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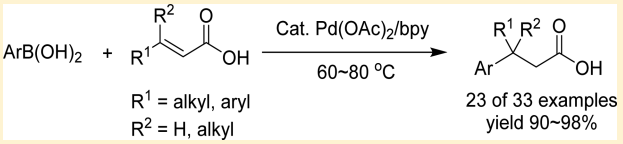
Pd(II)/Bipyridine-Catalyzed Conjugate Addition of Arylboronic Acids to α,β-Unsaturated Carboxylic Acids. Synthesis of β-Quaternary Carbons Substituted Carboxylic Acids

Rui Liu,[†] Zhenyu Yang,[†] Yuxin Ni, Kaixuan Song, Kai Shen, Shaohui Lin,* and Qinmin Pan*

State and Local Joint Engineering Laboratory for Novel Functional Polymeric Materials, Jiangsu Key Laboratory of Advanced Functional Polymer Design and Application, Key Laboratory of Organic Synthesis of Jiangsu Province, Green Polymer and Catalysis Technology Laboratory (GAPCT), College of Chemistry, Chemical Engineering and Materials Science, Soochow University, 199 Ren'ai Road, Suzhou 215123, P. R. China

Supporting Information

ABSTRACT: Pd(II)/bipyridine-catalyzed conjugate addition of arylboronic acids to α,β-unsaturated carboxylic acids (including β,β-disubstituted acrylic acids) was developed and optimized, which provided a mild and convenient method for the highly challenging synthesis of β-quaternary carbons substituted carboxylic acids.



INTRODUCTION

Transition-metal-catalyzed conjugate additions of organometallic reagents to α,β-unsaturated compounds are very powerful strategies to prepare β-substituted carbonyl molecules.[1,2] Feringa developed Cu(I)-catalyzed conjugate addition of alkylmetallic reagents to realize β-alkylation,[3] and Hayashi built an elegant Rh(I)-catalyzed conjugate addition system with organoboron compounds to different α,β-unsaturated electrophiles,[1a,2c,4] in which perfect asymmetric inductions were achieved. Compared with the well-documented Rh(I)-catalysis, Pd(II)-catalyzed conjugate addition was relatively rare,[5−8] and more economic. Uemura[6e] and Miyaura[6d] reported the Pd(II)-catalyzed conjugate addition of organoboron reagents to enones and enals, which started the Pd(II) version in conjugate addition research.

In the previous decade, we published a series of Pd(II)/2,2′-bipyridine(bpy)-catalyzed conjugate addition of arylboronic acids to α,β-unsaturated carbonyl compounds,[7,8d] and the electrophiles were expanded from enones and enals to inert α,β-unsaturated esters and amides. This Pd(II)/bpy catalysis was oxygen- and moisture-stable, and high addition yields were usually achieved under mild conditions. In 2010, we reported the first cationic Pd(II)/bpy-catalyzed conjugate addition of arylboronic acids to β,β-disubstituted enones,[8d] and quaternary carbon centers were successfully constructed with this highly efficient method. Stoltz finished the asymmetric version of this reaction with chiral pyridinooxazoline ligands,[8a,c] and highly enantioselective quaternary stereocenters were constructed. Also, the mechanism of this reaction was investigated with computational methods.[8a,9]

In our systematic investigation of Pd(II)-catalyzed conjugate addition, it is found that, in the literature, most substrates were focused on the α,β-unsaturated carboxylic derivatives, and α,β-unsaturated carboxylic acids were rarely studied. It might be the acidity of carboxylic acids which prevented its application. Actually, the only report we found about conjugate addition of arylboronic acids to α,β-unsaturated carboxylic acids was a Rh(I)-catalytic reaction by Breit,[10] and acrylic acid was the only reactive substrate. α- and β-substituted α,β-unsaturated carboxylic acids were inert to the above Rh(I)-catalytic reaction. There were some other reports about conjugate addition of organolithium reagents to α,β-unsaturated carboxylic acid,[11] in which excess and highly flammable organolithium reagents were used and an acidification process could not be avoided to get the β,β-disubstituted carboxylic acid products. In a Pd(0)-catalyzed one-pot synthesis of 3-arylpropanoic acid,[12] aryl iodide and acrylic acid were used as the starting materials, in which a hydrogenation was followed. Also, the Rh(I)-catalyzed hydrogenation of β,β-disubstituted acrylic acids could be used to synthesize β,β-disubstituted carboxylic acids.[13] Since our Pd(II)-bipyridine catalysis could be well performed in acetic acid,[7c] we thought it is highly consequential to expand the application of this methodology to α,β-unsaturated carboxylic acid and even β,β-disubstituted acrylic acids. Hopefully, β-arylpropionic acids can be synthesized directly, which avoided the hydrolysis step of carboxylic derivatives. Meanwhile, β-arylpropionic acids have been studied and reported as potent agonists and antagonists in medicinal chemistry.[14]

RESULTS AND DISCUSSION

Cinnamic acid was selected as the substrate to probe the reaction in air with HOAc/THF/H_2O as the solvent, which was the optimal solvent in our previous research,[7c] and the conjugate addition was not observed at room temperature (Table 1, entry 1). With 3.0 equiv of phenylboronic acid loading at 40 °C, 30% yield of the conjugate addition product

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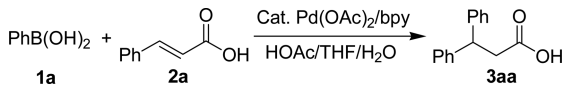
Table 1. $Pd(OAc)_2$/Bipyridine-Catalyzed Conjugate Addition of Phenylboronic Acid to Cinnamic Acid[a]



1a 2a 3aa

entry	solvent	temp (°C)	yield (%)[b]
1	HOAc/THF/H_2O	rt	0[c]
2	HOAc/THF/H_2O	40	30[c]
3	HOAc/THF/H_2O	60	81[c]
4	HOAc/THF/H_2O	80	98[c]
5	HOAc/THF/H_2O	100	82[c]
6	HOAc/THF/H_2O	80	97
7	THF/H_2O[d]	80	40
8	toluene/H_2O[d]	80	58
9	MeOH/H_2O[d]	80	53
10	acetone/H_2O[e]	80	57

[a]Reaction conditions: $Pd(OAc)_2$ (0.05 mmol, 5 mol %), bpy (0.10 mmol, 10 mol %), phenylboronic acid (2.00 mmol), cinnamic acid (1.00 mmol), HOAc/THF/H_2O = 1.0 mL/2.0 mL/0.6 mL, 24 h. [b]Isolated yield. [c]Phenylboronic acid (3.00 mmol). [d]Solvent/H_2O = 2.0 mL/0.6 mL. [e]Solvent/H_2O = 0.5 mL/2.5 mL.

was isolated after 24 h (Table 1, entry 2). Inspired by this initial result, the temperature tests showed that 80 °C was optimal, which gave a 98% yield after 24 h (Table 1, entries 3 and 4). At higher temperature (100 °C), palladium precipitate was observed in the reaction (Table 1, entry 5). Also, we tried to decrease the loading of arylboronic acids to 2.0 equiv, and the isolation yield was still up to 97% (Table 1, entry 6). The β-diphenylpropionic acid (**3aa**) product can be precipitated in water, and then extracted by dichloromethane to remove inorganic byproducts. Thus, column chromatography was unnecessary in its purification process, and NMR-pure product was obtained with an almost quantitative yield. Neutral solvents (THF, toluene, methanol, and acetone) were also surveyed, and only 40−58% yields were given (Table 1, entries 7−10), which means the acidic solvent was crucial to the complete conversion of α,β-unsaturated carboxylic acid.

With these optimal conditions, we started to explore the scope of different arylboronic acids and α,β-unsaturated carboxylic acids. First, a series of arylboronic acids were subjected to the optimal conditions with cinnamic acid as the substrate. It is found that most arylboronic acids with electron-donating groups (*p*-tolyl) and electron-withdrawing groups gave excellent yields (Table 2, entries 1−2, 4−7). In the case of *p*-methoxyphenylboronic acid (Table 2, entry 3), the yields were decreased to 55% due to the fast hydrolysis of arylboronic acid with electron-donating groups in the presence of Pd(II)-bpy, which was very similar to our previous results.[7c] In the solvent of acetone/H_2O, the yield was improved to 76% (Table 2, entry 3). When the chloro group was substituted on *p*-, *o*-, or *m*-positions of arylboronic acid (Table 2, entries 4−6), good to excellent yields were achieved. *p*-Fluorophenylboronic acid gave 95% yield of product (Table 2, entry 7), and the isolated yield of 2-naphthylboronic acid reaction was nearly quantitative (Table 2, entry 8). In the presence of (*E*)-2-phenylvinylboronic acid, the reaction gave a disordered mixture with Pd metal precipitate (Table 2, entry 9). For 2-furylboronic acid, no expected reaction was observed with only fast hydrolysis of 2-furylboronic acid (Table 2, entry 10). It revealed that this catalytic conjugate addition is insensitive to most arylboronic acids.

Then, phenylboronic acid was set as the invariable, and more α,β-unsaturated carboxylic acids were investigated. Different substitutes were introduced into the phenyl ring of cinnamic acid, and the reactions kept very high isolated yields (Table 2, entries 11−16). Even for 3-(*p*-nitrophenyl)propenoic acid, the reaction proceeded smoothly with a 94% yield (Table 2, entry 15). For 3-(*o*-nitrophenyl)propenoic acid (Table 2, entry 16), the yield decreased to 70%. More importantly, all the conjugate addition products of cinnamic acid series can be purified by simple water washing and solvent extractions without column chromatography. This strategy will be highly simple and efficient for the synthesis of β-diarylpropionic acids. In the case of crotonic acid (Table 2, entry 17), an 82% yield of conjugate addition was obtained. For acrylic acid, 3,3-diphenylpropanoic acid (**3aa**) was isolated as the main product (Table 2, entry 18), which was also similar to our previously reported conjugate addition result of ethyl acrylate.[7c] It is a diarylation product of acrylic acid with a high yield. For α-methylcinnamic acid, no reaction was observed after 24 h (Table 2, entry 19). The substrates screening demonstrated that this Pd(II)/bipyridine-catalyzed conjugate addition is mild and highly functional groups-tolerable, and most examples produced nearly quantitative yields of conjugate addition products.

With these results in hand, we started to survey the reactions of β,β-disubstituted acrylic acids. Up to now, all the β,β-disubstituted electrophiles used in Pd(II)-catalyzed conjugate addition of arylboronic acids were limited to enones, and β,β-disubstituted acrylate has been proved to be unreactive to cationic Pd(II) catalysis in our previous report.[8d] There were only very few examples to achieve the Rh(I)-catalyzed conjugate addition to β,β-disubstituted substrates.[15] The conjugate addition to β,β-disubstituted acrylic acids is highly challenging and would provide a highly efficient one-step preparation method for β-quaternary carbons substituted carboxylic acids.

First, 3,3-dimethylacrylic acid (**4a**) was chosen as the substrate for its smaller steric hindrance to probe the conjugate addition (Scheme 1). The reaction was first performed in acetic acid at 60 °C, with $Pd(OAc)_2$/bpy as catalysts. Surprisingly, 45% yield of 3-methyl-3-phenylbutanoic acid (**5aa**) was isolated as the conjugate addition product after 48 h, which was confirmed by ^1H, ^{13}C NMR and mass spectra. Inspired by this initial result, (*E*)-3-phenylbut-2-enoic acid (**4b**) as a typical β,β-disubstituted acrylic acid was prepared and subjected to different conditions to optimize the reaction.

Compared with 3,3-dimethylacrylic acid (**4a**), (*E*)-3-phenylbut-2-enoic acid (**4b**) was much less reactive, and the reaction in HOAc/THF/H_2O (Table 3, entry 1) only gave a 34% yield after 3 days, with most starting material **4b** remaining. It means the conjugate addition of arylboronic acids to β,β-disubstituted acrylic acids was highly challenging for the steric hindrance at the β position and low reactivity of substituted acrylic acids. As cationic Pd(II) with a bpy ligand has been proved to be a highly reactive catalyst for the conjugate addition to β,β-disubstituted enones in MeOH,[8d] **4b** was tested under cationic Pd(II) conditions in MeOH (Table 3, entries 2, 3). Unfortunately, only a trace of the target product was detected at 60 °C after 3 days, and completely no conjugate addition product was observed at 80 °C. CH_3NO_2 was a very good solvent for cationic Pd(II)-catalyzed nucleophilic addition of arylboronic acids to unsaturated electrophiles,[16] so we ran this reaction in CH_3NO_2, and no expected product could be detected (Table 3, entries 4, 5). In all of these entries with cationic Pd(II) catalysts

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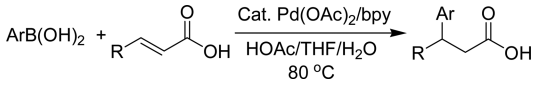
Table 2. $Pd(OAc)_2$/Bipyridine-Catalyzed Conjugate Addition of Arylboronic Acids to α,β-Unsaturated Carboxylic Acids[a]



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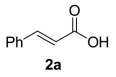
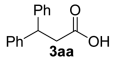
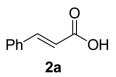
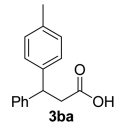
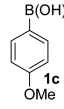
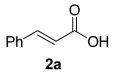
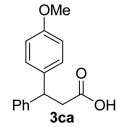
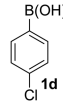
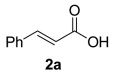
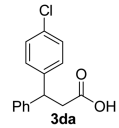
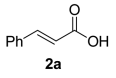
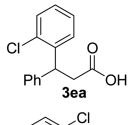
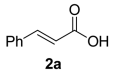
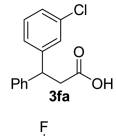
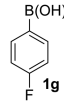
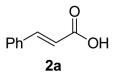
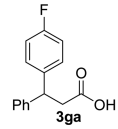
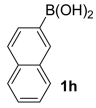
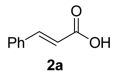
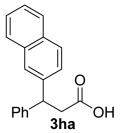
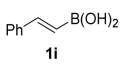
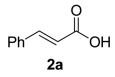
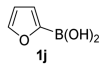
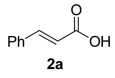
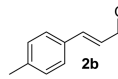
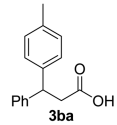
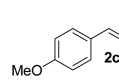
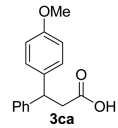
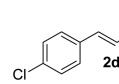
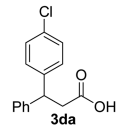
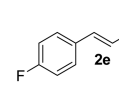
1	 1a	 2a	 3aa	97
2	 1b	 2a	 3ba	97
3	 1c	 2a	 3ca	55[c] 76[d]
4	 1d	 2a	 3da	96
5	 1e	 2a	 3ea	85
6	 1f	 2a	 3fa	95
7	 1g	 2a	 3ga	95
8	 1h	 2a	 3ha	98
9	 1i	 2a	---	Disordered[e]
10	 1j	 2a	---	NR[f]

entry	$ArB(OH)_2$	α,β-unsaturated carboxylic acid	product	yield (%)[b]
11	 1a	 2b	 3ba	98
12	 1a	 2c	 3ca	95
13	 1a	 2d	 3da	94
14	 1a	 2e	3ga	96
15	1a	2f	3af	94
16	1a	2g	3ag	70
17	1a	2h	3ah	82
18	1a	2i	3aa	95
19	1a	2j	---	NR

[a]Reaction conditions: $Pd(OAc)_2$ (0.05 mmol, 5 mol %), bpy (0.10 mmol, 10 mol %), arylboronic acid (2.00 mmol), α,β-unsaturated acid (1.00 mmol), HOAc/THF/H_2O = 1.0 mL/2.0 mL/0.6 mL, 80 °C, 24 h. [b]Isolated yield. [c]4.0 equiv of arylboronic acid. [d]2.0 equiv of arylboronic acid, acetone/H_2O = 0.5 mL/2.5 mL as solvent. [e]Disordered reaction with Pd precipitate. [f]No reaction with fast hydrolysis of 2-furylboronic acid.

Scheme 1. $Pd(OAc)_2$/bpy-Catalyzed Conjugate Addition of Phenylboronic Acid to 3,3-Dimethylacrylic Acid

(Table 3, entries 2–5), a very serious palladium black precipitate was observed with biphenyl formation, and the biphenyl was supposed to be formed by reductive elimination of diarylpalladium(II) species, which were generated by the double transmetalation between cationic Pd(II) and arylboronic acids. It is speculated that the high Lewis acidity of cationic Pd(II) would accelerate the transmetalation,[17] and it might not be good for the conversion of low reactive β,β-disubstituted acrylic acid substrates. It is hypothesized that the slower transmetalation of neutral $Pd(OAc)_2$/bpy with phenylboronic acid would help the conjugate addition.

Then, we turned back to the neutral $Pd(OAc)_2$/bpy catalyst and examined the temperature effects. In HOAc/THF/H_2O, the reaction hardly went at 40 °C (Table 3, entry 6), and the reaction at 80 °C gave a lower yield (22%) than at 60 °C (34%) (Table 3, entries 1, 7). Palladium black was also observed at 80 °C, so 60 °C was set as the optimal temperature. MeOH, *t*-BuOH, and CH_3NO_2 as solvents (Table 3, entries 8–10) were tried with neutral $Pd(OAc)_2$/bpy catalyst, and the reactions gave pretty low yields, but better than the results of cationic

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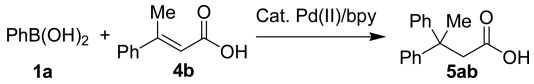
Table 3. Pd(II)/bpy-Catalyzed Conjugate Addition of Phenylboronic Acid to (*E*)-3-Phenylbut-2-enoic Acid[a]



entry	catalyst	solvent	temp (°C)	time (h)	yield (%)[b]
1	$Pd(OAc)_2$/bpy	HOAc/THF/H_2O	60	72	34[c,d]
2	$[Pd(bpy)(\mu\text{-}OH)]_2^{2+}2OTf^-$	CH_3OH	60	72	trace[e]
3	$[Pd(bpy)(\mu\text{-}OH)]_2^{2+}2OTf^-$	CH_3OH	80	72	0[e]
4	$[Pd(bpy)(\mu\text{-}OH)]_2^{2+}2OTf^-$	CH_3NO_2	60	72	0[e]
5	$[Pd(bpy)(\mu\text{-}OH)]_2^{2+}2OTf^-$	CH_3NO_2	80	72	0[e]
6	$Pd(OAc)_2$/bpy	HOAc/THF/H_2O	40	72	trace[c,d]
7	$Pd(OAc)_2$/bpy	HOAc/THF/H_2O	80	72	22[c,d]
8	$Pd(OAc)_2$/bpy	CH_3OH	60	72	24[c]
9	$Pd(OAc)_2$/bpy	*t*-BuOH	60	72	20[c]
10	$Pd(OAc)_2$/bpy	CH_3NO_2	60	72	31[c]
11	$Pd(OAc)_2$/bpy	CH_3NO_2	60	72	40[c,f]
12	$Pd(OAc)_2$/bpy	HOAc/THF/H_2O	60	72	58[c,d,f]
13	$Pd(OAc)_2$/bpy	HOAc/THF/H_2O	60	72	90[d,f,g]
14	$Pd(OAc)_2$/bpy	CH_3NO_2	60	72	91[f,g]
15	$Pd(OAc)_2$/bpy	H_2O	60	48	86[c]
16	$[Pd(bpy)(\mu\text{-}OH)]_2^{2+}2OTf^-$	H_2O	60	48	70[e]
17	$Pd(OAc)_2$/bpy	H_2O/acetone	60	48	96[c,h]
18	$Pd(OAc)_2$/bpy	H_2O/CH_3OH	60	48	89[c,h]
19	$Pd(OAc)_2$/bpy	H_2O/THF	60	48	90[c,h]
20	$Pd(OAc)_2$/bpy	acetone	60	48	20[c]

[a]Reaction conditions: phenylboronic acid (1.00 mmol), (*E*)-3-phenylbut-2-enoic acid (0.50 mmol). [b]Isolated yield. [c]$Pd(OAc)_2$ (0.025 mmol, 5 mol %), bpy (0.05 mmol, 10 mol %). [d]HOAc/THF/H_2O = 1.0 mL/2.0 mL/0.6 mL. [e]$[Pd(bpy)(\mu\text{-}OH)]_2^{2+}2OTf^-$ (0.0125 mmol, 5 mol % Pd(II)). [f]Phenylboronic acid (1.50 mmol). [g]$Pd(OAc)_2$ (0.050 mmol, 10 mol %), bpy (0.10 mmol, 20 mol %). [h]H_2O/solvent = 2.5 mL/0.5 mL.

Pd(II). Considering that the long reaction time would cause extra arylboronic acid consumption due to its protonolysis, 3 equiv of phenylboronic acid was loaded in CH_3NO_2 and HOAc/THF/H_2O (Table 3, entries 11, 12), and the yields were improved to a modest 58% yield. Furthermore, we increased the Pd(II) loading to 10 mol %, and conjugate addition yields in CH_3NO_2 and HOAc/THF/H_2O were improved to 90% and 91%. Although the complete conversion of *β*,*β*-disubstituted acrylic acid could be achieved by high catalyst loading and excess arylboronic acid, but 10 mol % of Pd(II) was unacceptable because it increased the cost and would restrict the application of this method.

In our research of Pd(II)/bpy-catalyzed conjugate addition of arylboronic acid to different electrophiles, water has been used as solvent in the conjugate addition of arylboronic acids to *α*,*β*-unsaturated carbonyl compounds,[7b] and reactions in aqueous solution have attracted so many chemists' interest for the cost and environmentally friendly concern.[18] Therefore, we tried this reaction in pure water with 5 mol % $Pd(OAc)_2$ and 2 equiv of phenylboronic acid. Surprisingly, 86% yield of conjugate addition product was isolated after 48 h (Table 3, entry 15), and for comparison, cationic Pd(II) gave a 70% yield in water (Table 3, entry 16). It means the solvent effect played an important role in this conjugate addition to *β*,*β*-disubstituted acrylic acids. Also, some water-miscible solvents were tried in the reaction, and it is found that acetone helped the complete conversion of acid substrates to give a 96% yield (Table 3, entry 17). Also, MeOH and THF contributed to a little yield increase in water (Table 3, entries 18, 19). Meanwhile, the reaction in pure acetone gave a very low yield (Table 3, entry 20). Thus, we finished the optimization of this challenging reaction with $Pd(OAc)_2$/bpy catalysts and aqueous solvents, but these reaction conditions was not suitable for the conjugate addition to *β*-monosubstituted acrylic acids (Table 1, entry 10).

With the optimized conditions in hand, a series of arylboronic acids and *β*,*β*-disubstituted acrylic acids were investigated to probe the scope of substrates. First, *p*-tolylboronic acid gave a pretty good 91% yield (Table 4, entry 2). The yield of the *p*-methoxyphenylboronic acid entry (Table 4, entry 3) dropped to 26% due to the fast protonolysis of arylboronic acids with strong electron-donating groups. For the arylboronic acids with electron-withdrawing groups (*p*-chloro and *p*-fluoro), nearly quantitative yields of conjugate addition products were obtained (Table 4, entries 4, 5). For the sterically hindered 2-naphthylboronic acid (Table 4, entry 6), the reaction in H_2O/acetone still gave 90% yield of addition product, which demonstrated that this strategy is a powerful tool to construct the quaternary carbons for low reactive *β*,*β*-disubstituted acrylic acids.

Then, the effect of substitutes on acrylic acids was investigated, and it revealed that the reaction was highly tolerable to the functional groups on acrylic acids. For all the *β*-electron-donating groups (*p*-tolyl and *p*-methoxyphenyl) substituted acids (Table 4, entries 7, 8), and *β*-electron-withdrawing groups (*p*-fluoro and *p*-nitrophenyl) substituted acids (Table 4, entries 9, 10), the reaction gave very high yield, and especially the (*E*)-3-(4-nitrophenyl)but-2-enoic acid (**4f**) (Table 4, entry 10) still afforded a 93% yield. When the *β*-alkyl substitute was changed to an ethyl group, excellent (97%) yield was maintained (Table 4, entry 11). In the case of *β*-diphenyl acrylic acid (**4h**), no reaction was observed with **4h** unreacted. It could be explained that the high stability and steric hindrance blocked the conjugate addition. For the relatively reactive 3,3-dimethylacrylic acid (**4a**), the reaction in H_2O/acetone gave a 92% yield. For *α*-methylcinnamic acid, no reaction was

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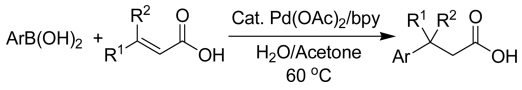
Table 4. $Pd(OAc)_2$/bpy-Catalyzed Conjugate Addition of Arylboronic Acids to β,β-Disubstituted Acrylic Acids[a]



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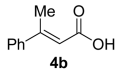
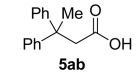
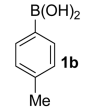
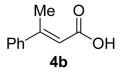
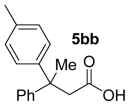
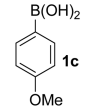
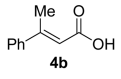
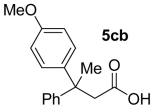
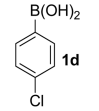
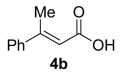
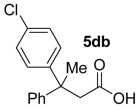
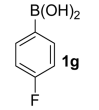
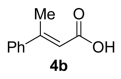
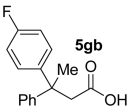
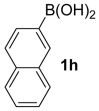
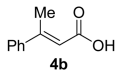
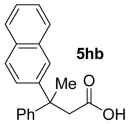
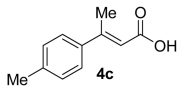
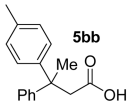
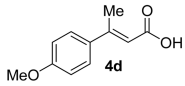
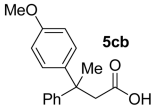
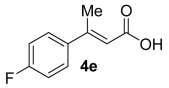
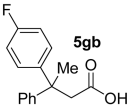
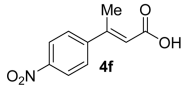
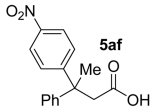
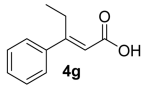
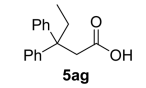
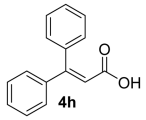
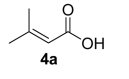
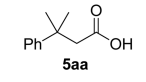
1	 1a	 4b	 5ab	96
2	 1b	 4b	 5bb	91
3	 1c	 4b	 5cb	26
4	 1d	 4b	 5db	98
5	 1g	 4b	 5gb	98
6	 1h	 4b	 5hb	90
7	 1a	 4c	 5bb	98
8	 1a	 4d	 5cb	97
9	 1a	 4e	 5gb	95
10	 1a	 4f	 5af	93
11	 1a	 4g	 5ag	97
12	 1a	 4h	---	NR
13	 1a	 4a	 5aa	92
14	 1a	2j	---	NR

[a]Reaction conditions: $Pd(OAc)_2$ (0.025 mmol, 5 mol %), bpy (0.05 mmol, 10 mol %), phenylboronic acid (1.00 mmol), β,β-disubstituted acrylic acid (0.50 mmol), H_2O/acetone = 2.5 mL/0.5 mL, in air, 60 °C, 48 h. [b]Isolated yield.

observed in H_2O/acetone either (Table 4, entry 14), which was the same as in HOAc/THF/H_2O (Table 2, entry 19).

In general, most arylboronic acids and β,β-disubstituted acrylic acids provided excellent conjugate addition yields, and the H_2O/acetone solvent was crucial to the complete substrates conversion. A series of β-quaternary carbons substituted carboxylic acids were synthesized very easily, and this reaction has very high potential in organic synthesis because the transformation of the carboxyl group to other functional groups can be realized conveniently.

In conclusion, a highly efficient and air-stable $Pd(OAc)_2$/bpy-catalyzed conjugate addition of arylboronic acids to α,β-unsaturated carboxylic acids (including β,β-disubstituted acrylic acids) was developed, and a highly challenging one-step synthesis of β-quaternary carbons substituted carboxylic acids was achieved in aqueous solution.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were used without further purification, and all the reactions were performed under an air atmosphere. Commercially available arylboronic acids were purchased from InnoChem Company (China), which were used as received. β,β-Disubstituted acrylic acids[19] and cationic Pd(II) $[Pd(bpy)(\mu\text{-}OH)]_2^{2+}2OTf^-$[16] were prepared according to the literature. NMR spectra were recorded on an Agilent 400 MHz spectrometer; chemical shifts were calibrated by TMS (0.0 ppm for ^1H NMR) or $CDCl_3$ (77.0 ppm for ^{13}C NMR) as internal references. Infrared spectra were obtained on a Nicolet iS 10 machine. Mass spectra were provided on Agilent 5973 machines. HRMS was performed on the Bruker microTOF-Q III instrument (ESI).

General Procedure for the Conjugate Addition of Arylboronic Acid to Cinnamic Acid. To a Schlenk tube with a cooling finger were added phenylboronic acid (**1a**) (244.0 mg, 2.00 mmol), cinnamic acid (**2a**) (148.0 mg, 1.00 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), bpy (15.6 mg, 0.10 mmol), HOAc (1.0 mL), THF (2.0 mL), and H_2O (0.6 mL) under an air atmosphere. The mixture was stirred and heated at 80 °C for 24 h until the substrate disappeared as monitored by TLC. The solution was transferred into a flask, and the solvent was removed under vacuum. 5 mL of water was added to the crude product, the mixture was heated to 60 °C for 5 min with stirring, and then water was removed by filtration. This process was repeated, and the product was dissolved in 10 mL of $CHCl_3$, dried with Na_2SO_4, filtered, and concentrated under vacuum. 218.5 mg of 3,3-diphenylpropionic acid (**3aa**) was isolated, with a 97% yield.

*3,3-Diphenylpropanoic Acid (**3aa**).*[13] White solid (218.5 mg, 97%). mp = 152−153 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−6.95 (m, 10H), 4.45 (t, J = 8.0 Hz, 1H), 3.01 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 143.2, 128.6, 127.6, 126.6, 46.6, 40.4. IR (KBr): ν = 1697, 3026 cm^{-1}; MS (ESI) m/z: 225 ($M - H^+$).

*3-Phenyl-3-p-tolylpropanoic Acid (**3ba**).*[13] White solid (233.0 mg, 97%). mp = 129−131 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50−6.91 (m, 9H), 4.48 (t, J = 8.0 Hz, 1H), 3.06 (d, J = 8.0 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 143.5, 140.3, 136.1, 129.3, 128.5, 127.5, 127.4, 126.5, 46.2, 40.5, 21.0. IR (KBr): ν = 1708, 3026 cm^{-1}; MS (ESI) m/z: 239 ($M - H^+$).

*3-(4-Methoxyphenyl)-3-phenylpropanoic Acid (**3ca**).*[13] White solid (141.0 mg, 55%). mp = 118−119 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.06 (m, 7H), 6.97−6.69 (m, 2H), 4.48 (t, J = 8.0 Hz, 1H), 3.76 (s, 3H), 3.05 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 158.2, 143.6, 135.4, 128.6, 128.5, 127.5, 126.5, 114.0, 55.2, 45.8, 40.6. IR (KBr): ν = 1707, 3028 cm^{-1}; MS (ESI) m/z: 255 ($M - H^+$).

*3-(4-Chlorophenyl)-3-phenylpropanoic Acid (**3da**).*[13] White solid (250.1 mg, 96%). mp = 112−113 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.08 (m, 9H), 4.49 (t, J = 8.0 Hz, 1H), 3.05 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 142.7, 141.7, 132.4, 129.0, 128.8, 128.7, 127.5, 126.8, 46.0, 40.2. IR (KBr): ν = 1709, 3028 cm^{-1}; MS (ESI) m/z: 259 ($M - H^+$).

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*3-(2-Chlorophenyl)-3-phenylpropanoic Acid (**3ea**).*[13] White solid (221.3 mg, 85%). mp = 138−139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46−7.05 (m, 9H), 5.03 (t, J = 8.0 Hz, 1H), 3.06 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 141.6, 140.5, 134.0, 130.0, 128.6, 128.2, 127.9, 127.6, 127.0, 126.8, 42.8, 39.6 ; IR (KBr) ν = 1701, 3028 cm^{-1}; MS (ESI) m/z: 259 (M − H$^+$); HRMS Calcd for $C_{15}H_{12}ClO_2^-$: 259.0531. Found: 259.0535.

*3-(3-Chlorophenyl)-3-phenylpropanoic Acid (**3fa**).* White solid (246.1 mg, 95%). mp = 101−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34−7.07 (m, 9H), 4.49 (t, J = 8.0 Hz, 1H), 3.06 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 145.3, 142.4, 134.4, 129.9, 128.8, 127.8, 127.5, 126.92, 126.89, 125.8, 46.3, 40.1 ; IR (KBr) ν = 1709, 3028 cm^{-1}; MS (ESI) m/z: 259 (M − H$^+$); HRMS Calcd for $C_{15}H_{12}ClO_2^-$: 259.0531. Found: 259.0534.

*3-(4-Fluorophenyl)-3-phenylpropanoic Acid (**3ga**).*[13] White solid (231.6 mg, 95%). mp = 110−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.09 (m, 7H), 7.05−6.84 (m, 2H), 4.50 (t, J = 8.0 Hz, 1H), 3.05 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 161.5 (d, J = 162.0 Hz), 143.0, 138.9 (d, J = 2.0 Hz), 129.1 (d, J = 6.0 Hz), 128.7, 127.5, 126.8, 115.4 (t, J = 14.0 Hz), 45.9, 40.5. ^{19}F NMR (375 MHz, $CDCl_3$) δ −116.3. IR (KBr): ν = 1709, 3029 cm^{-1}; MS (ESI) m/z: 243 (M − H$^+$).

*3-(2-Naphthyl)-3-phenylpropanoic Acid (**3ha**).*[13] White solid (270.1 mg, 98%). mp = 120−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.61 (m, 4H), 7.60−7.06 (m, 8H), 4.68 (t, J = 8.0 Hz, 1H), 3.21 (dd, J = 16.0, 8.0 Hz, 1H), 3.15 (dd, J = 16.0, 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 143.1, 140.6, 133.4, 132.2, 128.6, 128.3, 127.8, 127.7, 127.5, 126.7, 126.4, 126.1, 125.7, 125.6, 46.6, 40.3. IR (KBr): ν = 1707, 3055 cm^{-1}; MS (ESI) m/z: 275 (M − H$^+$).

*3-(4-Nitrophenyl)-3-phenylpropanoic Acid (**3af**).* White solid (255.0 mg, 94%). mp = 123−124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24−8.05 (m, 2H), 7.51−7.09 (m, 7H), 4.63 (t, J = 8.0 Hz, 1H), 3.13 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 150.7, 146.8, 141.5, 129.0, 128.6, 127.5, 127.3, 123.9, 46.4, 39.7. IR (KBr): ν = 1709, 3028 cm^{-1}; MS (ESI) m/z: 270 (M − H$^+$). HRMS Calcd for $C_{15}H_{12}NO_4^-$: 270.0763. Found: 270.0772.

*3-(2-Nitrophenyl)-3-phenylpropanoic Acid (**3ag**).* White solid (190.0 mg, 70%). mp = 150−151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82−7.74 (m, 1H), 7.56−7.47 (m, 1H), 7.39−7.19 (m, 7H), 5.22 (t, J = 8.0 Hz, 1H), 3.13 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 149.8, 141.1, 137.4, 132.7, 129.3, 128.8, 127.7, 127.5, 127.1, 124.6, 40.4, 39.9 ; IR (KBr) ν = 1712, 3029 cm^{-1}; MS (ESI) m/z: 270 (M − H$^+$); HRMS Calcd for $C_{15}H_{12}NO_4^-$: 270.0772. Found: 270.0765.

*3-Phenylbutyric Acid (**3ah**).*[13] White solid (134.3 mg, 82%). mp = 36−38 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.09 (m, 5H), 3.38−3.15 (m, 1H), 2.67 (dd, J = 16.0, 8.0 Hz, 1H), 2.57 (dd, J = 16.0, 8.0 Hz, 1H), 1.32 (d, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 145.4, 128.5, 126.7, 126.5, 42.6, 36.1, 21.8. IR (KBr): ν = 1701, 3041 cm^{-1}; MS (ESI) m/z: 163 (M − H$^+$).

General Procedure for the Preparation of (*E*)-3-Phenylbut-2-enoic Acid (4b).[19] Sodium hydride (1.7 g, 41.7 mmol, 1.5 equiv, 60% in mineral oil) was dissolved in THF (130 mL), and triethyl phosphonoacetate (9.3 g, 41.7 mmol, 1.5 equiv) was added dropwise to the suspension at 0 °C. The mixture was stirred until gas evolution had ceased. Then, acetophenone (3.3 g, 27.8 mmol, 1.0 equiv) in THF (10 mL) was added by syringe. The reaction was stirred at room temperature and monitored by TLC. The reaction mixture was quenched with saturated aqueous NH_4Cl solution. The organic phase was separated, and the aqueous layer was extracted with EtOAc. The combined organic phases were washed with saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, and concentrated under vacuum pressure. Purification by silica gel chromatography (PE:EA = 40:1 to 10:1) gave ethyl 3-phenylbut-2-enoate as an oil (5.1 g, yield 98%).

In a 50 mL round-bottom flask was placed ethyl 3-phenylbut-2-enoate (500.0 mg, 2.51 mmol), EtOH (5.4 mL) was added, and the reaction solution was stirred at room temperature. Next, aqueous NaOH solution (10%, 10.8 mL) added. The reaction was stirred until no raw material was monitored by TLC. Then, the mixture was acidified with HCl (1 N), and then extracted with diethyl ether. The combined organic phase was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under vacuum pressure. Purification by recrystallization (CH_2Cl_2/PE) produced (*E*)-3-phenylbut-2-enoic acid (**4b**) (386 mg, yield 95%).

*(E)-3-Phenylbut-2-enoic Acid (**4b**).*[13] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55−7.46 (m, 2H), 7.44−7.34 (m, 3H), 6.18 (s, 1H), 2.61 (s, 3H).

*(E)-3-(4-Tolyl)but-2-enoic Acid (**4c**).*[20] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47−7.36 (m, 2H), 7.23−7.14 (m, 2H), 6.17 (s, 1H), 2.59 (s, 3H), 2.38 (s, 3H).

*(E)-3-(4-Methoxyphenyl)but-2-enoic Acid (**4d**).*[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56−7.42 (m, 2H), 7.00−6.84 (m, 2H), 6.15 (s, 1H), 3.84 (s, 3H), 2.59 (s, 3H).

*(E)-3-(4-Fluorophenyl)but-2-enoic Acid (**4e**).*[22] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55−7.43 (m, 2H), 7.14−7.02 (m, 2H), 6.14 (s, 1H), 2.59 (s, 3H).

*(E)-3-(4-Nitrophenyl)but-2-enoic Acid (**4f**).*[23] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.35−8.19 (m, 2H), 7.71−7.52 (m, 2H), 6.23 (s, 1H), 2.63 (s, 3H).

*(E)-3-Phenylpent-2-enoic Acid (**4g**).*[24] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53−7.43 (m, 2H), 7.42−7.32 (m, 3H), 6.06 (s, 1H), 3.13 (q, J = 7.6 Hz, 2H), 1.09 (t, J = 7.6 Hz, 3H).

*3,3-Diphenylprop-2-enoic Acid (**4h**).*[25] ^{1}H NMR (400 MHz, $CDCl_3$) δ= 7.46−7.24 (m, 8H), 7.23−7.14 (m, 2H), 6.32 (s, 1H).

General Procedure for the Conjugate Addition of Arylboronic Acid to 3-Phenylbut-2-enoic Acid (4b). To a Schlenk tube were added phenylboronic acid (**1a**, 122 mg, 1.0 mmol), 3-phenylbut-2-enoic acid (**4b**, 81 mg, 0.5 mmol), $Pd(OAc)_2$ (5.86 mg, 0.025 mmol), bpy (7.81 mg, 0.05 mmol), H_2O (2.5 mL) and acetone (0.5 mL). The solution was stirred at 60 °C in air until no starting substrate was spotted as monitored by TLC. Water (8 mL) was added to the reaction, extracted with CH_2Cl_2 (10 mL × 3), dried over Na_2SO_4, and concentrated by vacuum. The residue was purified by column chromatography on silica gel (PE:EA = 5:1 to 1:1) to give 3,3-diphenylbutanoic acid (**5ab**, 115 mg, yield 96%).

*3,3-Diphenylbutanoic Acid (**5ab**).*[14] White solid (115 mg, 96%). mp = 100−101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31−7.25 (m, 4H), 7.23−7.14 (m, 6H), 3.16 (s, 2H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 148.0, 128.1, 127.0, 126.1, 46.1, 45.2, 27.9 ; IR (KBr) ν = 1708 cm^{-1}; MS (ESI) m/z: 239 (M − H$^+$); HRMS Calcd for $C_{16}H_{15}O_2^-$: 239.1078, Found: 239.1070.

*3-Phenyl-3-p-tolylbutanoic Acid (**5bb**).* White solid (116 mg, 91%). mp = 80−81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31−7.22 (m, 2H), 7.21−7.14 (m, 3H), 7.10−7.00 (m, 4H), 3.13 (s, 2H), 2.31 (s, 3H), 1.85 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 148.1, 145.1, 135.6, 128.8, 128.1, 126.9, 126.8, 126.1, 46.2, 44.9, 28.0, 20.9 ; IR (KBr) ν = 1709 cm^{-1}; MS (ESI) m/z: 253 (M − H$^+$); HRMS Calcd for $C_{17}H_{17}O_2^-$: 253.1234. Found: 253.1244.

*3-(4-Methoxyphenyl)-3-phenylbutanoic Acid (**5cb**).* White solid (35 mg, 26%). mp = 99−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32−7.23 (m, 2H), 7.21−7.14 (m, 3H), 7.13−7.03 (m, 2H), 6.86−6.75 (m, 2H), 3.78 (s, 3H), 3.13 (s, 2H), 1.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 157.7, 148.4, 140.0, 128.08, 128.06, 126.9, 126.1, 113.4, 55.2, 46.1, 44.6, 28.1 ; IR (KBr) ν = 1707 cm^{-1}; MS (ESI) m/z: 269 (M − H$^+$); HRMS Calcd for $C_{17}H_{17}O_3^-$: 269.1183. Found: 269.1191.

*3-(4-Chlorophenyl)-3-phenylbutanoic Acid (**5db**).* White solid (135 mg, 98%). mp = 100−101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32−7.19 (m, 5H), 7.19−7.00 (m, 4H), 3.12 (s, 2H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 147.7, 146.4, 132.0, 128.5, 128.24, 128.20, 126.8, 126.4, 45.9, 44.9, 28.0 ; IR (KBr) ν = 1709 cm^{-1}; MS (ESI) m/z: 273 (M − H$^+$); HRMS Calcd for $C_{16}H_{14}ClO_2^-$: 273.0688. Found: 273.0696.

*3-(4-Fluorophenyl)-3-phenylbutanoic Acid (**5gb**).* White solid (127 mg, 98%). mp = 125−126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32−7.25(m, 2H), 7.22−7.08 (m, 5H), 6.99−6.89 (m, 2H), 3.12 (s, 2H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 161.2 (d, J = 163.0 Hz), 148.0, 143.5, 128.7, 128.2, 126.8, 126.3, 114.8 (d, J = 14.0 Hz), 46.1, 44.8, 28.2 ; ^{19}F NMR (375 MHz, $CDCl_3$) δ −117.1; IR

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(KBr) ν = 1707 cm^{-1}; MS (ESI) *m/z*: 257 ($M - H^+$); HRMS Calcd for $C_{16}H_{14}FO_2^-$: 257.0983. Found: 257.0994.

*3-(2-Naphthyl)-3-phenylbutanoic Acid (**5hb**).* White solid (131 mg, 90%). mp = 159−160 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.86−7.73(m, 3H), 7.72−7.66 (m, 1H), 7.51−7.42 (m, 2H), 7.28−7.23 (m, 2H), 7.22−7.12 (m, 4H), 3.26 (s, 2H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 147.8, 145.2, 133.0, 131.9, 128.2, 128.1, 127.8, 127.4, 127.0, 126.4, 126.2, 126.0, 125.8, 124.6, 45.7, 45.3, 27.8 ; IR (KBr) ν = 1708 cm^{-1}; MS (ESI) *m/z*: 289 ($M - H^+$); HRMS Calcd for $C_{20}H_{17}O_2^-$: 289.1234. Found: 289.1235.

*3-(4-Nitrophenyl)-3-phenylbutanoic Acid (**5af**).* Yellow oil (133 mg, 93%). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.18−8.07 (m, 2H), 7.41−7.19 (m, 5H), 7.17−7.08 (m, 2H), 3.20 (s, 2H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 155.3, 146.7, 146.2, 128.5, 128.1, 126.8, 126.7, 123.3, 45.7, 45.5, 27.8; IR (KBr) ν = 1708 cm^{-1}; MS (ESI) *m/z*: 284 ($M - H^+$); HRMS Calcd for $C_{16}H_{14}NO_4^-$: 284.0928. Found: 284.0931.

*3,3-Diphenylpentanoic Acid (**5ag**).* White solid (123 mg, 97%). mp = 123−124 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30−7.22 (m,4H), 7.21−7.08 (m,6H), 3.12 (s, 2H), 2.36 (q, *J* = 7.2 Hz, 2H), 0.69 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 147.0, 127.9, 127.7, 126.1, 48.9, 41.8, 30.4, 8.7 ; IR (KBr) ν = 1707 cm^{-1}; MS (ESI) *m/z*: 253 ($M - H^+$); HRMS Calcd for $C_{17}H_{17}O_2^-$: 253.1234. Found: 253.1239.

*3-Methyl-3-phenylbutanoic Acid (**5aa**).*[26] White solid (82 mg, 92%). mp = 56−58 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40−7.34 (m, 2H), 7.34−7.27(m, 2H), 7.22−7.16 (m, 1H), 2.64 (s, 2H), 1.46 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 147.9, 128.2, 126.0, 125.3, 48.0, 37.0, 28.8 ; IR (KBr) ν = 1706 cm^{-1}; MS (ESI) *m/z*: 177 ($M - H^+$); HRMS Calcd for $C_{11}H_{13}O_2^-$: 177.0921, Found: 177.0929.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01248.

Characterization data of substrates and NMR spectra of product compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: linshaohui@suda.edu.cn (S.L.).
*E-mail: qpan@suda.edu.cn (Q.P.).

ORCID

Shaohui Lin: 0000-0003-1825-0860

Author Contributions

†These authors contributed equally.

Notes

The authors declare no competing financial interest.

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