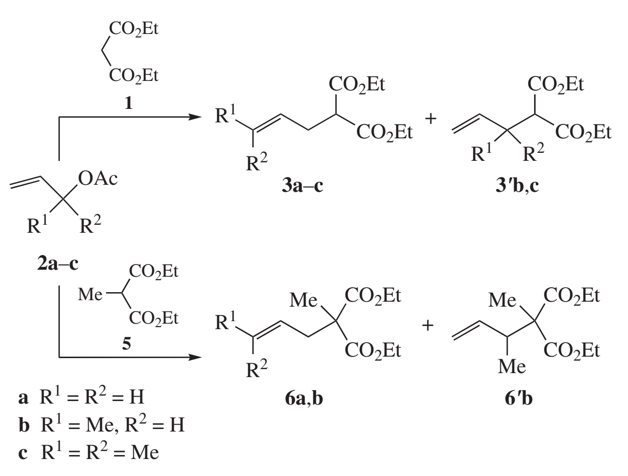
Table 2 Coupling between diethyl malonate **1** and allyl acetate **2a** in CH$_2$Cl$_2$ under phase transfer conditions.[a]

Entry	PTC	Ligand	Product composition (GC), %		
			3a	**4a**	unreacted **1**
1	**IL1**	PPh$_3$	87	13	—
2	**IL2**	PPh$_3$	47	0	53
3	**IL2**	PBu$_3$	2	0	98
4	**IL3**	PPh$_3$	89	0	11
5	**IL3**	PBu$_3$	48	0	52
6	**IL4**	PPh$_3$	75	0	25
7	**IL4**	PBu$_3$	15	0	85
8	**IL5**	PPh$_3$	0	100	0
9	**IL5**	PBu$_3$	0	100	0
10	**IL5**	PCy$_3$	4	0	96
11	**IL6**	PPh$_3$	0	100	0
12	**IL6**	PBu$_3$	0	100	0
13	**IL7**	PPh$_3$	0	100	0
14	**IL7**	PBu$_3$	0	100	0
15	**IL8**	PPh$_3$	1	99	0
16	**IL9**	PPh$_3$	2	98	0
17	**IL10**	PPh$_3$	0	100	0
18	**IL11**	PPh$_3$	0	100	0
19	**IL11**	PBu$_3$	0	100	0
20	Bu$_4$NBr[9(b),10(c)]	PPh$_3$	0	100	0
21	—	PPh$_3$	75	25	0
22	**IL1**	—	3	0	97
23	**IL5**	—	2	0	98

[a] *Conditions*: AllOAc (2.4 equiv.), Pd(dba)$_2$ (2 mol%), PR$_3$ (~8 mol%), K$_2$CO$_3$ (2.5 equiv.), IL (~13 mol%), CH$_2$Cl$_2$ (3 ml mmol^{-1}), 20 °C, 18–24 h.

PTC (entry 21) showed that the reaction proceeded at incomplete conversion into **4a**, the total conversion having been deeper than that in the cases of **IL1–4** (entries 1–7) thus confirming the inhibition effect of 1,3-dialkylimidazolium salts. Experiments performed in the absence of phosphine (entries 22, 23) gave almost nothing of the products and were accompanied by rapid precipitation of Pd black from Pd(dba)$_2$. Although this was not unexpected, we anticipated somehow that **IL1**-derived NHC (entry 22) should have stabilized palladium in the solution.

The PTC conditions were found applicable to some other CH-acids and allylic acetates (Scheme 2, Table 3). Experiments with but-3-en-2-yl acetate **2b** were carried out with equimolar ratio of reactants (entries 1–4), otherwise easy formation of diallylation products, namely diethyl di(but-2-en-1-yl)malonate and diethyl (but-2-en-1-yl)(but-1-en-3-yl)malonate,[7(b)] would



Scheme 2 *Reagents and conditions*: Pd(dba)$_2$, phosphine, K$_2$CO$_3$, CH$_2$Cl$_2$, IL (cat.), 20 °C.

[†] *Reaction between diethyl malonate* **1** *and allyl acetate* **2a** *in ILs.* A Schlenk tube was charged with diethyl malonate (40 mg, 0.25 mmol) and corresponding IL (0.5 g), and the mixture was three times deaerated by evacuation and filling with argon. PPh$_3$ (5.5 mg, 20 μmol) and Pd(dba)$_2$ (3 mg, 5 μmol) were added, and the mixture was stirred at ambient temperature for *ca*. 30 min which resulted in colour change due to the formation of palladium phosphine complex. Allyl acetate (0.075 ml, ~0.6 mmol) was added, followed in 10 min by freshly powdered K$_2$CO$_3$ (104 mg, 0.75 mmol). Each opening of the Schenk tube was followed by evacuation and filling with argon. The mixture was stirred at ambient temperature for 18–24 h. A probe was triturated with hexane, and the hexane extract was analyzed by GC, comparing peak retention times with those of the authentic samples.

[‡] *Reactions of CH-acids and allylic acetates under PTC conditions.* A Schlenk tube was charged with the corresponding CH-acid (0.5 mmol), IL (20 mg), and dichloromethane (1.5 ml). The mixture was three times deaerated by careful evacuation (300 Torr, dichloromethane started boiling) and filling with argon. Phosphine (0.04 mmol) and Pd(dba)$_2$ (6 mg, 0.01 mmol) were added, and the mixture was stirred until the colour grew pale. Allylic acetate (0.5–1.5 mmol) was added, and the mixture was stirred for 10 min, followed by freshly powdered K$_2$CO$_3$ (138–207 mg, 1–1.5 mmol). Each opening of the Schenk tube was followed by evacuation and filling with argon. The mixture was stirred at ambient temperature for 18–24 h. A probe was treated with water and extracted with hexane and analyzed by GC, comparing peak retention times with those of the authentic samples obtained and characterized previously.[9(a),(b),10(c)]

Table 3 Coupling between CH acids and allylic acetates in CH_2Cl_2 using ILs as PTCs.[a]

Entry	CH acid	Allylic acetate	PTC	Ligand	Product composition (GC) (%)	
					products	unreacted **1**, **5**
1	**1**	**2b**[b]	**IL5**	PPh_3	47 (**3b**) + 43 (**3′b**)	16
2	**1**	**2b**[b]	**IL7**	PPh_3	35 (**3b**) + 46 (**3′b**)	19
3	**1**	**2b**[b]	**IL7**	PBu_3	24 (**3b**) + 59 (**3′b**)	17
4	**1**	**2b**[b]	**IL11**	PPh_3	42 (**3b**) + 42 (**3′b**)	10
5	**1**	**2c**	**IL7**	PPh_3	4 (**3c**) + 96 (**3′c**)	—
6	**1**	**2c**	**IL7**	PBu_3	14 (**3c**) + 67 (**3′c**)	19
7	**5**	**2a**	**IL5**	PPh_3	100 (**6a**)	—
8	**5**	**2b**	**IL5**	PPh_3	54 (**6b**) + 5 (**6′b**)	41

[a] *Conditions*: allylic acetate (2.4 equiv.), $Pd(dba)_2$ (2 mol%), PR_3 (~8 mol%), K_2CO_3 (2.5 equiv.), IL (~13 mol%), CH_2Cl_2 (3 ml mmol^{-1}), 20 °C, 18–24 h. [b] 1 equiv. **2b**.

bring complications to analysis of the reaction mixture. In general, reaction between **1** and **2b** gave mixture of regioisomers **3b** and **3′b** in close amounts. In case of 2-methylbut-3-en-2-yl acetate **2c** the ‘branched’ product **3′c** was mostly formed (entries 5, 6, *cf.* ref. 6), the fraction of the ‘normal’ product **3c** being somewhat higher on application of tributylphosphine as the ligand (entry 6). Disubstitution products never formed even with the use of excess **2c**, moreover, the conversion of malonate **1** was often incomplete.

Less acidic diethyl methylmalonate **5** reacted smoothly with allyl acetate **2a** to give product **6a** (Scheme 2, Table 3, entry 7). In the case of but-3-en-2-yl acetate **2b** the conversion of **5** was incomplete (entry 8), while 2-methylbut-3-en-2-yl acetate **2c** gave none of the expected product.

In summary, based on extended number of both ILs and substrates one may conclude that ILs can serve both as media and PTC for TTR. The better reaction outcome is provided by chemically inert ILs, while base-sensitive 1,3-dialkylimidazolium ones form NHCs which reduce the catalyst activity. Most probably, phosphine ligands should be preferable for the TTR, although testing other 1,3-disubstituted imidazolium salts as additives, especially with bulky substituents, and other reaction conditions seems not undesirable (the NHC complexes were reported[7] to provide good yields under some other conditions and with other substrates).

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