Ligand Effects in Palladium-Catalyzed Allylic Alkylation in Ionic Liquids

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Received August 15, 2000

Palladium-catalyzed allylic alkylation with a variety of active methylene compounds has been carried out in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]). Phosphine ligands are found to exert a profound effect on the active palladium species, with the more electron-donating ones such as PCy_3 affording faster rates and the strong electron acceptors such as $P(OPh)_3$ affording extremely low conversions. In the most commonly used molecular solvent, THF, the reaction is slower and the choice of ligands is more limited. These observations may be accounted for by the allylpalladium intermediate existing in different forms in the two solvents.

Introduction

Room-temperature ionic liquids, consisting of 1,3-dialkylimidazolium cations and their counterions, have attracted growing interest in the past few years.[1,2] Desirable properties, such as thermal stability, lack of vapor pressure, and wide liquid range, have promoted these ionic liquids as potential replacements for organic solvents both on laboratory and industrial scales. Ionic liquids also offer the potential for easy catalyst/product separation, owing to their limited and/or thermally adjustable miscibility with organic solvents and water and their extremely low vapor pressure. To date, a number of catalytic reactions have been carried out in these and related ionic liquids; recent examples include Friedel Crafts reactions,[3] Diels−Alder reactions,[4] alkylations,[5] olefin dimerization and oligomerization,[6] hydrogenation,[7] hydroformylation,[8] Heck reaction,[9] and allylic allylation and amination.[10] These studies establish the feasibility of ionic liquids as a viable alternative to organic solvents for homogeneous catalysis and chemical synthesis, although they have seldom revealed how the ionic nature of the imidazolium ionic liquids might affect the catalytic behavior of a metal complex for a given type of reaction.

Palladium(0)-catalyzed allylic alkylation of soft carbon nucleophiles represents a very useful tool for organic synthesis.[11] In addition to common organic solvents, the reaction has been examined in aqueous and fluorous phases in order to facilitate catalyst separation.[12] We recently reported that the allylation of the active methylene compounds **2a**−**f** by 1,3-diphenylallyl acetate proceeds smoothly in the [bmim][BF_4] ionic liquid in the presence of $Pd(OAc)_2/PPh_3$, and when the hydrophilic phosphine $P(3\text{-}C_6H_4SO_3Na)_3$ instead of PPh_3 is used as ligand, easy catalyst/product separation can be attained (Scheme 1).[10] Somewhat surprisingly, a considerably longer reaction time was required for a complete conversion of the acetate with the nucleophiles **2b**−**f**. In particular, the reaction with the amido malonate **2f** required heating at 50 °C for 12 h to complete. In the wake of these results, we wondered whether these allylation reactions were sensitive to changes in the stereoelectronic properties of ligands, as is true of

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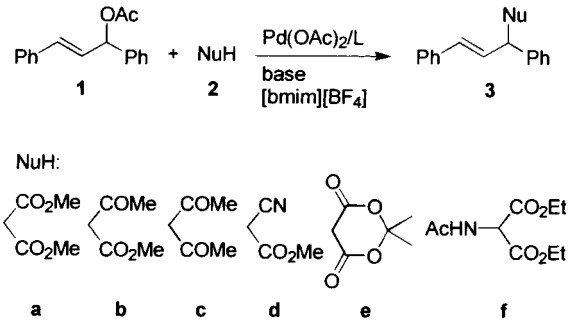
10.1021/om000712y CCC: $20.00
Publication on Web 12/02/2000

Scheme 1



reaction in common organic solvents,[13] and if so, could we optimize the performance of palladium catalysts via an informed choice of ligands? We report herein that ligands do play a significant role in affecting the allylation reaction in [bmim][BF_4], and the reaction performs markedly better in terms of reaction rates and can be effected by a wider range of phosphines in the ionic liquid than in the molecular solvent THF.

Results and Discussion

From our initial study of allylation catalyzed by palladium in the presence of PPh_3 in [bmim][BF_4], dimethyl malonate **2a** proved to be the most effective nucleophile, from the six we tried.[10] To study the effect of changing steric and electronic properties of phosphines on the allylation, we carried out a series of reactions, holding **2a** constant throughout, but with a variety of phosphine ligands with diverse stereoelectronic properties. For comparison, the same screening was also undertaken in THF. Through experimentation with PPh_3 as ligand, we first established the premium palladium/ligand combinations and then applied these conditions to the allylation reactions of **2a** using other phosphine ligands.

The allylation of **2a** by the racemic 3-acetoxy-1,3-diphenylprop-1-ene **1** was investigated first. **1** was considered as an appropriate allylic precursor for studying ligand effects on Pd-catalyzed allylation in ionic liquids, as the added complication of regioselectivity would be nil. Initial experimentation was undertaken to optimize reaction protocol and establish premium catalyst performance. The catalyst or catalyst precursor was formed by heating $Pd(OAc)_2$ (2 mol %, based on the acetate) with PPh_3 (8 mol %) in [bmim][BF_4] at 80 °C for 20 min. The ionic liquid was then cooled to ambient temperature, and the reaction initiated by addition of substrates and base (DBU or K_2CO_3). ^1H NMR monitoring shows that the reaction is complete in 5 h reaction time when using $Pd(OAc)_2/PPh_3$ as catalyst precursor and K_2CO_3 as base. If a Pd(0) precursor, $Pd_2(dba)_3$ (dba = dibenzylideneacetone), is used instead, the initial rate is faster, indicating that the slower initial rate with $Pd(OAc)_2$ is due to the reduction of Pd(II) to Pd(0). It is generally assumed that the first step of the catalytic cycle involves oxidative addition of **1** to a Pd(0) complex.[11] The salient features of the reaction have been summarized before and are briefly mentioned below.[10] First, as with allylic alkylations in molecular solvents,[11] no reaction takes place in the ionic liquid without PPh_3. Second, the reaction rate decreases markedly when the molar ratio of $PPh_3/Pd(OAc)_2$ is less than 4:1. Thus, with 3 equiv of PPh_3, the conversion of the acetate was only 50% after 15 h reaction time, and with 1 equiv of PPh_3, a much lower conversion of 13% was observed. Third, the reaction was slower without initial heating of $Pd(OAc)_2$ and PPh_3 in [bmim][BF_4]. Thus, heating of $Pd(OAc)_2$ and PPh_3 with the substrates in the absence of [bmim][BF_4] followed by reaction in the ionic liquid at ambient temperature for 15 h afforded only a 68% conversion.

Table 1. Palladium-Catalyzed Allylic Alkylation in [bmim][BF_4] with 2a−f[a]

NuH	time (h)	conv (%)[b]	yield (%)[c]
2a	6	100	91
2b	5	27	
2b	15	100	87[d]
2c	5	0	
2c	15	100	54[e]
2d	5	0	
2d	14	100	88[d]
2e	5	34	
2e	15	100	79
2f[f]	5	30	
2f[f]	12	100	86

[a] General reaction conditions: 1.0 mmol of 3-acetoxy-1,3-diphenylprop-1-ene, 2 mol % $Pd(OAc)_2$, 8 mol % PPh_3, 1.5 mmol of dimethyl malonate, and 2.0 mmol of DBU in 1 mL of [bmim][BF_4] at ambient temperature. Before starting the reaction, $Pd(OAc)_2$ and PPh_3 were heated at 80 °C for 20 min in the ionic liquid. [b]Of the acetate. [c]Isolated yield. [d]The product was a 1:1 mixture of two diastereoisomers. [e]Low yield due to some double alkylation. [f]Reaction was carried out at 50 °C.

Using the procedures developed for **2a**, the allylation, with DBU as base, was extended to the active methylene compounds **2b**−**f**. The results are summarized in Table 1. In contrast with the allylation of **2a**, the complete allylation of **2b**−**f** requires a much longer reaction time under identical conditions, none of the nucleophiles affording conversion higher than 40% in the first 5 h. In fact, the allylation of the amido malonate **2f** was too sluggish at ambient conditions; hence heating at 50 °C for 12 h was required to complete the reaction. The lower rates with **2b**−**f** may be due to probably lower nucleophilicity of their conjugate bases; their pK_a values are lower than that of **2a**.[14] Because the only variable in these reactions is the nucleophile, the results obtained are an indication that the overall allylation in the ionic liquid is controlled by the nucleophilic attack at the intermediate allylpalladium species, which results from the oxidative addition mentioned above. Consistent with this, our preliminary UV monitoring of the reaction of **1** with **2a** in [bmim][BF_4] showed that a rapid equilibrium was established upon mixing **1** with the active palladium species pregenerated in the ionic liquid, and the equilibrium was followed by slower nucleophilic attack by **2a** in the presence of DBU. Replacing DBU with K_2CO_3 resulted in even lower conversions for these substrates. This can be partly accounted for by the lower solubility of the latter in

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Table 2. Palladium-Catalyzed Allylation of 2a in [bmim][BF_4] and THF in the Presence of Various Phosphine Ligands[a]

			[bmim][BF_4]		THF	
ligand	$^{FT}\chi$[b]	θ[b]	time (h)	conv (%)	time (h)	conv (%)
P^tBu_3	0	182	22	75	22	0
PCy_3	1.40	170	1	100	20	0
P^nBu_3	5.25	136	1	100	1	100
$P(4\text{-}C_6H_4OMe)_3$	10.50	145	1	100	1	80
PPh_3	13.25	145	6	100	6	33
$P(4\text{-}C_6H_4CF_3)_3$	20.5	145	20	0	20	0
$P(OPh)_3$	30.20	128	18	0	18	0

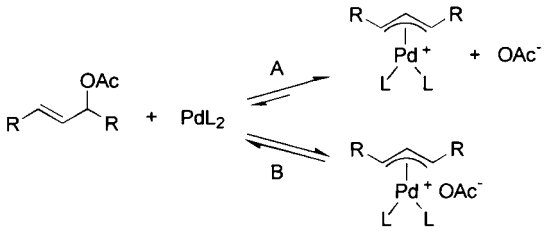
[a] The reaction conditions were the same as the general reaction conditions given in Table 1, unless otherwise indicated. [b]Reference 15.

[bmim][BF_4]. DBU forms a homogeneous solution with the reaction mixture, whereas K_2CO_3 is only partially soluble in the ionic liquid under the reaction conditions employed. For the reactions involving methyl acetoacetate **2b** and methyl cyanoacetate **2d**, the product was a 1:1 mixture of two diastereoisomers.

Prompted by the somehow puzzling results, we repeated the allylation reaction of **2a** using a series of phosphine ligands, ranging from strong σ donors such as PCy_3 to strong π acceptors such as $P(OPh)_3$, maintaining the optimal reaction protocol established with PPh_3. Table 2 summarizes the results obtained. Also included in Table 2 are the electronic parameter $^{FT}\chi$ and cone angle θ values of the phosphines,[15] the former reflecting the σ donor/π acceptor properties of the phosphines; the smaller the value, the more electron-donating the phosphines. Evidently, ligands impose a marked effect on the activity of palladium, with the more electron-donating phosphines enhancing the reaction rates compared with PPh_3, and the more electron-accepting phosphines providing little or no reaction. Thus, the quantitative allylation of **2a**, which was previously achieved in 6 h with PPh_3, was now complete within 1 h using the more electron-donating $P(4\text{-}C_6H_4OMe)_3$, P^nBu_3, or PCy_3. However, the reaction is less effective with P^tBu_3, with a conversion of 75% in 22 h reaction time. P^tBu_3 is the most basic or electron-rich as well as the most bulky ligand tested, as indicated by its $^{FT}\chi$ and cone angle θ. And so both electronic and steric effects could contribute to the slowing of the allylation. For the two good π acceptors, $P(4\text{-}C_6H_4CF_3)_3$ and $P(OPh)_3$, no conversion of the acetate was observed in ca. 20 h. Comparison of the three phosphines with the same cone angle, $P(4\text{-}C_6H_4OMe)_3$, PPh_3, and $P(4\text{-}C_6H_4CF_3)_3$, is more revealing, showing clearly that increasing π acceptor capability of the phosphine leads to decreasing reaction rates.

To aid comparison of [bmim][BF_4] and organic solvents as media for allylic alkylation, parallel reactions were run in THF (Table 2). It is apparent again that better donor ligands afford faster reactions in comparison with PPh_3. However, the reactions are in general slower in THF than in the ionic liquid, and the choice of ligands is limited in the former. Thus, there is only one ligand, P^nBu_3, that afforded a comparative conversion in both solvents, and with PPh_3 and PCy_3, both of which produce active catalysts in [bmim][BF_4], a much lower conversion or no conversion at all was observed in THF. PCy_3 and the strong π acceptor phosphines have previously been shown to be less effective in similar allylation reactions in THF.[13c]

Scheme 2



A: in [bmim][BF_4]; B: in THF; L: phosphine

One explanation for the sharp contrast between the ionic liquid and the molecular solvent could be their differing effects on the intermediate allylpalladium complex arising from the oxidative addition of acetate **1** to the active catalyst, $Pd(0)L_2$ (L = phosphine) (Scheme 2). In [bmim][[BF_4], the allylpalladium intermediate may exist as free cations, but in THF, it probably forms ion pairs with the acetate anions. Recent studies indeed reveal that analogous cationic allylpalladium species (R = H) exist as tight ion pairs with the anionic acetate in THF but as free ions in the more polar DMF.[16a] The oxidative addition step is further shown to be reversible in the molecular solvents, with the acetate leaving group capable of competing with an added nucleophile for attack at the allyl moiety, thus reproducing the allylic acetate.[16] The consequence of the ion pairing in THF is that the charge density of the palladium is decreased and steric hindrance around the palladium increased; both factors are expected to hamper the nucleophilic attack at the coordinated allyl group. The ion pair-induced steric hindrance could also make more difficult the coordination of sterically bulky ligands such as PCy_3 to palladium or the attack by nucleophiles at the allylpalladium species containing such ligands, thus further reducing the reaction rates when these ligands are employed. In the polar ionic environment provided by [bmim][BF_4], ion pairing between the allylpalladium cation and acetate anion may not occur, since the solvent anions could easily exchange places with the acetate ions.[17] Surprisingly, however, the allylic alkylation of **2a** by **1** in DMF, where free ions may also be expected to form, is significantly slower than that in either [bmim][BF_4] or THF. The reason for this is not immediately clear, although it could be due to differing equilibrium constants for the oxidative addition reactions in DMF and THF.[16a] The formation of the ionic species could be favored in the ionic liquid, as the reverse reaction generates neutral species in an ionic environment. In addition, the reaction in THF could be affected by the coordination of acetate ions and solvent molecules to the palladium, while such coordination is less likely to occur in [bmim]-

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Table 3. Allylation Catalyzed by Palladium/ P(4-$C_6H_4OMe)_3$ in [bmim][BF_4][a]

NuH	time (h)	conv (%)	yield (%)[b]
2a	1	100	94
2c	10	100	52[c]
2d	0.5	100	90[d]
2f	5	100	95

[a] The reaction conditions were the same as the general reaction conditions given in Table 1, unless otherwise indicated. [b]Isolated yield. [c]Low yield due to some double alkylation. [d]The product was a 1:1 mixture of two diastereoisomers.

[BF_4].[18] The solvation energies of the reactants and the transition states of the nucleophilic attack could also be altered on going from the molecular THF to the ionic [bmim][BF_4].[19] All these factors could contribute to the higher rates observed in the latter.

Irrespective of why the electron-donating phosphines perform better in the ionic liquid than in THF in the allylation reaction, these ligands could provide a solution to the sluggish allylation of **2b**−**f** when using PPh_3 as ligand. Sufficiently faster reactions were indeed observed with P(4-$C_6H_4OMe)_3$ in [bmim][BF_4]. Table 3 summarizes the results for the nucleophiles **2a**, **c**, **d**, and **f**, the last three of which were the most difficult to allylate in the presence of PPh_3. The most dramatic ligand-induced rate enhancement was found for the allylation of **2d**. Here, quantitative conversion to product was achieved within 0.5 h as opposed to 14 h using PPh_3. Likewise, the allylation of **2f** now proceeded readily at ambient temperature and was complete within 5 h, whereas a temperature of 50 °C and 12 h had previously been necessary. These results show again how subtle change in ligand electronic properties can bring about dramatic acceleration or deceleration in the allylation rates in ionic liquids.

Conclusions

We have demonstrated that palladium-catalyzed allylation of various soft carbon nucleophiles can be effectively performed in the room-temperature ionic liquid [bmim][BF_4] by a careful choice of phosphine ligands. The rate of nucleophilic attack at the allylpalladium species in the ionic liquid medium is greatly enhanced by more electron-rich or σ-donating phosphines. With strong π-accepting phosphines, little or no reaction takes place. We further show that the allylation reaction is in general faster in the ionic liquid than in the molecular solvent THF. More significantly, the ionic liquid allows a wider range of phosphines to be effective for the allylation than does THF. The difference with the two solvents reflects differing steric and electronic properties of the allylpalladium intermediates in the two solvents. While both the steric and electronic effects of the phosphines appear to be important in THF, the electronic effects of the ligands dominate in the ionic liquid. This is so probably because of the formation of tight ion pairs in THF and reversible nucleophilic attack by the anionic acetate at the cationic allylpalladium species, both of which may be expected to diminish in the ionic environment provided by [bmim][BF_4].

It has been speculated for some time that the unique ionic environment imposed by an ionic liquid on a chemical reaction may change its course, and so one could expect to see a general "ionic liquid effect".[1] The results presented here point to the existence of some ionic liquid effect, that is, the effect of an ionic liquid on the steric and electronic properties of an ionic reaction intermediate. Together with previous studies, our results demonstrate that ionic liquids such as [bmim][BF_4] represent indeed a viable alternative to common organic solvents for reaction chemistry, and this will particularly be so when the use of volatile organic solvents needs to be reconsidered.

Experimental Section

All reactions were carried out in oven-dried glassware under argon, using standard Schlenk and vacuum line techniques. [bmim][BF_4] was prepared according to published procedures and vacuum-dried and stored under argon.[20] THF was freshly distilled from sodium benzophenone under nitrogen immediately prior to use. Racemic 3-acetoxy-1,3-diphenylprop-1-ene **1** was synthesized according to a literature method.[21] Compounds **2a**−**f**, $Pd(OAc)_2$, and all the phosphine ligands used were purchased from commercial suppliers and used as received without further purification. Reaction progress was monitored by TLC and ^{1}H NMR analysis; [bmim][BF_4] was removed by passing the reaction sample through a pad of silica gel. NMR spectra were recorded on a Gemini 300 spectrometer at 300.10 (^{1}H) and 75.46 MHz (^{13}C) in ppm with reference to TMS internal standard in $CDCl_3$. Abbreviations for NMR spectral multiplicities: s = singlet, d = doublet, m = multiplet, and dd = doublet of doublets. Elemental analyses were performed by the Microanalysis Laboratory, Department of Chemistry, University of Liverpool. Mass spectra were recorded on a VG7070E mass spectrometer.

General Procedure for the Allylic Alkylation of 1 with 2a−**f.** A dry Schlenk tube, equipped with a magnetic stir bar, was charged with $Pd(OAc)_2$ (4.5 mg, 2 mol %), phosphine ligand (8 mol %), and [bmim][BF_4] (1−2 mL). The reaction mixture was stirred at 80 °C for 20 min and then allowed to cool to room temperature. After repeated degassing under oil pump vacuum and flushing with argon, **1** (252.0 mg, 1.0 mmol), **2** (1.5 mmol), and base (DBU or K_2CO_3) (2.0 mmol) were added. Upon completion, the reaction was quenched by the addition of distilled water and the product extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and analyzed by NMR. Product purification was achieved either by recrystallization from diethyl ether/*n*-hexane or by flash column chromatography.

(*E*)-2-(1,3-Diphenylprop-2-enyl)propanedioic acid dimethyl ester 3a[22] was obtained in >90% yield as a colorless crystalline solid. ^{1}H NMR: 3.52 (s, 3H), 3.70 (s, 3H), 3.95 (d, J = 10.8 Hz, 1H), 4.27 (dd, J = 8.4, 1H), 6.35 (dd, J = 15.8 Hz, 1H), 6.49 (d, 1H), 7.3 (m, 10H). ^{13}C NMR: 49.2, 52.4, 52.6, 57.7, 126.5, 127.2, 127.6, 127.9, 128.5, 128.8, 129.3, 131.9, 136.96, 140.3, 167.9, 168.3. MS (EI): m/z 324 (M^+, 10.9). Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.04; H, 6.21. Found: C, 73.74; H, 6.27.

(*E*)-2-Acetyl-3,5-diphenylpent-4-enoic acid methyl ester 3b was obtained in 87% yield as a white powder as a 1:1 mixture of two diastereoisomers. ^{1}H NMR: 2.00 (s, 3H), 2.27 (s, 3H), 3.45 (s, 3H), 3.67 (s, 3H), 4.10 (d, J = 11.1 Hz, 1H), 4.12 (d, J = 11.1 Hz, 1H), 4.28 (dd, J = 8.2 Hz, 1H), 4.31 (dd, J = 8.2 Hz, 1H), 6.25 (dd, J = 15.8 Hz, 1H), 6.29 (dd, J = 15.8

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Hz, 1H), 6.43 (d, 1H), 6.46 (d, 1H), 7.24 (m, 20H). ^{13}C NMR: 29.9, 30.0, 48.8, 49.0, 52.3, 52.6, 65.2, 65.5, 126.5, 127.2, 127.3, 127.7, 127.8, 128.0, 128.1, 128.6, 128.8, 129.0, 129.3, 129.6, 131.7, 132.1, 136.8, 137.00, 140.2, 140.6, 168.2, 168.5, 201.4, 201.6. MS (EI): *m*/*z* 308 (M^+, 0.1). Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.94; H, 6.49. Found: C, 77.80; H, 6.55.

(*E*)-3-(1,3-Diphenylprop-2-enyl)pentane-2,4-dione 3c[23] was obtained in 53% yield as a white powder. The low yield was a result of double alkylation. ^{1}H NMR: 1.92 (s, 3H), 2.22 (s, 3H), 4.34 (d, J = 4.1 Hz, 2H), 6.20 (m, 1H), 6.43 (d, J = 15.8 Hz, 1H), 7.28 (m, 10H). ^{13}C NMR: 29.7, 29.9, 49.2, 74.6, 126.4, 127.3, 127.7, 128.0, 128.6, 129.1, 129.4, 131.8, 202.9. MS (EI): *m*/*z* 292 (M^+, 0.4). Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.20; H, 6.84. Found: C, 81.98; H, 6.91.

(*E*)-2-Cyano-3,5-diphenylpent-4-enoic acid methyl ester 3d[24] was obtained in 88% yield as a viscous white oil as a 1:1 mixture of two diastereoisomers. ^{1}H NMR: 3.71 (s, 3H), 3.72 (s, 3H), 3.91 (d, J = 6.0 Hz, 1H), 3.95 (d, J = 7.6 Hz, 1H), 4.21 (dd, J = 7.8 Hz, 1H), 4.25 (dd, J = 7.8 Hz, 1H), 6.44 (dd, J = 15.8 Hz, 1H), 6.52 (dd, J = 15.6 Hz, 1H), 6.59 (d, 1H), 6.61 (d, 1H), 7.33 (m, 20H). ^{13}C NMR: 44.4, 44.8, 49.1, 49.4, 53.5, 115.4, 125.8, 126.7, 126.8, 127.2, 127.8, 128.1, 128.3, 128.5, 128.8, 129.2, 133.4, 134.5, 136.4, 138.2, 138.9, 165.6. MS (EI): *m*/*z* 291 (M^+, 1.7). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.31; H, 5.83; N, 4.81. Found: C, 78.71; H, 5.89; N, 4.17.

(*E*)-Isopropylidene *trans*-2-phenylethenylphenylmethylmalonate 3e[25] was obtained in 79% yield as a white powder. ^{1}H NMR: 1.48 (s, 3H), 1.7 (s, 3H), 3.95 (d, J = 2.8 Hz, 1H), 4.73 (dd, J = 9.2 Hz, 1H), 6.65 (d, J = 15.8 Hz, 1H), 6.88 (dd, 1H), 7.30 (m, 10H). ^{13}C NMR: 27.7, 28.3, 47.6, 52.6, 105.4, 126.7, 127.5, 127.9, 128.1, 128.6, 128.8, 133.5, 139.9, 164.5. MS (EI): *m*/*z* 336 (M^+, 0.2). Anal. Calcd for $C_{21}H_{20}O_4$: C, 75.01; H, 5.95. Found: C, 75.00; H, 5.89.

(*E*)-2-Acetylamino-2-(1,3-diphenylallyl)malonic acid diethyl ester 3f was obtained in 86% yield as a white powder. ^{1}H NMR: 1.14 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.93 (s, 3H), 4.07 (m, 2H), 4.26 (m, 2H), 4.80 (d, J = 7.3 Hz, 1H), 6.28 (d, J = 15.9 Hz, 1H), 6.59 (s, 1H), 6.75 (dd, 1H), 7.30 (m, 10H). ^{13}C NMR: 13.8, 13.9, 23.1, 53.0, 62.4, 62.6, 69.0, 126.4, 127.2, 127.6, 128.4, 128.5, 128.8, 129.6, 132.4, 137.6, 138.5, 167.0, 167.6, 169.0. MS (EI): *m*/*z* 410 (M^+, 0.1). Anal. Calcd for $C_{24}H_{28}NO_5$: C, 70.26; H, 6.82; N, 3.41. Found: C, 70.74; H, 6.70; N, 3.28.

Acknowledgment. We are indebted to the EPSRC for a QUOTA Studentship (J.R.) and a postdoctoral research fellowship (W.C.). We are also grateful to the University of Liverpool Graduates Association (Hong Kong) for financial support (L.X.).

OM000712Y

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