up to 93% yield

E/Z > 20:1

# Phosphine-Catalyzed Cross-Coupling of Benzyl Halides and Fumarates

Tingting Yan, Kaki Raveendra Babu, Yong Wu, Yang Li, Yuhai Tang, and Silong Xu\*



under metal-free conditions. Mechanistic studies suggest a catalytic cycle involving phosphorus ylide formation, Michael addition, water-assisted hydrogen transfer, and phosphine elimination.

Phosphine catalysis<sup>1</sup> has been established as a versatile platform for new reaction development. Extant examples include Morita-Baylis-Hillman reaction,<sup>2</sup> Rauhut-Currier reaction,<sup>3</sup> Michael reaction,<sup>4</sup> Umpolung addition,<sup>5</sup> isomerization,<sup>6</sup> and annulation reactions like Lu's [3+2],<sup>7</sup> Kwon's [4+2],<sup>8</sup> Tong's [4+1],<sup>9</sup> [4+3],<sup>10</sup> [4+4],<sup>11</sup> etc. To date, the substrates for phosphine catalysis have centered on electrophilic unsaturated substances,<sup>1d</sup> while the more prevalent electrophilic saturated compounds, e.g., organic halides, have seldom been investigated in this regard, presumably due to the difficulty of realizing the catalytic cycle of thus-formed phosphonium salts and ylides.<sup>12</sup>

Recently, organocatalytic cross-coupling reactions<sup>13</sup> have attracted significant attention because of their novel mechanism, complementary scope, and metal-free conditions. In particular, Huang and co-workers<sup>14</sup> in 2018 have disclosed an elegant Suzuki-type cross-coupling of benzyl halides with arylboronic acids using a single organic sulfide catalyst (Scheme 1a). The novel process involves the formation of a zwitterionic boron "ate" intermediate that undergoes a 1,2metalate shift and protodeboronation to afford the products. As part of our interest in the organophosphorus chemistry,<sup>15</sup> we hypothesized a phosphine-catalyzed olefinic cross-coupling reaction between alkyl halides 1 and electron-poor alkenes 2 (Scheme 1b). Mechanistically, an  $S_N 2$  reaction of a phosphine catalyst with alkyl halides 1 followed by deprotonation produces ylide A. Michael reaction of A on alkenes 2 would generate an intermediate B, which undergoes hydrogen transfer to afford species C. Final elimination then furnishes an isomeric Heck-type product 3 with the release of the catalyst. The vicinal electron-withdrawing groups on the alkenes 2 would facilitate both Michael reaction and hydrogen transfer steps. The merits<sup>1a,b,12</sup> of phosphines like pronounced nucleophilicity, good leaving-group ability, and facile stabilization of ylides support the proposal; however, serious challenges remain, such as competitive Rauhut-Currier reaction,<sup>3</sup> attack of the ylide on halides,<sup>16</sup> and carbanion-triggered oligomerization.

Scheme 1. Two Types of Organocatalytic Cross-Coupling

exclusive selectivity of alkyl over arvl halides

excellent E-selectivity of olefination



We commenced the investigation by treating benzyl bromide 1a, fumarate 2a, and K<sub>2</sub>CO<sub>3</sub> with several aryl phosphine catalysts (Table 1, entries 1-5). Only a trace amount of desired product 3a could be detected by NMR. However, trialkylphosphines turned out to be effective, among which PBu<sub>3</sub> afforded product **3a** in 18% yield (entries 6-8).<sup>1</sup> Screening of common solvents indicated that toluene was the best that provided the product in 50% yield (entries 9-14).

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#### Table 1. Survey of Conditions<sup>4</sup>

	+ MeO₂C、 →Br	CO <sub>2</sub> Me	conditions		O <sub>2</sub> Me
1a	:	2a		3a	021116
entry	catalyst	base	solvent	T (°C)	yield (%) <sup>b</sup>
1	PPh <sub>2</sub>	K <sub>2</sub> CO <sub>2</sub>	THF	60	trace
2	$P(4-MeOC_6H_4)_3$	$K_2CO_3$	THF	60	trace
3	$P(2-furyl)_3$	K <sub>2</sub> CO <sub>3</sub>	THF	60	trace
4	$PPh_2(2-Py)$	$K_2CO_3$	THF	60	trace
5	DPPE	$K_2CO_3$	THF	60	trace
6	PMe <sub>3</sub>	$K_2CO_3$	THF	60	14
7	PBu <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	THF	60	18
8	PCy <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	THF	60	9
9	PBu <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	1,4-dioxane	60	35
10	PBu <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	toluene	60	50
11	PBu <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	60	trace
12	PBu <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	DMF	60	trace
13	PBu <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	DCM	60	trace
14	PBu <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	cyclohexane	60	15
15	PBu <sub>3</sub>	$K_2CO_3$	toluene	40	5
16	PBu <sub>3</sub>	$K_2CO_3$	toluene	80	36
17	PBu <sub>3</sub>	$K_2CO_3$	toluene	100	32
18	PBu <sub>3</sub>	Et <sub>3</sub> N	toluene	60	trace
19	PBu <sub>3</sub>	$Na_2CO_3$	toluene	60	trace
20	PBu <sub>3</sub>	NaOH	toluene	60	51
21	PBu <sub>3</sub>	КОН	toluene	60	28
22	PBu <sub>3</sub>	NaH	toluene	60	35
23	PBu <sub>3</sub>	$Cs_2CO_3$	toluene	60	69
24 <sup>c</sup>	PBu <sub>3</sub>	$Cs_2CO_3$	toluene	60	80
25 <sup>c,d</sup>	PBu <sub>3</sub>	$Cs_2CO_3$	toluene	60	93
26 <sup><i>c</i>-<i>e</i></sup>	PBu <sub>3</sub>	$Cs_2CO_3$	toluene	60	78
$27^{c,d,f}$	PBu <sub>3</sub>	$Cs_2CO_3$	toluene	60	79
$28^{c,d,g}$	PBu <sub>3</sub>	$Cs_2CO_3$	toluene	60	28

<sup>*a*</sup>Under a N<sub>2</sub> atmosphere and anhydrous conditions, the phosphine catalyst (0.02 mmol, 10 mol %) was added to the mixture of **1a** (0.24 mmol) and **2a** (0.2 mmol) in the solvent (1.0 mL), which was then stirred at the specified temperature for 48 h. DPPE, 1,2-bis-(diphenylphosphino)ethane. <sup>*b*</sup>Isolated yield. <sup>*c*</sup>With 20 mol % PBu<sub>3</sub>. <sup>*d*</sup>The PBu<sub>3</sub> was added in two portions over 24 h. <sup>*c*</sup>With 1.0 equiv of water introduced. <sup>*f*</sup>With 1.0 equiv of methanol adopted. <sup>*g*</sup>Using benzyl chloride **1a**' instead of **1a**.

Examination of the temperature revealed that 60 °C was optimal (entries 15–17). Subsequently, the influence of bases on the reaction was checked (entries 18–23). It was found that  $Cs_2CO_3$  stood out, giving a 69% yield of **3a**. Employing additives such as NaI, 4 Å molecular sieves,  $Bu_4NBr$ , and 18-crown-6 could not further improve the reaction (not shown). Finally, it was found that an increased amount of PBu<sub>3</sub> (20 mol %) led to an 80% yield of **3a** (entry 24). Furthermore, when the catalyst was added in two portions over 24 h, the yield was increased to 93% (entry 25). It is noteworthy that the reaction tolerates the presence of water and methanol yet gives slightly lower yields (entries 26 and 27). Compared to benzyl bromide **1a**, benzyl chloride **1a**' was less efficient (entry 28).

Under the optimized conditions, the substrate scope of the phosphine-catalyzed cross-coupling was investigated (Table 2). First, substitution at the *para* position of benzyl bromides was examined. Alkyl and aryl groups were well tolerated, giving products 3b-d in 71–83% yields (entries 2–4, respectively). Methoxyl- and trifluoromethoxyl-substituted benzyl bromides

#### Table 2. Substrate Scope<sup>a</sup>

Ar	$R_{\rm H} + RO_{2}C_{\rm H}$	PBu <sub>3</sub> ( Cs <sub>2</sub> CO <sub>3</sub>	20 mol % (1. 2 equ	aiv.)	CO <sub>2</sub> R
1	2	:O <sub>2</sub> R toluene,	60 °C, 4	8 h	3 CO <sub>2</sub> R
entry	Ar in 1	R in 2	3	yield (%) <sup>b</sup>	$E:Z^{c}$
1	C <sub>6</sub> H <sub>5</sub>	Me	3a	93 (77) <sup>d</sup>	20:1
2	4-Me-C <sub>6</sub> H <sub>4</sub>	Me	3b	83	20:1
3	$4\text{-Ph-}C_6H_4$	Me	3c	73 <sup>e</sup>	20:1
4	$4$ - $^{t}Bu$ - $C_{6}H_{4}$	Me	3d	71	20:1
5	4-MeO-C <sub>6</sub> H <sub>4</sub>	Me	3e	61	20:1
6	$4-CF_3O-C_6H_4$	Me	3f	70 <sup>e</sup>	20:1
7	$4-F-C_6H_4$	Me	3g	86	20:1
8	4-Cl-C <sub>6</sub> H <sub>4</sub>	Me	3h	85	20:1
9	$4-Br-C_6H_4$	Me	3i	87	20:1
10	$4-I-C_6H_4$	Me	3j	79	20:1
11	$4-MeO_2C-C_6H_4$	Me	3k	41 <sup>e</sup>	20:1
12	4-CN-C <sub>6</sub> H <sub>4</sub>	Me	31	24	20:1
13	$4-CF_3-C_6H_4$	Me	3m	45	20:1
14	3-Me-C <sub>6</sub> H <sub>4</sub>	Me	3n	75	20:1
15	3-Cl-C <sub>6</sub> H <sub>4</sub>	Me	30	77	20:1
16	3-MeO-C <sub>6</sub> H <sub>4</sub>	Me	3p	70	20:1
17	3,5-di-Cl-C <sub>6</sub> H <sub>3</sub>	Me	3q	41	20:1
18	2-Cl-C <sub>6</sub> H <sub>4</sub>	Me	3r	30	20:1
19	2-naphthyl	Me	3s	81	20:1
20	C <sub>6</sub> H <sub>5</sub>	Et	3t	84 (75) <sup>d</sup>	20:1
21	C <sub>6</sub> H <sub>5</sub>	Bu	3u	77	20:1
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<sup>*a*</sup>Under a N<sub>2</sub> atmosphere and anhydrous conditions, PBu<sub>3</sub> (0.04 mmol, 20 mol %) was added in two portions over 24 h to the mixture of 1 (0.24 mmol) and 2 (0.2 mmol) in toluene (1.0 mL) at 60 °C for 48 h. <sup>*b*</sup>Isolated yield. <sup>*c*</sup>Identified by an NMR assay. <sup>*d*</sup>Yields in parentheses are from reactions using maleates instead of fumarates. <sup>*e*</sup>Yields from a 0.4 mmol scale.

were also feasible, providing 3e and 3f in 61% and 70% yields, respectively (entries 5 and 6, respectively). Halide substituents, including fluoride, chloride, bromide, and iodide, were all compatible, affording 3g-j, respectively, in 79-87% yields (entries 7-10, respectively). However, electron-withdrawing groups such as methoxylcarbonyl, cyano, and trifluoromethyl decreased the efficiency, generating products 3k-m, respectively, in lower yields (entries 11-13, respectively). Substitution at the meta position of benzyl bromides also worked well, as demonstrated by the formation of 3n-q in 41-77%yields (entries 14-17, respectively). 2-Chlorobenzyl bromide furnished an only 30% yield of product 3r, probably due to the steric hindrance arising from the ortho substitution (entry 18). It was found that 2-bromomethylnaphthalene could provide 3s in 81% yield (entry 19). Unfortunately, under standard conditions, other types of organic bromides, such as allylic bromide and butyl bromide, were ineffective, leading to no reaction or complex mixtures (see the Supporting Information). Subsequently, a variation of fumarates were investigated. Changing the alkyl groups of fumarates with an ethyl group or a butyl group exerted a trivial influence, leading to the formation of products 3t and 3u in good yields (entries 20 and 21, respectively). Methyl maleate with a cis alkene also worked well, producing 3a and 3t in good yields (entries 1 and 20, respectively). However, beyond fumarates and maleates, other activated olefins such as maleimides and ethyl (E)-4-oxo-4phenylbut-2-enoate were inefficient substrates, leading to very low yields of the desired products or complicated mixtures (see the Supporting Information).

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It is noteworthy that all products 3 were obtained in exclusive *E*-selectivity of the trisubstituted double bond. In addition, aryl halides are untouched in the reaction because phosphines are inherently selective toward alkyl halides. To explore the synthetic utility of the methodology, sequential Heck-type cross-coupling reactions starting from 4-bromobenzyl bromide **1i** were demonstrated (Scheme 2). The





phosphine-catalyzed cross-coupling of 1i with fumarate 2a provided 3i in 70% yield, which was followed by a Pd-catalyzed Heck cross-coupling with alkenes 4, leading to the formation of products 5a-c in 58-74% yields with excellent *E*,*E*-selectivity.

To clarify the mechanism, <sup>31</sup>P and <sup>1</sup>H NMR monitoring of the reaction of benzyl bromide **1a**, fumarate **2a**, PBu<sub>3</sub>, and  $Cs_2CO_3$  was conducted (Scheme 3a), which suggested the



formation of a phosphonium **6a** (<sup>31</sup>P NMR  $\delta$  31.61) in a significant amount (for details, see the Supporting Information). On the contrary, when phosphonium salt **6a** was treated with fumarate **2a** in the presence of Cs<sub>2</sub>CO<sub>3</sub>, desired product **3a** was obtained in 70% yield<sup>19</sup> (Scheme 3b). The results suggest that the phosphine attacks the benzyl bromide to form phosphonium **6a** to initiate the reaction.

To inspect the proton transfer step of the mechanism, deuteration experiments were conducted (Scheme 4). When





1.0 equiv of  $D_2O$  was introduced into the mixture of 1a and 2a under the standard conditions (Scheme 4a), product  $3a \cdot d_3$  was obtained in 80% yield with deuterium incorporated at both the olefinic =C-H hydrogen (38% D) and  $-CH_2-$  protons (15% D). For comparison, non-deuterium product 3a was treated with  $D_2O$  (1.0 equiv) under the same condition, which afforded  $3a \cdot d_2$  in 85% yield with deuterium only at the  $-CH_2$ unit (41% D) (Scheme 4b). These results suggest that the olefinic =C-H hydrogen was deuterated during the catalytic cycle, while the  $-CH_2-$  protons may be deuterated after the reaction because of their acidity. Accordingly, it implies that water is involved in the mechanism of cross-coupling.

To further elucidate the mechanism, DFT calculations for the phosphine-catalyzed cross-coupling of benzyl bromide 1a and fumarate 2a were performed (Figure 1). To simplify the



Figure 1. Gibbs free energy profile for the PMe<sub>3</sub>-catalyzed crosscoupling of 1a and 2a. Relative energies in kilocalories per mole.

computation, trimethylphosphine is used instead of tributylphosphine. We computed that the formation of phosphonium 6a and phosphorus ylide A was exothermic with the energies of -19.3 and -41.3 kcal mol<sup>-1</sup>, respectively. The attack of ylide A on fumarate 2a to form adduct B was calculated to bear an activation barrier of 18.7 kcal mol<sup>-1</sup> (Ts-1). The following hydrogen transfer to approach intermediate C may proceed in a 1,2-H shift process (path a) or a tandem 1,3-H/1,2-H shift via ylide C' (path b). However, both of these processes show high activation barriers, that is, 43.5 kcal  $mol^{-1}$  for the 1,2-H shift of path a (Ts-2) and 52.3 kcal  $mol^{-1}$ for the 1,2-H shift of path b (Ts-4). On the basis of the deuteration experiments described above, we conceived that the hydrogen transfer may be assisted by a trace amount of water in the solvent.<sup>20</sup> Therefore, for the water-assisted 1,2-H shift of path a (Ts-6, colored pink), the activation barrier decreases to 29.9 kcal mol<sup>-1</sup>; for the water-assisted 1,2-shift of path b (Ts-7, colored blue), the activation energy is only 8.6 kcal mol<sup>-1</sup>. Thus, the water-assisted stepwise 1,3-H/1,2-H shift via transition states TS-3 and TS-7 may account for the hydrogen transfer step. This also corroborates the results of the deuterium experiments in which the olefinic =C-H hydrogen was deuterated by D<sub>2</sub>O (Scheme 4a). Finally, it was shown that the elimination of phosphine to form product 3a is fast with an activation barrier of 2.0 kcal mol<sup>-1</sup>. The formation of the E-product is computed to be both kinetically and thermodynamically favored (see the Supporting Information). The overall reaction of the cross-coupling is highly exothermic that releases 67.7 kcal mol<sup>-1</sup> of energy.

In summary, we have developed a phosphine-catalyzed olefinic cross-coupling between benzyl bromides and fumarates. The reaction produces trisubstituted alkenes in good yields and excellent stereoselectivity. As supported by control experiments and DFT calculations, the catalytic cycle is believed to encompass the formation of a phosphorus ylide, Michael reaction of the ylide on fumarate, water-assisted hydrogen transfer, and final phosphine elimination. To the best of our knowledge, this reaction constitutes the first phosphinecatalyzed cross-coupling of simple alkyl halides with alkenes. Future efforts will focus on exploring other phosphinecatalyzed reactions involving alkyl halides as substrates.

## ASSOCIATED CONTENT

#### **1** Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01214.

Analytical data, experimental details, DFT calculation data, and NMR spectra (PDF)

## AUTHOR INFORMATION

## **Corresponding Author**

Silong Xu – School of Chemistry and Xi'an Key Laboratory of Sustainable Energy Materials Chemistry, Xi'an Jiaotong University, Xi'an 710049, P. R. China; orcid.org/0000-0003-3279-9331; Email: silongxu@mail.xjtu.edu.cn

## Authors

- Tingting Yan School of Chemistry and Xi'an Key Laboratory of Sustainable Energy Materials Chemistry, Xi'an Jiaotong University, Xi'an 710049, P. R. China
- Kaki Raveendra Babu School of Chemistry and Xi'an Key Laboratory of Sustainable Energy Materials Chemistry, Xi'an Jiaotong University, Xi'an 710049, P. R. China

Yong Wu – School of Chemistry and Xi'an Key Laboratory of Sustainable Energy Materials Chemistry, Xi'an Jiaotong University, Xi'an 710049, P. R. China

- Yang Li School of Chemistry and Xi'an Key Laboratory of Sustainable Energy Materials Chemistry, Xi'an Jiaotong University, Xi'an 710049, P. R. China; orcid.org/0000-0002-9311-3412
- Yuhai Tang School of Chemistry and Xi'an Key Laboratory of Sustainable Energy Materials Chemistry, Xi'an Jiaotong University, Xi'an 710049, P. R. China

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c01214

#### Notes

The authors declare no competing financial interest.

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