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# Water works: an efficient palladium-catalyzed cross-coupling reaction between boronic acids and bromoacetate with aminophosphine ligand

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ABSTRACT

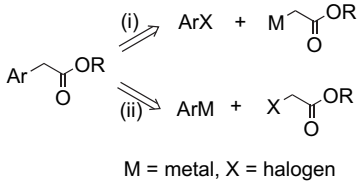
Water greatly restrained the formation of self-coupling of boronic acids in a palladium-catalyzed cross-coupling reaction between boronic acids and ethyl bromoacetate with an aminophosphine ligand; good to excellent yields of cross-coupling product were obtained.



## 1. Introduction

α-Aryl carboxylic acids are of significant importance since many of them are commercially used as non-steroidal anti-inflammatory and analgesic drugs.[1] Continuing demands exist for general and efficient procedures to supersede the current syntheses that need multiple steps, special or toxic reagents, and usually are conducted under harsh reaction conditions. Transition metal-catalyzed C–C bond-forming reactions, characterized by mild reaction conditions, that are high yielding and tolerate a wide range of functional groups, have been widely applied in organic syntheses.

There are two general reaction pathways to realize the arylation of corresponding esters to generate α-aryl carboxylic acid derivatives reported by transition metal-catalyzed reactions (Scheme 1). Reactions via pathway (i), which involves a palladium-catalyzed coupling reaction between aryl halide electrophiles and enolates, were extensively studied by Buchwald[2] and Hartwig.[3] In these reactions, bulky, electron-rich phosphine ligands and/or carbene ligands were employed. Pathway (ii) is another promising alternative to achieve the coupling reaction by employing α-halocarbonyl compounds and aryl metal as the substrates. Because arylboronic acids are readily available, fairly stable, and broadly compatible with an array of functional groups,[4] they were usually used as the aryl metallic reagents.




**Scheme 1.**

Gooßen published the first paper that efficiently fulfilled the cross-coupling reaction between arylboronic acids and bromoacetic acid derivatives by employing trinaphthyl phosphine as ligand[5] without the traditional utilization of highly toxic thallium salt as base.[6] Deng discovered that $Cu_2O$ served as co-catalyst to suppress the homo-coupling reaction of arylboronic acids and thus enhanced the efficiency for the cross-coupling reaction between arylboronic acids and ethyl bromoacetate or bromoacetamide with commercially available $Pd(PPh_3)_4$ as catalyst.[7] Luo found that hydroquinone accelerated the reaction remarkably,[8] and this offers another entry to achieve cross-coupling of α-halogenated carbonyl compounds and boronic acids rather than self-coupling of boronic acids.[9] Employing a nickel catalyst, Lei reported an efficient cross-coupling between arylboronic acids and ethyl bromoacetate.[10]

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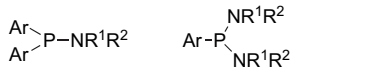
Aminophosphine ligands (Scheme 2) that we had applied to the Suzuki–Miyaura and Sonogashira coupling reactions[11] are easily-accessible, finely-tunable, efficient, and cheap ligands; however, they were only recently employed as ligands in transition metal-catalyzed cross-coupling reactions.[12] A few reports on the coordinative chemistry of aminophosphine compounds revealed that the function of amino groups was more diversified from alkoxy groups in phosphates.[13] In mono- and di-aminophosphines, alkyl and/or aryl amino groups served as strong electron-donating groups, making the phosphines stronger σ-donor ligands. Hartwig reported that both the enolate itself and ligand structure determine the connection pattern of the enolate to palladium during his study toward the reductive elimination of a palladium intermediate in palladium-catalyzed α-arylation of carbonyl compounds.[14] Gooßen found that the sterically bulky and moderately electron-donating phosphines were suitable ligands for the cross-coupling reaction between arylboronic acids and bromoacetate. This enlightening discovery prompted us to test our aminophosphine ligands in this reaction.




**L1** **L2**

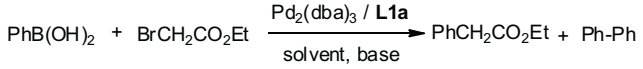
**L1a, L2a:** Ar = Ph, $R^1 = R^2 = Pr^i$
**L1b, L2b:** Ar = Ph, $R^1$-$R^2 = (CH_2)_5$
**L1c, L2c:** Ar = Ph, $R^1$-$R^2 = (CH_2)_2O(CH_2)_2$
**L1d, L2d:** Ar = Ph, $R^1$-$R^2 = (CH_2)_4$

**Scheme 2.**

## 2. Results and discussion

We chose phenylboronic acid (**1a**) and ethyl bromoacetate (**2**) as substrates, **L1a** as ligand and $Pd_2(dba)_3$ as palladium species to investigate the cross-coupling reaction. A degassed Schlenk reaction tube was charged with ethyl bromoacetate (2 mmol), phenylboronic acid (3 mmol), potassium carbonate (6 mmol), $Pd_2(dba)_3$ (0.05 mmol), ligand **L1a** (0.15 mmol), and THF (5 mL). The resulting suspension was refluxed for 8 h under nitrogen atmosphere. Besides the desired cross-coupling product, the homo-coupling product of phenylboronic acid, was also formed (Table 1, entry 1).

**Table 1**
Effect of solvents using **L1a** as ligand[a]



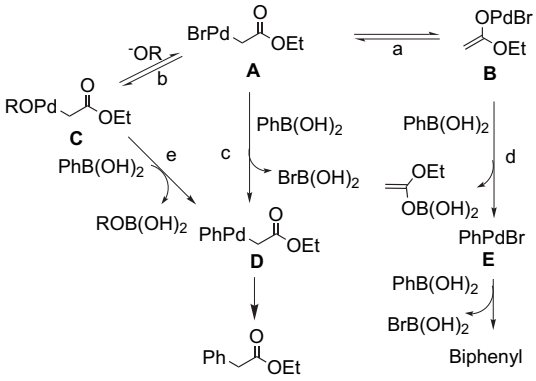

**1a** **2** **3a** **4a**

| Entry | Solvent | **3a** (%)[b] | **4a** (mg)[c] |
|---|---|---|---|
| 1 | THF | 75 | 70 |
| 2 | Dioxane | 34 | 88 |
| 3 | Toluene | 33 | 33 |
| 4 | Ethanol | 66 | 49 |
| 5 | DMF | 16 | 51 |
| 6 | Acetone | 38 | 65 |
| 7 | THF/$H_2O$[d] | 91 | 41 |
| 8 | Dioxane/$H_2O$[d] | 65 | 67 |
| 9 | Toluene/$H_2O$[d] | 70 | 78 |
| 10 | Ethanol/$H_2O$[d] | 35 | 34 |

[a] All reactions were run with phenylboronic acid (3 mmol), ethyl bromoacetate (2 mmol), $K_2CO_3$ (6 mmol), Pd (0.05 mmol), and ligand **L1a** (0.15 mmol) in 5 mL of solvent at 65 °C for 8 h.
[b] Isolated yields based on ethyl bromoacetate.
[c] Isolated mass.
[d] Organic solvent 4.5 mL, water 0.5 mL.

To optimize the reaction conditions, we first tested the solvent effect in reactions between phenylboronic acid and bromoacetate. We found that THF and ethanol were suitable solvents, and water plays a dramatic role in controlling the selectivity between homo-coupling and cross-coupling reactions. When 10% (v/v) of $H_2O$ was added, the yield of cross-coupling was greatly increased and the quantity of biphenyl was obviously decreased. This is quite different from previous reports, in which water was detrimental to the cross-coupling.[5,8,9]

To explain why water can improve the selectivity, the equilibrium between the C–Pd and O–Pd species should be considered (Scheme 3). After the oxidative addition of Pd(0) with ethyl bromoacetate, two possible palladium species may be formed. If a C–Pd bond-containing complex **A** is the only species, transmetallation in the presence of phenylboronic acid will proceed via route *c* to generate complex **D**, which is transformed to ethyl phenylacetate after reductive elimination. However, if complex **B** (a palladium enolate) is the predominant species (equilibrium a), or its presence is not negligible, the transmetallation step might be a different story. Because boron is oxophilic, the $B(OH)_2$ moiety could replace PdBr in complex **B** to generate a new boron-containing enolate and a palladium complex PhPdBr (**E**). **E** is formally the direct oxidative addition product of Pd(0) and bromobenzene, which undergoes further transmetallation with phenylboronic acid to yield biphenyl as the product. When water was added, there would exist $OH^-$ in the basic system, which displaces the halide in species **A** to give an hydroxopalladium species **C** in solution (equilibrium b),[4a,15] transmetallation in the presence of phenylboronic acid will proceed via route e to generate complex D, which also undergoes reductive elimination to give ethyl phenylacetate. The addition of water favors equilibrium b, and thus leads to the decrease of the formation of biphenyl product and the increase of cross-coupling product.



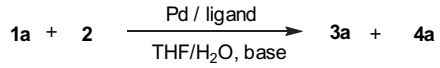

**Scheme 3.**

We then turned our attention to ligands, palladium species, and the effect of bases. The results are summarized in Table 2. Only **L1a** is a highly effective ligand in this reaction (Table 2, entry 1), while other ligands are inferior. In our previous work,[11] ligands **L1b** and **L1c** were workable ligands in the Suzuki–Miyaura cross-coupling reaction; however, they gave poor yields in this reaction (Table 2, entries 3–8).

When different palladium sources were tested, tris(dibenzylideneacetone) dipalladium(0) turned out to be the best palladium (0) precursors. Palladium(II) acetate gave products with moderate yields, $PdCl_2(MeCN)_2$ and $Pd(PPh_3)_4$ gave products with poor yields along with much more biaryl product (Table 2, entries 9–11).

The choice of the base also affects the product selectivity (Table 2, entries 12–15). $K_2CO_3$ is the most suitable base, $K_3PO_4$ and KF are also workable bases, NaOAc and $NEt_3$ are significantly less active.

**Table 2**
The effects of ligands, palladium sources, and bases[a]

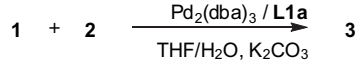



| Entry | Palladium source | Ligand | Base | **3a** (%)[b] | **4a** (mg)[c] |
|---|---|---|---|---|---|
| 1 | $Pd_2(dba)_3$ | **L1a** | $K_2CO_3$ | 91 | 41 |
| 2 | $Pd_2(dba)_3$ | **L1b** | $K_2CO_3$ | 27 | 139 |
| 3 | $Pd_2(dba)_3$ | **L1c** | $K_2CO_3$ | 15 | 232 |
| 4 | $Pd_2(dba)_3$ | **L1d** | $K_2CO_3$ | 18 | 182 |
| 5 | $Pd_2(dba)_3$ | **L2a** | $K_2CO_3$ | 42 | 81 |
| 6 | $Pd_2(dba)_3$ | **L2b** | $K_2CO_3$ | 25 | 143 |
| 7 | $Pd_2(dba)_3$ | **L2c** | $K_2CO_3$ | 11 | 231 |
| 8 | $Pd_2(dba)_3$ | **L2d** | $K_2CO_3$ | 16 | 147 |
| 9 | $Pd(OAc)_2$ | **L1a** | $K_2CO_3$ | 79 | 87 |
| 10 | $PdCl_2(MeCN)_2$ | **L1a** | $K_2CO_3$ | 58 | 72 |
| 11 | $Pd(PPh_3)_4$ | **L1a** | $K_2CO_3$ | 42 | 124 |
| 12 | $Pd_2(dba)_3$ | **L1a** | $K_3PO_4$ | 69 | 52 |
| 13 | $Pd_2(dba)_3$ | **L1a** | KF | 62 | 33 |
| 14 | $Pd_2(dba)_3$ | **L1a** | NaOAc | 32 | 11 |
| 15 | $Pd_2(dba)_3$ | **L1a** | $NEt_3$ | 21 | 27 |

[a] All reactions were run with phenylboronic acid (3 mmol), ethyl bromoacetate (2 mmol), base (6 mmol), Pd (0.05 mmol) and ligand (0.15 mmol) in 5 mL of solvent ($THF/H_2O$=9:1, v/v) at 65 °C for 8 h.
[b] Isolated yields based on ethyl bromoacetate.
[c] Isolated mass.

The generality and selectivity of the reaction were investigated using a number of arylboronic acids and alkenylboronic acids in combination with ethyl bromoacetate; the results are summarized in Table 3.

**Table 3**
Pd-catalyzed synthesis of arylacetic acid derivatives[a]




| Entry | R–$B(OH)_2$ | **3** | Yield[b] (%) |
|---|---|---|---|
| 1 | Phenyl | **3a** | 90 |
| 2 | *o*-Tolyl | **3b** | 91 |
| 3 | *m*-Tolyl | **3c** | 90 |
| 4 | *p*-Tolyl | **3d** | 98 |
| 5 | *p*-Chlorophenyl | **3e** | 98 |
| 6 | *p*-Formylphenyl | **3f** | 92 |
| 7 | *p*-Trifluoromethylphenyl | **3g** | 85 |
| 8 | *p*-Trifluoromethoxyphenyl | **3h** | 84 |
| 9 | *p*-Methoxyphenyl | **3i** | 97 |
| 10 | *p*-(*tert*-Butyl)phenyl | **3j** | 90 |
| 11 | 1,3-Benzodioxol-5-yl | **3k** | 97 |
| 12 | 2,6-Dimethylphenyl | **3l** | 60 |
| 13 | 1-Naphthyl | **3m** | 88 |
| 14 | 2-Methoxy-1-Naphthyl | **3n** | 86 |
| 15 | (*E*)-Styryl | **3o** | 94 |
| 16 | (*E*)-3-(Benzyloxy)prop-1-enyl | **3p** | 84 |

[a] All reactions were run with phenylboronic acid (3 mmol), ethyl bromoacetate (2 mmol), $K_2CO_3$ (6 mmol), Pd (0.05 mmol), and **1a** (0.15 mmol) in 5 mL of solvent ($THF/H_2O$=9:1, v/v,) at 65 °C for 8 h.
[b] Isolated yields based on ethyl bromoacetate.

As illustrated in Table 3, most substrates gave good to excellent yields. Electron-poor and electron-rich compounds are equally suitable for the transformation (Table 3, entries 1–11), sterically hindered compounds gave moderate yields (Table 3, entry 12), 1-naphthylboronic acid, 2-methoxy-1-naphthylboronic acid, and alkenylboronic acid also gave good yields (Table 3, entries 13–16).

## 3. Conclusions

In conclusion, we have applied aminophosphine as an efficient ligand in a palladium-catalyzed cross-coupling reaction between boronic acids and ethyl bromoacetate successfully. We optimized the reaction condition and found that water was crucial in the cross-coupling reaction. A number of arylboronic acids and alkenylboronic acids were tested and good to excellent yields were obtained.

## 4. Experimental section

### 4.1. Ethyl 2-phenylacetate (3a)

A degassed Schlenk reaction tube was charged in sequence with $PhB(OH)_2$ (3 mmol), potassium carbonate (6 mmol), $Pd_2(dba)_3$ (0.05 mmol), ligand **L1a** (0.15 mmol), THF (4.5 mL), water (0.5 mL), and ethyl bromoacetate (2 mmol). The resulting mixture was degassed by freeze–thaw techniques and was kept stirring for 8 h at 65 °C. The reaction was quenched with water (5 mL), and the solution was extracted with ethyl acetate (3×10 mL). The organic layers were combined, and dried over sodium sulfate. The solvent evaporated in vacuo to give the crude product, which was purified by flash chromatography (PE then 2% EA/PE), biphenyl (41.2 mg, a white solid) and **3a** (295.2 mg, 90%, a colorless oil) were obtained in sequence. Characterization of **3a**: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.35–7.30 (m, 5H), 4.17 (q, $J$=7.0 Hz, 2H), 3.63 (s, 2H), 1.27 (t, $J$=7.2 Hz, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): 171.6, 134.1, 129.2, 128.5, 127.0, 60.8, 41.4, 14.1.

### 4.2. Ethyl 2-*o*-tolylacetate (3b)

$^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.19–7.17 (m, 4H), 4.16 (q, $J$=7.2 Hz, 2H), 3.63 (s, 2H), 2.32 (s, 3H), 1.25 (t, $J$=7.0 Hz, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): 171.7, 137.1, 133.2, 130.6, 130.4, 127.6, 126.3, 61.0, 39.5, 19.8, 14.4.

### 4.3. Ethyl 2-*m*-tolylacetate (3c)

$^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.23–7.20 (m, 1H), 7.11–7.07 (m, 3H), 4.16 (q, $J$=7.2 Hz, 2H), 3.57 (s, 2H), 2.34 (s, 3H), 1.25 (t, $J$=7.0 Hz, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): 171.9, 138.4, 134.3, 130.2, 128.7, 128.0, 126.5, 61.0, 41.6, 21.6, 14.4.

### 4.4. Ethyl 2-*p*-tolylacetate (3d)

$^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.18–7.11 (m, 4H), 4.14 (q, $J$=7.2 Hz, 2H), 3.56 (s, 2H), 2.32 (s, 3H), 1.24 (t, $J$=7.0 Hz, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): 171.6, 136.4, 130.9, 129.0, 128.9, 60.6, 40.8, 20.9, 14.0.

### 4.5. Ethyl 2-(4-chlorophenyl)acetate (3e)

$^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.30–7.26 (m, 2H), 7.23–7.20 (m, 2H), 4.16 (q, $J$=7.1 Hz, 2H), 3.58 (s, 2H), 1.25 (t, $J$=7.0 Hz, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): 171.4, 133.2, 132.8, 130.9, 128.9, 61.2, 40.9, 14.4.

### 4.6. Ethyl 2-(4-formylphenyl)acetate (3f)

$^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 10.0 (s, 1H), 7.85 (d, $J$=8.4 Hz, 2H), 7.46 (d, $J$=8.0 Hz, 2H), 4.16 (q, $J$=7.2 Hz, 2H), 3.71 (s, 2H), 1.26 (t, $J$=7.0 Hz, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): 192.0, 170.8, 141.2, 135.5, 130.2, 130.1, 61.3, 41.6, 14.3.

### 4.7. Ethyl 2-(4-(trifluoromethyl)phenyl)acetate (3g)

$^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.58 (d, $J$=8.0 Hz, 2H), 7.40 (d, $J$=8.0 Hz, 2H), 4.16 (q, $J$=7.2 Hz, 2H), 3.68 (s, 2H), 1.26 (t, $J$=7.2 Hz, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): 171.0, 138.3, 129.9, 129.4, 125.7, 123.0, 61.4, 41.3, 14.3.

### 4.8. Ethyl 2-(4-(trifluoromethoxy)phenyl)acetate (3h)

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.31 (d, $J$=8.4 Hz, 2H), 7.17 (d, $J$=8.4 Hz, 2H), 4.16 (q, $J$=7.2 Hz, 2H), 3.62 (s, 2H), 1.26 (t, $J$=7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): 171.3, 148.5, 133.0, 130.8, 121.2, 119.4, 61.2, 40.7, 14.2. IR (KBr): $\nu$ 2358, 2339, 1735, 1509, 1253, 1217, 1153, 1030, 922 cm$^{-1}$. HRMS (MICROMASS GCT-MS EI) exact mass calcd for ($C_{11}H_{11}F_3O_3$): $m/z$ 248.0660, found $m/z$ 248.0633.

### 4.9. Ethyl 2-(4-methoxyphenyl)acetate (3i)

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.20 (m, 2H), 6.86 (m, 2H), 4.15 (q, $J$=6.8 Hz, 2H), 3.79 (s, 3H), 3.55 (s, 2H), 1.25 (t, $J$=7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): 172.2, 158.9, 130.5, 126.5, 114.2, 61.0, 55.4, 40.7, 14.4.

### 4.10. Ethyl 2-(4-*tert*-butylphenyl)acetate (3j)

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.34 (d, $J$=8.4 Hz, 2H), 7.22 (d, $J$=8.4 Hz, 2H), 4.15 (q, $J$=7.2 Hz, 2H), 3.58 (s, 2H), 1.31 (s, 9H), 1.26 (t, $J$=7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): 172.0, 150.0, 131.4, 129.2, 125.7, 61.0, 41.1, 34.7, 31.6, 14.5.

### 4.11. Ethyl 2-(benzo[*d*][1,3]dioxol-5-yl)acetate (3k)

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.79–6.72 (m, 3H), 5.94 (s, 2H), 4.15 (q, $J$=7.2 Hz, 2H), 3.51 (s, 2H), 1.25 (t, $J$=7.0 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): 171.9, 147.9, 146.9, 127.9, 122.6, 109.9, 108.4, 101.2, 61.1, 41.2, 14.4.

### 4.12. Ethyl 2-(2,6-dimethylphenyl)acetate (3l)

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.09–7.02 (m, 3H), 4.15 (q, $J$=7.2 Hz, 2H), 3.68 (s, 2H), 2.33 (s, 6H), 1.24 (t, $J$=6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): 171.5, 137.4, 132.0, 128.3, 127.2, 60.9, 36.7, 20.5, 14.5.

### 4.13. Ethyl 2-(naphthalen-1-yl)acetate (3m)

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.01–7.98 (m, 1H), 7.86–7.77 (m, 2H), 7.54–7.41 (m, 4H), 4.15 (q, $J$=7.2 Hz, 2H), 4.05 (s, 2H), 1.21 (t, $J$=6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): 171.9, 134.1, 132.4, 131.0, 129.0, 128.3, 128.2, 126.8, 126.1, 125.8, 124.1, 61.2, 39.6, 14.5.

### 4.14. Ethyl 2-(2-methoxynaphthalen-1-yl)acetate (3n)

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.73–7.70 (m, 2H), 7.62 (s, 1H), 7.42–7.39 (m, 1H), 7.34–7.29 (m, 1H), 7.10 (s, 1H), 4.16 (q, $J$=7.2 Hz, 2H), 3.90 (s, 3H), 3.76 (s, 2H), 1.24 (t, $J$=6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): 171.9, 156.3, 134.4, 130.2, 128.9, 127.6, 126.7, 126.4, 126.3, 125.3, 124.0, 105.4, 60.9, 55.7, 37.0, 14.5.

### 4.15. (*E*)-Ethyl 4-phenylbut-3-enoate (3o)

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38–7.20 (m, 5H), 6.49 (d, $J$=15.6 Hz, 1H), 6.30 (dt, $J$=16.0, 7.2 Hz 1H), 4.17 (q, $J$=7.2 Hz, 2H), 3.24 (dd, $J$=6.8, 1.2 Hz, 2.0 H), 1.28 (t, $J$=7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): 171.8, 137.1, 133.6, 128.8, 127.7, 126.5, 122.1, 61.0, 38.7, 14.5.

### 4.16. (*E*)-Ethyl 5-(benzyloxy)pent-3-enoate (3p)

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.34–7.24 (m, 5H), 5.88–5.69 (m, 2H), 4.49 (s, 2H), 4.13 (q, $J$=7.0 Hz, 2H), 4.00 (d, $J$=7.2 Hz, 2H), 3.09 (d, $J$=6.6 Hz, 2H), 1.25 (t, $J$=7.0 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): 171.3, 138.0, 130.2, 128.2, 127.6, 127.4, 125.5, 71.9, 70.0, 60.5, 37.6, 14.0.

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