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Rhodium(III)-Catalyzed Azacycle-Directed Intermolecular Insertion of Arene C−H Bonds into α-Diazocarbonyl Compounds

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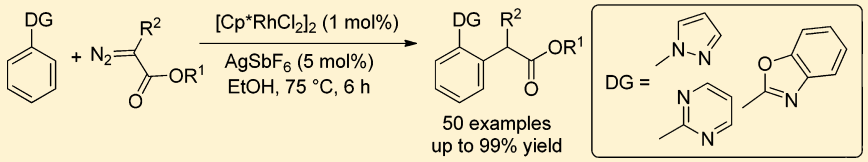
Supporting Information



ABSTRACT: Cp*Rh(III)-catalyzed intermolecular C−C couplings between activated α-diazocarbonyl compounds and arenes bearing a range of azacyclic directing groups have been achieved. This catalytic alkylation reaction operates under mild conditions with good functional group tolerance.

INTRODUCTION

The last several decades have witnessed the remarkable progress of C−C coupling reactions via a C−H activation pathway, particularly using rhodium catalysts.[1] While Rh(I) and Rh(II) catalysts are both well-known in serving this purpose, it has been recently well documented that under chelation assistance, Rh(III) complexes can efficiently catalyze the activation of sp^2 C−H bonds, leading to diversified couplings of arenes and olefins with various unsaturated substrates.[2] On the other hand, transition metal-catalyzed redox-neutral insertion of an aromatic C−H bond into an electron-deficient π bond is highly attractive because this method represents an atom-economic strategy to construct C−C bonds without using any oxidant.[3] Recent studies have established that Rh(III) complexes are also highly active in catalyzing the addition of sp^2 C−H bonds into unsaturated polar groups, such as imines,[4] aldehydes,[5] isocyanates,[6a] and isocyanides.[6b] However, the insertion of aromatic C−H bonds into carbenoids is still underexplored and is mostly limited to intramolecular reactions.[7] So far only very few systems of intermolecular carbeninod insertion into *heteroaromatic* C−H bonds have been achieved, probably because of low reactivity and poor regioselectivity.[8] Recently, Wang and Miura independently reported the coupling of azoles with *N*-tosylhydrazones.[9] In 2010, Yu demonstrated the Ru(II)-catalyzed functionalization of indoles by α-aryldiazoesters with excellent regioselectivity.[10] However, the intermolecular carbenoid insertion into *aromatic* C−H bonds proved to be even more challenging. In 2009, Jung reported the first Rh(II)-catalyzed intermolecular functionalization of phenyl C−H bonds using diazo compounds, where only two examples were provided and a large excess of the arene substrate was required.[11] Significant progress was made by Yu's group, who elegantly achieved Cp*Rh(III)-catalyzed intermolecular insertion of aromatic C−H bonds into α-diazomalonates.[12] At the same time, a similar work was underway in our laboratories.

Although Yu's group accomplished the C−C coupling of diazomalonates with arenes bearing four classes of directing groups (ketone oxime, amine, acid, and pyridine),[12] the scope of this coupling needs expansion and the selectivity of this type of coupling needs further exploration. Herein, we report our findings on the intermolecular alkylation of arenes using α-diazocarbonyl compounds.

RESULTS AND DISCUSSION

We initiated our studies with the coupling of *N*-phenylpyrazole and ethyl diazomelonate using $[Cp^*RhCl_2]_2$ as a catalyst in the presence a silver salt additive (Table 1). It was found that while almost all the Ag(I) additives examined can effect this coupling, those with a less coordinating anion such as $AgSbF_6$ proved to be most effective when EtOH was designated as the solvent. Reactions performed in other solvents such as DCE and THF gave slightly lower yield of **3a**, but essentially no desired reaction occurred when MeCN was used (Table 1, entry 15). A rather low loading (1 mol %) of the rhodium catalyst was necessary when the temperature was increased to 75 °C (entry 16). Thus the optimal yield was obtained when a $[Cp^*RhCl_2]_2/AgSbF_6$ (1 mol %/5 mol %) catalyst was applied, and product **3a** was obtained in 95% HPLC yield (92% isolated yield). This observation is in contrast to those reported by Yu in the reaction of acetophenone *O*-methyl oxime and dimethyl diazomelonate,[12] where using AgOAc as an additive, EtOH proved to be an inappropriate solvent because of the undesired insertion of the carbenoid into EtO−H bond, instead of the C(aryl)−H bond. These results indicate that a combination of the silver salt and the solvent plays a vital role for an efficient coupling.

Under the optimal conditions, the scope of the dizao substrate was next examined. A series of diazomalonates

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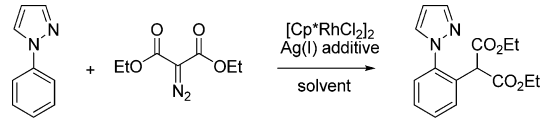
Table 1. Optimization Studies[a]



1a 2a 3a

entry	$[Cp^*RhCl_2]_2$ (mol %)	additive (mol %)	solvent	T (°C)	yield (%, HPLC)[b]
1	4	AgOAc (20)	EtOH	75	87
2	4	AgF (20)	EtOH	75	58
3	4	$AgSbF_6$ (20)	EtOH	75	94
4	4	$AgNO_3$ (20)	EtOH	75	81
5	4	AgOTf (20)	EtOH	75	85
6	4	$AgNTf_2$ (20)	EtOH	75	89
7	4	$AgPF_6$ (20)	EtOH	75	89
8	2	$AgSbF_6$ (10)	MeOH	60	85
9	2	$AgSbF_6$ (10)	EtOH	60	95
10	2	$AgSbF_6$ (10)	^{t}BuOH	60	13
11	2	$AgSbF_6$ (10)	THF	60	84
12	2	$AgSbF_6$ (10)	DCE	60	86
13	2	$AgSbF_6$ (10)	DMF	60	17
14	2	$AgSbF_6$ (10)	toluene	60	17
15	2	$AgSbF_6$ (10)	CH_3CN	60	3
16	1	$AgSbF_6$ (5)	EtOH	75	95

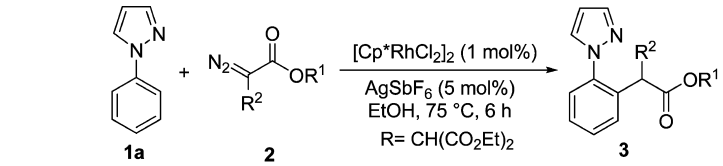
[a]Condition: **1a** (0.2 mmol), **2a** (1.2 equiv), $[Cp^*RhCl_2]_2$, Ag(I) additive in solvent (2 mL), 6 h. [b]HPLC yield.

smoothly coupled with **1a** in yield ranging from 52 to 92% in EtOH or DCE. In the case of methyl, benzyl, and isopropyl esters, DCE was used to avoid any transesterification product (Table 2, **3a**–**3d**). Besides these diazomalonates, high coupling efficiency was also achieved when one of the ester groups was replaced by another electron-withdrawing group such as phosphonate and sulfonyl (**3e**, **3f**), although a diminished yield was obtained when an amide or benzoyl group was used (**3g** and **3h**).

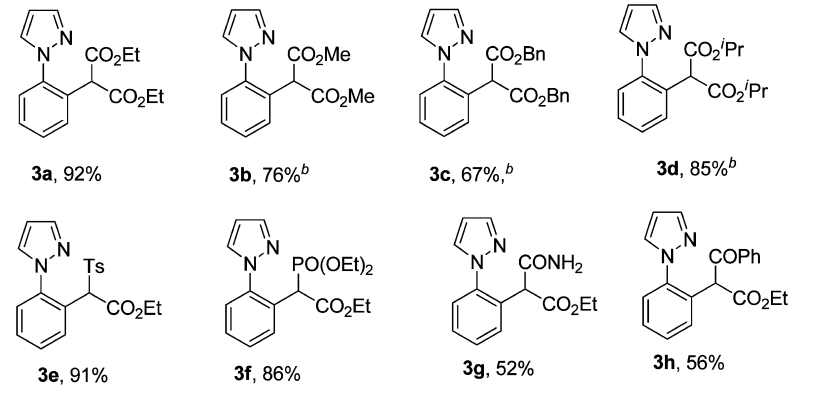
The scope of the pyrazole substrate was next assessed in the coupling with diethyl diazomelonate under our standard conditions (Table 3). Different electron-donating, -withdrawing, and halogen substitutents in the pyrazole ring were tolerated, and the coupling products were isolated in 72–94% yield, indicative of good functional group compatibility and tolerance of steric hindrance of the directing group (**3i**–**3l**). Substitutents in the phenyl ring were next examined. Both donating (**3m**–**3r**) and withdrawing groups (**3s**–**3v**) were allowed, and the expected products were isolated in good to high yield. In particular, an unprotected *para* amino-functionalized *N*-phenylpyrazole can be alkylated in high efficiency, and product **3r** was isolated in 88% yield. All the *ortho*-substituted phenylpyrazoles reacted with high efficiency, with no detrimental steric effect of these *ortho* substituents (**3m**, **3p**, **3s**, and **3w**). When a *meta*-methyl-substituted substrate was applied, the coupling occurred selectively at the less congested position (**3n**). It is noteworthy that no dialkylation product was detected for all the *N*-phenylpyrazoles examined.

We next investigated the reactivity of 2-arylpyrimidines for this reaction (Table 4). To avoid any complication of dialkylations, an *o*-Me blocking group was introduced into the phenyl ring (**4a**). The standard conditions proved well applicable for the coupling of **4a** with a series of activated diazo compounds to readily give the corresponding coupling product in high yield (**5a**–**5e**), and the yields are generally higher than those for *N*-phenylpyrazoles. These results indicated that steric hindrance of the *o*-Me group posed no issue. Besides an *o*-Me, other *ortho* substituents such as OMe, F, and Cl groups all gave equally good results (**5f**–**5h**). Selective dialkylation can be readily achieved for arenes without an *ortho* blocking group when an excess of diethyl diazomelonate was introduced. Thus 2-phenylpyrimidines with a broad scope of electron-donating and -withdrawing *para* substitutents underwent dialkylation in 78–99% yield (**5k**–**5o**). This high-yielding coupling also applies to a *meta*-Cl substituted substrate (**5p**), indicative of the tolerance of a halogen group. Besides dialkylation, monoalkylation of simple 2-phenylpyrimidine has also been achieved when the $AgSbF_6$ additive was replaced by AgF, under which conditions the monoalkylation product (**5i**) was isolated

Table 2. Rh(III)-Catalyzed Alkylation of *N*-Phenylpyrazole (1a) with α-Diazocarbonyl Compounds[a]



1a 2 3



3a, 92% **3b**, 76%[b] **3c**, 67%,[b] **3d**, 85%[b]

3e, 91% **3f**, 86% **3g**, 52% **3h**, 56%

[a]Conditions: **1a** (0.2 mmol), **2** (0.24 mmol), $[Cp^*RhCl_2]_2$ (1 mol %), $AgSbF_6$ (5 mol %), EtOH (2 mL), 75 °C, 6 h. [b]In DCE (2 mL), 75 °C, 24 h.

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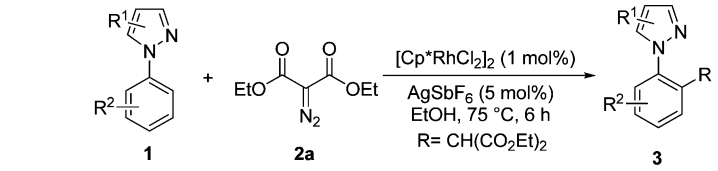
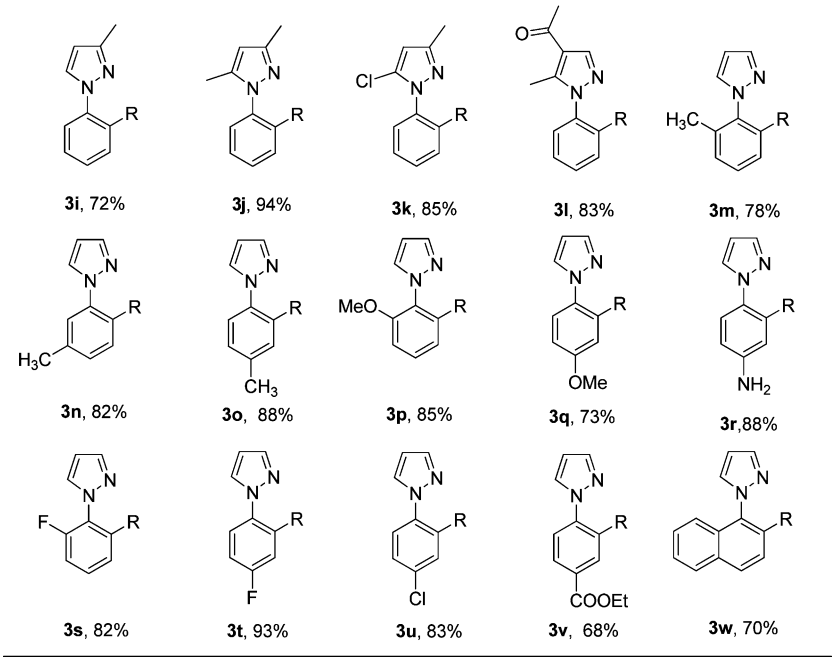
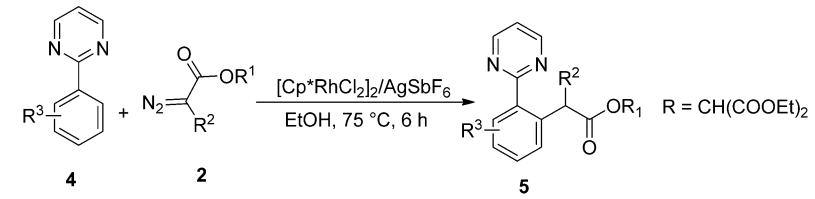
Table 3. Rh(III)-Catalyzed Alkylation of *N*-Arylpyrazoles with Diethyl 2-Diazomalonate (2a)[a]

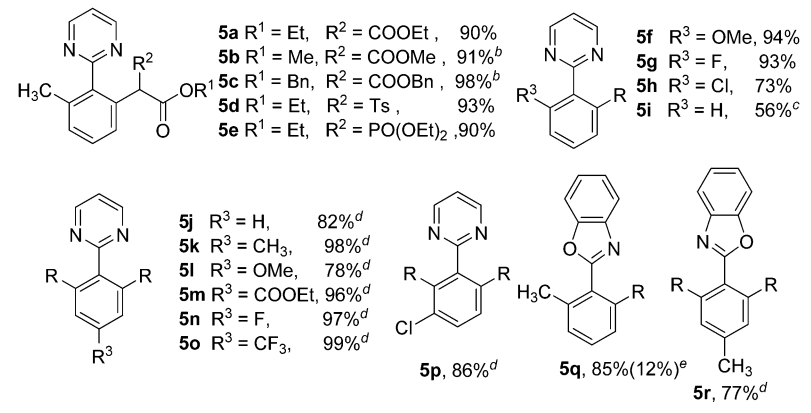




[a]Conditions: **1** (0.2 mmol), **2a** (0.24 mmol), $[Cp^*RhCl_2]_2$ (1 mol %), $AgSbF_6$ (5 mol %), EtOH (2 mL), 75 °C, 6 h.

Table 4. Rh(III)-Catalyzed Mono- and Dialkylation of 2-Arylpyrimidines[a]





[a]Conditions: **4** (0.2 mmol), **2** (1.2 equiv), $[Cp^*RhCl_2]_2$ (1 mol %), $AgSbF_6$ (5 mol %), EtOH (2 mL), 75 °C, 6 h. [b]In DCE (2 mL), 75 °C, 24 h. [c]AgF (5 mol %). [d]**4** (0.2 mmol), **2** (3 equiv), $[Cp^*RhCl_2]_2$ (2 mol %), $AgSbF_6$ (10 mol %), EtOH (2 mL), 75 °C, 6 h. [e]Value in parentheses correspond to HPLC yield for 10 h at 75 °C in MeOH using $[Cp^*RhCl_2]_2$ (2 mol %), AgOAc (10 mol %).

in 66% as a major product, together with the minor dialkylation product (30% yield). We noted that the reactions of the pyrimidine substrates with the methyl or benzyl ester of α-diazomalonates proceeded quickly in EtOH, but there were some transesterification byproducts, which were difficult to separate from the desired product. Therefore, 1,2-dichloro-

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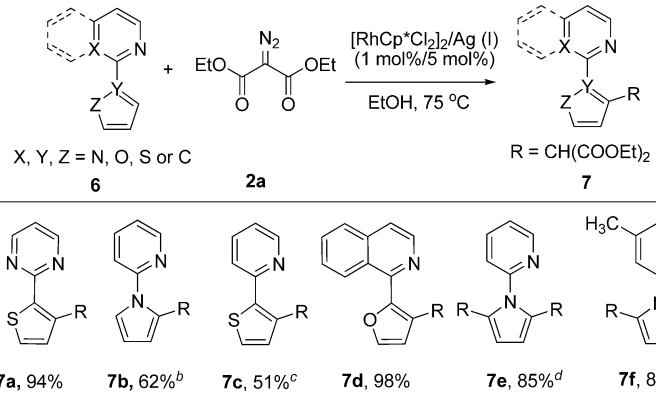
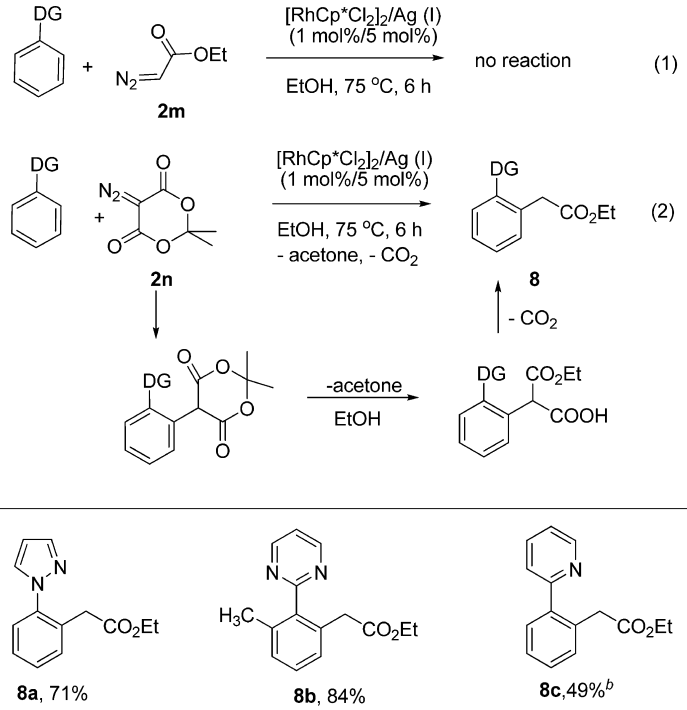
Table 5. Rh(III)-Catalyzed Alkylation of Heteroaromatics with Diethyl 2-Diazomalonate (2a)[a]



[a]Conditions: **6** (0.2 mmol), **2a** (1.2 equiv), $[Cp^*RhCl_2]_2$ (1 mol %), $AgSbF_6$ (5 mol %), EtOH (2 mL), 75 °C, 6 h. [b]AgF (5 mol %). [c]48 h. [d]**2a** (3 equiv), $[Cp^*RhCl_2]_2$ (2 mol %), $AgSbF_6$ (10 mol %).

Scheme 1. Rh(III)-Catalyzed Alkylation of Arenes with the Diazo Derivative of Meldrum's Acid 2i[a]



[a]Conditions: arene (0.2 mmol), **2n** (1.2 equiv), $[Cp^*RhCl_2]_2$ (1 mol %), $AgSbF_6$ (5 mol %), EtOH (2 mL), 75 °C, 6 h. [b]AgF (5 mol %).

ethane (DCE) was chosen as the solvent (Table 4, **5b**, **5c**). In addition, the smooth *ortho*-alkylation also can be carried out using a related benzoxazole directing group (**5q**, **5r**). In comparison, Yu's conditions ($[Cp^*RhCl_2]_2$/AgOAc) turned out to be inapplicable for these benzoxazole substrates, under which only traces of the product could be detected (**5q**).

The arene is not limited to a benzene platform, and heteroarenes such as furans, thiophenes and pyroles can also undergo the same insertion into α-diazomalonates to afford to the desired alkylated product in good to high yields (Table 5). Analogously, dialkylation could also take place for pyrrole rings without any *ortho* blocking group.

In contrast to the efficient coupling using these diazo compounds activated by two withdrawing groups, however, no desired reaction occurred when simple ethyl diazoacetate (**2m**) was used (Scheme 1, eq 1), suggesting that the two electron-withdrawing groups are crucial to ensure high reactivity. Interestingly, when the diazo derivative of Meldrum's acid (**2n**) was coupled with *N*-phenylpyrazole under the standard conditions, product **8a** was isolated in 71% yield as a result of C−C coupling in tandem with ethanolysis of the acetal functionality followed by decarboxyation (**8a**). The successful isolation of products **8a**−**8c** offers an applicable path to circumvent the poor reactivity of ethyl diazoacetate (**2m**).

To probe the C−H activation step in the reaction of *N*-phenylpyrazole (**1a**) and diethyl diazomelonate, KIE was measured using an equimolar mixture of **1a** and **1a**-d_5. ^{1}H NMR analysis of the product mixture gave KIE (k_H/k_D) = 4.0. This large value suggests that cleavage of the C−H bond (cyclometalation) is involved in the turnover-limiting step.

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Despite this information, it remains a question whether the reaction proceeds via a Rh-carbene pathway or via a S_N^2-like denitrogenative pathway with concomitant Rh−C(aryl) bond cleavage.[12]

CONCLUSION

We have extended the scope of rhodium(III)-catalyzed azacycle-directed C−H activation of (hetero)arenes and coupling with activated diazo esters, leading to the alkylation of C−H bonds under mild conditions. A broad scope of (hetero)aromatics assisted by a directing group (pyrazole, pyrimidine, and oxazole) has been alkylated with good functional group compatibility. Silver additive played an important role, and both $AgSbF_6$ and AgF can be used as an optimal additive, depending on the entity of the substrate. Future work on C−H activation/coupling with other electrophilic unsaturated substrates is underway in our laboratory.

EXPERIMENTAL SECTION

General Information. Commercially available reagents were used without further purification. Solvents were treated prior to use according to the standard methods. All reactions were carried out under an atmosphere of argon using standard Schlenk techniques. NMR spectra were recorded at room temperature in $CDCl_3$ on 400 or 500 MHz spectrometers. Column chromatography was performed on silica gel 300−400 mesh. Mixture of petroleum ether (boiling rang 60−90 °C) and ethyl acetate were used as an eluant. When solvent gradients were used, the increase in polarity was made from neat petroleum ether to mixtures of ethyl acetate/petroleum ether, with ethyl acetate being increased by 10% each time until the isolation of the product.

General Procedure for the Rh(III)-Catalyzed *ortho* C−H Functionalizations Arenes with Diazo Compounds (1a as an example). A dried 10 mL Schlenk tube equipped with a magnetic stirrer was charged with 1-phenyl-1*H*-pyrazole **1a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (1 mg, 2 μmol), $AgSbF_6$ (3 mg, 10 μmol), and EtOH (2 mL) under Ar. After the reaction mixture was stirred at room temperature for 1 h, diazo compound **2a** (0.24 mmol) was then added in one pot, and the mixture was stirred at 75 °C for 6 h. The reaction mixture was cooled to room temperature and then filtered through a pad of Celite and concentrated under reduced pressure. The residue was then charged on silica gel column and eluted with a mixture of ethyl acetate/petroleum ether (1:8) to give the desired product **3a**. (All the following reactions were carried out using this procedure unless otherwise indicated.)

*Diethyl 2-(2-(1H-pyrazol-1-yl)phenyl)malonate (**3a**).* Colorless oil 56 mg, 92% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.68−7.59 (m, 2H), 7.47−7.36 (m, 2H), 7.33 (d, *J* = 7.8 Hz, 1H), 6.43 (d, *J* = 1.5 Hz, 1H), 4.89 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 4H), 1.23 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 140.9, 139.6, 130.8, 130.1, 128.9, 128.7, 128.4, 125.8, 106.7, 61.7, 52.6, 13.8; HRMS (ESI−Orbitrap) calcd for $C_{16}H_{18}N_2O_4H^+$ [M + H] 303.1339, found 303.1332.

*Dimethyl 2-(2-(1H-pyrazol-1-yl)phenyl)malonate (**3b**).* Following the general procedure except DCE as solvent and reacted for 24 h. Colorless oil 42 mg, 76% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 1.5 Hz, 1H), 7.67−7.64 (m, 1H), 7.63−7.60 (m, 1H), 7.47−7.39 (m, 2H), 7.35−7.32 (m, 1H), 6.46−6.43 (m, 1H), 4.96 (s, 1H), 3.72 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 141.2, 139.8, 131.1, 130.4, 129.1, 128.9, 128.8, 126.1, 107.0, 53.0, 52.4; HRMS (ESI−TOF) calcd for $C_{14}H_{14}N_2O_4Na^+$ [M + Na] 297.0846, found 297.0854.

*Dibenzyl 2-(2-(1H-pyrazol-1-yl)phenyl)malonate (**3c**).* Following the general procedure except DCE as solvent and reacted for 24 h. Colorless oil 57 mg, 67% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 1.8, 0.4 Hz, 1H), 7.60−7.57 (m, 2H), 7.45−7.38 (m, 2H), 7.36−7.31 (m, 7H), 7.30−7.26 (m, 4H), 6.42−6.38 (m, 1H), 5.19 (q, *J* = 12.4 Hz, 4H), 5.08 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 141.2, 139.9, 135.4, 131.0, 130.5, 129.1, 128.8, 128.6, 128.6, 128.4, 128.3, 125.9, 107.0, 67.5, 53.0; HRMS (ESI−TOF) calcd for $C_{26}H_{22}N_2O_4Na^+$ [M + Na] 449.1472, found 449.1471.

*Diisopropyl 2-(2-(1H-pyrazol-1-yl)phenyl)malonate (**3d**).* Following the general procedure except DCE as solvent and reacted for 24 h. Colorless oil 56 mg, 85% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72−7.68 (m, 1H), 7.65 (dd, *J* = 2.4, 0.5 Hz, 1H), 7.61 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.46−7.37 (m, 2H), 7.36−7.31 (m, 1H), 6.45−6.41 (m, 1H), 5.10−5.01 (m, 2H), 4.80 (s, 1H), 1.24 (d, *J* = 6.3 Hz, 6H), 1.21 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 141.0, 140.0, 131.1, 130.3, 129.4, 128.8, 128.6, 126.1, 106.9, 69.5, 53.3, 21.6; HRMS (ESI−TOF) calcd for $C_{18}H_{22}N_2O_4Na^+$ [M + Na] 353.1472, found 353.1480.

*Ethyl 2-(2-(1H-pyrazol-1-yl)phenyl)-2-tosylacetate (**3e**).* Colorless oil 70 mg, 91% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−7.99 (m, 1H), 7.64 (s, 1H), 7.40 (dd, *J* = 5.7, 3.5 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 3H), 7.22−7.16 (m, 1H), 7.13 (d, *J* = 8.1 Hz, 2H), 6.33 (s, 1H), 5.84 (s, 1H), 4.22−4.04 (m, 2H), 2.33 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 145.1, 141.3, 140.6, 134.8, 131.7, 131.4, 130.3, 129.4, 129.1, 128.3, 125.9, 123.8, 106.9, 67.8, 62.6, 21.6, 13.8; HRMS (ESI−Orbitrap) calcd for $C_{20}H_{20}N_2O_4SH^+$ [M + H] 385.1217, found 385.1208.

*Ethyl 2-(2-(1H-pyrazol-1-yl)phenyl)-2-(diethoxyphosphoryl) acetate (**3f**).* Colorless oil 63 mg, 86% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.70 (dd, *J* = 5.5, 1.9 Hz, 2H), 7.46−7.33 (m, 2H), 7.30 (d, *J* = 7.7 Hz, 1H), 6.42 (t, *J* = 2.1 Hz, 1H), 4.63 (d, *J* = 24.7 Hz, 1H), 4.16 (dd, *J* = 13.9, 7.0 Hz, 2H), 4.07−3.99 (m, 2H), 3.99−3.87 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 6H), 1.12 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3 (d, *J* = 3.9 Hz), 141.1, 139.9 (d, *J* = 8.5 Hz), 131.5, 131.4 (d, *J* = 4.7 Hz), 128.6 (d, *J* = 2.6 Hz), 128.5 (d, *J* = 2.6 Hz), 127.3 (d, *J* = 6.9 Hz), 126.5 (d, *J* = 1.9 Hz), 106.8, 63.2 (dd, *J* = 10.1, 6.8 Hz), 62.0, 45.3 (d, *J* = 134.8 Hz), 16.3 (dd, *J* = 12.6, 6.1 Hz), 14.0; HRMS (ESI−Orbitrap) calcd for $C_{17}H_{23}N_2O_5PH^+$ [M + H] 367.1417, found 367.1404.

*Ethyl 2-(2-(1H-pyrazol-1-yl)phenyl)-3-amino-3-oxopropanoate (**3g**).* Colorless oil 28 mg, 52% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.94 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.79−7.75 (m, 1H), 7.73 (dd, *J* = 2.4, 0.5 Hz, 1H), 7.47 (td, *J* = 7.7, 1.4 Hz, 1H), 7.41 (td, *J* = 7.7, 1.6 Hz, 1H), 7.27 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.52−6.48 (m, 1H), 5.51 (s, 1H), 4.86 (s, 1H), 4.24−4.09 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 168.5, 141.1, 138.9, 131.7, 131.5, 129.7, 128.9, 128.8, 125.6, 107.4, 61.8, 51.7, 14.1; HRMS (ESI−TOF) calcd for $C_{14}H_{15}N_3O_3Na^+$ [M + Na] 296.1006, found 296.1004.

*Ethyl 2-(2-(1H-pyrazol-1-yl)phenyl)-3-oxo-3-phenylpropanoate and (E)-Ethyl 2-(2-(1H-pyrazol-1-yl)phenyl)-3-hydroxy-3-phenylacrylate (4:1) (**3h**).* Colorless oil 37 mg, 56% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.56 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.73 (s, 1H), 7.60 (s, 1H), 7.46 (d, *J* = 6.8 Hz, 2H), 7.34 (dd, *J* = 9.3, 5.9 Hz, 5H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.18−7.09 (m, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 6.45 (s, 1H), 6.30 (s, 1H), 5.99 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.04 (dd, *J* = 7.1, 3.7 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 172.6, 171.2, 168.9, 141.3 140.4, 139.4, 135.6, 134.2, 133.6, 131.1, 130.9, 130.0, 129.6, 129.4, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 127.8, 127.3, 126.2, 125.0, 107.1, 106.6, 61.8, 61.2, 55.2, 14.1; HRMS (ESI−TOF) calcd for $C_{20}H_{18}N_2O_3Na^+$ [M + Na] 357.1215, found 357.1203.

*Diethyl 2-(2-(3-methyl-1H-pyrazol-1-yl)phenyl)malonate (**3i**).* Colorless oil 46 mg, 72% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60−7.56 (m, 1H), 7.54 (d, *J* = 2.2 Hz, 1H), 7.40−7.36 (m, 2H), 7.32−7.29 (m, 1H), 6.20 (d, *J* = 2.2 Hz, 1H), 4.91 (s, 1H), 4.19 (qd, *J* = 7.1, 0.5 Hz, 4H), 2.32 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 150.3, 139.9, 131.6, 130.3, 128.9, 128.8, 128.2, 125.8, 106.8, 61.8, 53.1, 14.1, 13.6; HRMS (ESI−TOF) calcd for $C_{17}H_{20}N_2O_4Na^+$ [M + Na] 339.1321, found 339.1331.

*Diethyl 2-(2-(3,5-dimethyl-1H-pyrazol-1-yl)phenyl)malonate (**3j**).* White solid 62 mg, mp 55−56 °C, 94% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.45 (td, *J* = 7.6, 1.4 Hz, 1H), 7.40 (td, *J* = 7.6, 1.6 Hz, 1H), 7.24 (dd, *J* = 7.7, 1.4 Hz, 1H), 5.96 (s, 1H), 4.48 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 4H), 2.26 (s, 3H), 2.06 (d, *J* =

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0.4 Hz, 3H), 1.22 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 149.3, 141.1, 138.8, 132.0, 130.20, 129.2, 128.7, 127.8, 105.8, 61.8, 52.6, 14.1, 13.6, 11.4; HRMS (ESI-Orbitrap) calcd for $C_{18}H_{22}N_2O_4H^+$ [M + H] 331.1652, found 331.1654.

*Diethyl 2-(2-(5-chloro-3-methyl-1H-pyrazol-1-yl)phenyl)-malonate (**3k**).* Colorless oil 60 mg, 85% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, J = 7.9, 1.5 Hz, 1H), 7.46 (dd, J = 7.7, 1.4 Hz, 1H), 7.40 (td, J = 7.7, 1.5 Hz, 1H), 7.28 (dd, J = 7.8, 1.3 Hz, 1H), 6.15 (s, 1H), 4.49 (s, 1H), 4.15 (q, J = 7.1 Hz, 4H), 2.26 (s, 3H), 1.20 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 150.3, 137.0, 131.5, 130.4, 129.7, 129.0, 128.6, 128.1, 105.3, 61.9, 52.6, 14.1, 14.0; HRMS (ESI−TOF) calcd for $C_{17}H_{19}ClN_2O_4Na^+$ [M + Na] 373.0931, found 373.0944.

*Diethyl 2-(2-(4-acetyl-5-methyl-1H-pyrazol-1-yl)phenyl)-malonate (**3l**).* Colorless oil 59 mg, 83% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.69 (dd, J = 7.9, 1.4 Hz, 1H), 7.53 (td, J = 7.7, 1.4 Hz, 1H), 7.45 (td, J = 7.7, 1.5 Hz, 1H), 7.21 (dd, J = 7.8, 1.3 Hz, 1H), 4.34 (s, 1H), 4.21−4.07 (m, 4H), 2.50−2.44 (m, 3H), 2.35 (s, 3H), 1.19 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.3, 167.5, 144.8, 142.3, 137.4, 131.5, 130.6, 130.2, 129.0, 127.6, 120.7, 62.1, 52.3, 28.7, 14.0, 11.7; HRMS (ESI−TOF) calcd for $C_{19}H_{22}N_2O_5Na^+$ [M + Na] 381.1426, found 381.1418.

*Diethyl 2-(3-methyl-2-(1H-pyrazol-1-yl)phenyl)malonate (**3m**).* Colorless oil 49 mg, 78% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.52 (d, J = 9.9 Hz, 2H), 7.47 (d, J = 7.4 Hz, 1H), 7.36 (d, J = 7.3 Hz, 1H), 6.53 (s, 1H), 4.35−4.15 (m, 5H), 2.08 (s, 3H), 1.29 (t, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 140.9, 139.2, 136.7, 131.8, 131.6, 130.6, 129.4, 127.2, 106.5, 61.9, 52.6, 17.5, 14.1; HRMS (ESI−Orbitrap) calcd for $C_{17}H_{20}N_2O_4H^+$ [M + H] 317.1496, found 317.1461.

*Diethyl 2-(4-methyl-2-(1H-pyrazol-1-yl)phenyl)malonate (**3n**).* White solid 52 mg, mp 91−93 °C, 82% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 0.8 Hz, 1H), 7.65 (d, J = 2.4 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 7.17 (d, J = 0.6 Hz, 1H), 6.43 (t, J = 2.0 Hz, 1H), 4.82 (s, 1H), 4.19 (q, J = 7.1 Hz, 4H), 2.38 (s, 3H), 1.23 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 141.0, 139.7, 139.2, 131.1, 130.2, 129.5, 126.8, 126.1, 106.8, 61.9, 52.5, 21.0, 14.1; HRMS (ESI−TOF) calcd for $C_{17}H_{20}N_2O_4Na^+$ [M + Na] 339.1315, found 339.1329.

*Diethyl 2-(5-methyl-2-(1H-pyrazol-1-yl)phenyl)malonate (**3o**).* Colorless oil 56 mg, 88% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 1.5 Hz, 1H), 7.60 (d, J = 2.3 Hz, 1H), 7.40 (s, 1H), 7.20 (d, J = 1.9 Hz, 2H), 6.43−6.38 (m, 1H), 4.83 (s, 1H), 4.18 (qd, J = 7.1, 2.1 Hz, 4H), 2.40 (s, 3H), 1.23 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 140.9, 138.7, 137.5, 131.1, 130.6, 129.6, 128.8, 125.9, 106.7, 61.8, 52.6, 21.3, 14.0; HRMS (ESI−TOF) calcd for $C_{17}H_{20}N_2O_4Na^+$ [M + Na] 339.1315, found 339.1327.

*Diethyl 2-(3-methoxy-2-(1H-pyrazol-1-yl)phenyl)malonate (**3p**).* White solid 56 mg, mp 91−93 °C, 85% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 1.5 Hz, 1H), 7.53 (d, J = 2.1 Hz, 1H), 7.42 (t, J = 8.2 Hz, 1H), 7.19 (dd, J = 8.0, 1.1 Hz, 1H), 7.00 (dd, J = 8.4, 1.0 Hz, 1H), 6.47−6.38 (m, 1H), 4.42 (s, 1H), 4.17 (q, J = 7.1 Hz, 4H), 3.75 (s, 3H), 1.22 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 155.2, 140.8, 132.9, 132.8, 130.0, 129.2, 121.4, 111.8, 106.2, 61.9, 56.2, 52.8, 14.1; HRMS (ESI−TOF) calcd for $C_{17}H_{20}N_2O_5Na^+$ [M + Na] 355.1264, found 355.1274.

*Diethyl 2-(5-methoxy-2-(1H-pyrazol-1-yl)phenyl)malonate (**3q**).* Colorless oil 48 mg, 73% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71−7.64 (m, 1H), 7.56 (dd, J = 2.3, 0.4 Hz, 1H), 7.24 (d, J = 8.7 Hz, 1H), 7.15 (d, J = 2.8 Hz, 1H), 6.91 (dd, J = 8.7, 2.9 Hz, 1H), 6.40 (t, J = 2.1 Hz, 1H), 4.72 (s, 1H), 4.18 (qd, J = 7.1, 1.9 Hz, 4H), 3.83 (s, 3H), 1.23 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 159.6, 140.8, 133.2, 131.4, 130.7, 127.5, 115.2, 114.3, 106.6, 61.9, 55.7, 52.7, 14.1; HRMS (ESI−TOF) calcd for $C_{17}H_{20}N_2O_5Na^+$ [M + Na] 355.1270, found 355.1285.

*Diethyl 2-(5-amino-2-(1H-pyrazol-1-yl)phenyl)malonate (**3r**).* Colorless oil 56 mg, 88% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, J = 1.8, 0.4 Hz, 1H), 7.52 (dd, J = 2.3, 0.5 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 2.6 Hz, 1H), 6.63 (dd, J = 8.4, 2.6 Hz, 1H), 6.39−6.36 (m, 1H), 4.61 (s, 1H), 4.17 (qd, J = 3.6, 1.1 Hz, 4H), 3.99−3.61 (m, 2H), 1.23−1.20 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 147.2, 140.6, 131.4, 130.3, 127.5, 115.6, 115.2, 114.9, 106.3, 61.9, 52.4, 14.1; HRMS (ESI−Orbitrap) calcd for $C_{16}H_{19}N_3O_4H^+$ [M + H] 318.1454, found 318.1447.

*Diethyl 2-(3-fluoro-2-(1H-pyrazol-1-yl)phenyl)malonate (**3s**).* Colorless oil 52 mg, 82% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 1.5 Hz, 1H), 7.61 (t, J = 2.0 Hz, 1H), 7.46−7.39 (m, 2H), 7.21 (ddd, J = 9.6, 6.8, 2.9 Hz, 1H), 6.49−6.45 (m, 1H), 4.66 (s, 1H), 4.19 (q, J = 7.1 Hz, 4H), 1.23 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 157.3 (d, J = 251.4 Hz), 141.5, 133.0, 132.8 (d, J = 1.9 Hz), 130.0 (d, J = 8.4 Hz), 128.4 (d, J = 13.0 Hz), 125.5 (d, J = 3.6 Hz), 116.2 (d, J = 20.3 Hz), 107.0, 62.1, 52.7 (d, J = 1.9 Hz), 14.1; HRMS (ESI−TOF) calcd for $C_{16}H_{17}FN_2O_4Na^+$ [M + Na] 343.1065, found 343.1070.

*Diethyl 2-(5-fluoro-2-(1H-pyrazol-1-yl)phenyl)malonate (**3t**).* Colorless oil 60 mg, 93% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 1.5 Hz, 1H), 7.62−7.59 (m, 1H), 7.39 (dd, J = 9.4, 2.9 Hz, 1H), 7.31 (dd, J = 8.7, 5.2 Hz, 1H), 7.11 (ddd, J = 8.7, 7.6, 2.9 Hz, 1H), 6.45−6.42 (m, 1H), 4.78 (d, J = 0.8 Hz, 1H), 4.24−4.14 (m, 4H), 1.24 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 162.1 (d, J = 248.7 Hz), 141.3, 136.2 (d, J = 2.9 Hz), 131.6 (d, J = 8.8 Hz), 131.3, 128.0 (d, J = 8.9 Hz), 117.4 (d, J = 24.5 Hz), 115.9 (d, J = 22.8 Hz), 107.1, 62.2, 52.7, 14.0; HRMS (ESI−TOF) calcd for $C_{16}H_{17}FN_2O_4Na^+$ [M + Na] 343.1065, found 343.1082.

*Diethyl 2-(5-chloro-2-(1H-pyrazol-1-yl)phenyl)malonate (**3u**).* Colorless oil 60 mg, 83% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74−7.70 (m, 1H), 7.66−7.61 (m, 2H), 7.39 (dd, J = 8.5, 2.4 Hz, 1H), 7.30−7.25 (m, 1H), 6.48−6.41 (m, 1H), 4.88 (s, 1H), 4.25−4.17 (m, 4H), 1.25 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 141.4, 138.5, 134.4, 131.1, 130.7, 130.6, 129.1, 127.2, 107.3, 62.2, 52.6, 14.1; HRMS (ESI−TOF) calcd for $C_{16}H_{17}ClN_2O_4Na^+$ [M + Na] 359.0769, found 359.0778.

*Diethyl 2-(5-(ethoxycarbonyl)-2-(1H-pyrazol-1-yl)phenyl) malonate (**3v**).* Colorless oil 51 mg, 68% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.08 (d, J = 8.3 Hz, 1H), 7.72 (s, 2H), 7.40 (d, J = 8.1 Hz, 1H), 6.46 (s, 1H), 5.09 (s, 1H), 4.46−4.31 (m, 2H), 4.21 (q, J = 6.9 Hz, 4H), 1.38 (t, J = 7.0 Hz, 3H), 1.24 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 165.4, 143.0, 141.7, 132.1, 130.9, 130.3, 130.2, 128.8, 125.4, 107.6, 62.1, 61.4, 53.2, 14.4, 14.1; HRMS (ESI−Orbitrap) calcd for $C_{19}H_{22}N_2O_6H^+$ [M + H] 375.1551, found 375.1554.

*Diethyl 2-(1-(1H-pyrazol-1-yl)naphthalen-2-yl)malonate (**3w**).* Colorless oil 49 mg, 70% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 8.7 Hz, 1H), 7.91−7.85 (m, 2H), 7.76 (d, J = 8.7 Hz, 1H), 7.67 (dd, J = 2.3, 0.5 Hz, 1H), 7.52 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.44 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.15 (dd, J = 8.5, 0.8 Hz, 1H), 6.60−6.56 (m, 1H), 4.46 (s, 1H), 4.26−4.15 (m, 4H), 1.24 (t, J = 11.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 167.7, 141.2, 136.4, 133.6, 133.1, 131.3, 129.7, 129.0, 127.8, 127.7, 127.1, 126.1, 123.3, 106.7, 77.4, 77.2, 76.9, 62.0, 52.8, 14.1.; HRMS (ESI−TOF) calcd for $C_{20}H_{20}N_2O_4Na^+$ [M + Na] 375.1315, found 375.1308.

*Diethyl 2-(3-methyl-2-(pyrimidin-2-yl)phenyl)malonate (**5a**).* Colorless oil 59 mg, 90% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (d, J = 4.9 Hz, 2H), 7.38 (d, J = 0.4 Hz, 1H), 7.33 (t, J = 7.7 Hz, 1H), 7.27−7.21 (m, 2H), 4.43 (s, 1H), 4.14 (qd, J = 7.1, 3.2 Hz, 4H), 2.13 (s, 3H), 1.18 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 167.1, 157.1, 139.1, 136.4, 131.3, 130.2, 128.8, 126.7, 119.2, 61.6, 55.3, 20.4, 14.0; HRMS (ESI−TOF) calcd for $C_{18}H_{20}N_2O_4Na^+$ [M + Na] 351.1315, found 351.1313.

*Dimethyl 2-(3-methyl-2-(pyrimidin-2-yl)phenyl)malonate (**5b**).* Following the general procedure except DCE as solvent and reacted for 24 h. White solid 55 mg, mp 107−108 °C, 91% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (d, J = 4.9 Hz, 2H), 7.42−7.30 (m, 2H), 7.26 (dd, J = 8.0, 3.1 Hz, 2H), 4.49 (s, 1H), 3.67 (s, 6H), 2.13 (s, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 167.1, 157.2, 139.1, 136.6, 131.0, 130.4, 129.0, 126.8, 119.3, 54.9, 52.8, 20.4.; HRMS (ESI−Orbitrap) calcd for $C_{16}H_{16}N_2O_4H^+$ [M + H] 301.1183, found 301.1178.

*Dibenzyl 2-(3-methyl-2-(pyrimidin-2-yl)phenyl)malonate (**5c**).* Following the general procedure except DCE as solvent and reacted

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for 24 h. Colorless oil 89 mg, 98% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J = 4.9 Hz, 2H), 7.35 (dd, J = 7.7, 0.9 Hz, 1H), 7.33−7.28 (m, 7H), 7.27−7.23 (m, 5H), 7.16 (t, J = 4.9 Hz, 1H), 5.13 (dd, J = 33.4, 12.4 Hz, 4H), 4.57 (s, 1H), 2.15 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 167.0, 157.1, 139.1, 136.6, 135.6, 131.1, 130.5, 128.9, 128.6, 128.4, 128.3, 126.9, 119.2, 67.3, 55.3, 20.5; HRMS (ESI−Orbitrap) calcd for $C_{28}H_{24}N_2O_4H^+$ [M + H] 453.1809, found 453.1799.

*Ethyl 2-(3-methyl-2-(pyrimidin-2-yl)phenyl)-2-tosylacetate (**5d**).* Colorless oil 76 mg, 93% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (d, J = 4.9 Hz, 2H), 7.55−7.51 (m, 1H), 7.44−7.40 (m, 2H), 7.30−7.27 (m, 1H), 7.26 (dd, J = 5.6, 4.3 Hz, 1H), 7.23 (t, J = 7.7 Hz, 1H), 7.17 (dd, J = 8.5, 0.5 Hz, 2H), 5.55 (s, 1H), 4.28−4.11 (m, 2H), 2.40 (s, 3H), 2.14 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4, 165.4, 157.1, 145.0, 140.2, 137.3, 134.2, 131.8, 130.1, 129.2, 128.5, 127.6, 126.4, 119.2, 70.5, 62.5, 21.8, 20.8, 14.0; HRMS (ESI−TOF) calcd for $C_{22}H_{22}N_2O_4SNa^+$ [M + Na] 433.1192, found 433.1199.

*Ethyl 2-(diethoxyphosphoryl)-2-(3-methyl-2-(pyrimidin-2-yl)-phenyl)acetate (**5e**).* Yellow oil 71 mg, 90% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (dd, J = 4.8, 4.3 Hz, 2H), 7.85 (d, J = 7.7 Hz, 1H), 7.32 (td, J = 7.8, 3.6 Hz, 1H), 7.25 (td, J = 4.9, 3.6 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 4.23 (dd, J = 24.5, 3.4 Hz, 1H), 4.12 (dqd, J = 10.8, 7.3, 3.7 Hz, 2H), 4.03−3.89 (m, 4H), 2.06 (d, J = 3.4 Hz, 3H), 1.17 (dddd, J = 10.8, 9.1, 7.0, 3.8 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7 (d, J = 3.3 Hz), 167.3, 157.2, 139.5 (d, J = 8.9 Hz), 136.4 (s), 130.0 (d, J = 1.7 Hz), 129.1 (d, J = 7.0 Hz), 128.5, 127.9 (d, J = 4.8 Hz), 119.3, 63.2 (dd, J = 69.0, 6.8 Hz), 61.8, 48.3 (d, J = 134.7 Hz), 20.5, 16.3 (d, J = 5.7 Hz), 14.1; ^{31}P NMR (202 MHz, $CDCl_3$) δ 19.3; HRMS (ESI−TOF) calcd for $C_{19}H_{25}N_2O_5PNa^+$ [M + Na] 415.1393, found 415.1383.

*Diethyl 2-(3-methoxy-2-(pyrimidin-2-yl)phenyl)malonate (**5f**).* Colorless oil 56 mg, 94% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J = 4.9 Hz, 2H), 7.39 (t, J = 8.1 Hz, 1H), 7.24 (t, J = 4.9 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 4.41 (s, 1H), 4.13 (qd, J = 7.1, 2.8 Hz, 4H), 3.70 (s, 3H), 1.17 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 164.9, 157.1, 157.0, 132.6, 129.9, 129.1, 121.2, 119.24, 110.9, 61.6, 55.9, 54.8, 14.0; HRMS (ESI−TOF) calcd for $C_{18}H_{20}N_2O_5Na^+$[M + Na] 367.1264, found 367.1276.

*Diethyl 2-(3-fluoro-2-(pyrimidin-2-yl)phenyl)malonate (**5g**).* White solid 62 mg, mp 89−90 °C, 93% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (d, J = 4.9 Hz, 2H), 7.48−7.42 (m, 1H), 7.39 (dd, J = 7.9, 1.0 Hz, 1H), 7.30 (t, J = 4.9 Hz, 1H), 7.18 (ddd, J = 9.5, 8.2, 1.2 Hz, 1H), 4.81 (s, 1H), 4.25−4.11 (m, 4H), 1.22 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 162.7, 160.5 (d, J = 249.8 Hz), 157.2, 133.8 (d, J = 2.0 Hz), 130.6 (d, J = 9.1 Hz), 127.6 (d, J = 14.5 Hz), 125.2 (d, J = 3.3 Hz), 119.6, 115.8 (d, J = 22.2 Hz), 61.8, 54.7 (d, J = 2.2 Hz), 14.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ −115.6; HRMS (ESI−TOF) calcd for $C_{17}H_{17}FN_2O_4Na^+$ [M + Na] 355.1065, found 355.1054.

*Diethyl 2-(3-chloro-2-(pyrimidin-2-yl)phenyl)malonate (**5h**).* White solid 51 mg, mp 79−80 °C, 73% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92−8.82 (m, 2H), 7.52 (dd, J = 7.8, 1.2 Hz, 1H), 7.46 (dd, J = 8.1, 1.2 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.32 (t, J = 4.9 Hz, 1H), 4.42 (s, 1H), 4.21−4.09 (m, 4H), 1.19 (dd, J = 9.2, 5.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 165.0, 157.3, 138.4, 133.4, 133.1, 129.9, 129.6, 127.9, 119.9, 61.9, 55.1, 14.0; HRMS (ESI−TOF) calcd for $C_{17}H_{17}ClN_2O_4Na^+$ [M + Na] 371.0769, found 371.0789.

*Diethyl 2-(2-(pyrimidin-2-yl)phenyl)malonate (**5i**).* A mixture of 2-phenylpyrimidine (0.2 mmol), $[Cp^*RhCl_2]_2$ (1 mg, 2 μmol, 1 mol %), and AgF (1 mg, 10 μmol, 5 mol %) was stirred in EtOH (2 mL) for 1 h under Ar. Then **2a** (0.24 mmol, 1.2 equiv) was added. The was kept at 75 °C for 6 h. After cooling to rt, the mxture was filtered through a pad of Celite and then concentrateed under reduced pressure. The residue was purified by flash column chromatography to give the **5i** as colorless oil, 35 mg in 66% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, J = 4.9 Hz, 2H), 8.15−8.07 (m, 1H), 7.53−7.42 (m, 3H), 7.19 (t, J = 4.9 Hz, 1H), 5.61 (s, 1H), 4.22 (dtt, J = 10.8, 7.1, 3.7 Hz, 4H), 1.23 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 166.0, 156.9, 137.6, 132.6, 131.2, 130.2, 129.9, 128.2, 118.9, 61.5, 55.8, 14.1; HRMS (ESI−TOF) calcd for $C_{17}H_{18}N_2O_4Na^+$ [M + Na] 337.1159, found 337.1171.

Procedure of Disubstitution of Arenes with Diazo Compounds (for 5j−5p, 5r, 7e, and 7f). A dried 10 mL Schlenk tube equipped with a magnetic stirrer was charged with 2-arylpyrimidine **4** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mg, 4 μmol, 2 mol %), $AgSbF_6$ (7 mg, 20 μmol, 10 mol %), and EtOH (2 mL) under Ar. After the reaction mixture was stirred at room temperature for 1 h, diazo compound **2a** (1.5 mmol, 3 equiv) was then added, and the mixture was heated at 75 °C for 6 h. The reaction mixture was cooled to room temperature and then filtered through a pad of Celite and concentrated under reduced pressure. The residue was then purified by flash column chromatography to give the desired product.

*Tetraethyl 2,2′-(2-(pyrimidin-2-yl)-1,3-phenylene) dimalonate (**5j**).* White solid 77 mg, mp 91−92 °C, 82% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (d, J = 4.9 Hz, 2H), 7.58−7.53 (m, 2H), 7.49 (dd, J = 8.7, 6.9 Hz, 1H), 7.29 (t, J = 4.9 Hz, 1H), 4.60 (s, 2H), 4.17 (q, J = 7.1 Hz, 8H), 1.21 (t, J = 7.1 Hz, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 165.7, 157.0, 139.0, 132.2, 129.3, 129.3, 119.5, 61.8, 55.6, 14.1; HRMS (ESI−TOF) calcd for $C_{24}H_{28}N_2O_8Na^+$ [M + Na] 495.1738, found 495.1728.

*Tetraethyl 2,2′-(5-methyl-2-(pyrimidin-2-yl)-1,3-phenylene) dimalonate (**5k**).* White solid 95 mg, mp 127−128 °C, 98% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (d, J = 4.9 Hz, 2H), 7.34 (d, J = 0.5 Hz, 2H), 7.24 (t, J = 4.9 Hz, 1H), 4.62 (s, 2H), 4.16 (q, J = 7.1 Hz, 8H), 2.41 (s, 3H), 1.20 (t, J = 7.1 Hz, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 165.7, 156.9, 139.2, 136.2, 132.0, 129.9, 119.2, 61.6, 55.5, 21.7, 14.1; HRMS (ESI−TOF) calcd for $C_{25}H_{30}N_2O_8Na^+$ [M + Na] 509.1900, found 509.1910.

*Tetraethyl 2,2′-(5-methoxy-2-(pyrimidin-2-yl)-1,3-phenylene) dimalonate (**5l**).* White solid 78 mg, mp 113−114 °C, 78% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (d, J = 4.9 Hz, 2H), 7.24 (d, J = 4.9 Hz, 1H), 7.10 (s, 2H), 4.69 (s, 2H), 4.18 (tt, J = 7.2, 3.7 Hz, 8H), 3.84 (s, 3H), 1.21 (t, J = 7.1 Hz, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 165.6, 159.8, 156.9, 133.8, 131.8, 119.0, 115.0, 61.7, 55.7, 55.5, 14.1; HRMS (ESI−TOF) calcd for $C_{25}H_{30}N_2O_9Na^+$ [M + Na] 525.1849, found 525.1873.

*Tetraethyl 2,2′-(5-(ethoxycarbonyl)-2-(pyrimidin-2-yl)-1,3-phenylene) dimalonate (**5m**).* White solid 105 mg, mp 71−72 °C, 96% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (d, J = 4.9 Hz, 2H), 8.22 (s, 2H), 7.32 (t, J = 4.9 Hz, 1H), 4.61 (s, 2H), 4.38 (q, J = 7.1 Hz, 2H), 4.22−4.14 (m, 8H), 1.38 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 165.6, 165.0, 157.2, 142.7, 132.8, 131.3, 130.5, 119.8, 61.9, 61.3, 55.7, 14.4, 14.1; HRMS (ESI−TOF) calcd for $C_{27}H_{32}N_2O_{10}Na^+$ [M + Na] 567.1955, found 567.1940.

*Tetraethyl 2,2′-(5-fluoro-2-(pyrimidin-2-yl)-1,3-phenylene) dimalonate (**5n**).* White solid 95 mg, mp 89−90 °C, 97% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (d, J = 4.9 Hz, 2H), 7.32 (d, J = 9.4 Hz, 2H), 7.29 (t, J = 4.9 Hz, 1H), 4.61 (d, J = 0.7 Hz, 2H), 4.17 (q, J = 7.1 Hz, 8H), 1.21 (t, J = 7.1 Hz, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 165.0, 162.4 (d, J = 248.2 Hz), 157.1, 135.3 (d, J = 3.0 Hz), 134.5 (d, J = 8.7 Hz), 119.5, 116.7 (d, J = 23.2 Hz), 62.0, 55.4, 14.0; HRMS (ESI−TOF) calcd for $C_{24}H_{27}FN_2O_8Na^+$ [M + Na] 513.1649, found 513.1666.

*Tetraethyl 2,2′-(2-(pyrimidin-2-yl)-5-(trifluoromethyl)-1,3-phenylene) dimalonate (**5o**).* White solid 107 mg, mp 106−107 °C, 99% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (d, J = 4.9 Hz, 2H), 7.87 (s, 2H), 7.35 (t, J = 4.9 Hz, 1H), 4.61 (s, 2H), 4.22−4.15 (m, 8H), 1.22 (t, J = 7.1 Hz, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 164.7, 157.3, 142.2, 133.2, 131.2 (q, J = 32.9 Hz), 126.5 (d, J = 3.6 Hz), 123.8 (d, J = 272.7 Hz), 120.0, 62.1, 55.4, 14.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ −62.8; HRMS (ESI−TOF) calcd for $C_{25}H_{27}F_3N_2O_8Na^+$ [M + Na] 563.1617, found 563.1629.

*Tetraethyl 2,2′-(4-chloro-2-(pyrimidin-2-yl)-1,3-phenylene) dimalonate (**5p**).* White solid 87 mg, mp 122−123 °C, 86% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (d, J = 4.9 Hz, 2H), 7.54 (s, 2H), 7.31 (t, J = 4.9 Hz, 1H), 4.58 (s, 1H), 4.48 (s, 1H), 4.25−4.11 (m, 8H), 1.21 (td, J = 7.1, 5.0 Hz, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 167.0, 165.5, 157.2, 141.7, 135.9, 131.3, 131.1, 130.8, 130.4,

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119.9, 62.0, 61.8, 55.2, 55.0, 14.1; HRMS (ESI−Orbitrap) calcd for $C_{24}H_{27}ClN_2O_8H^+$ [M + H] 507.1529, found 507.1531.

*Diethyl 2-(2-(benzo[d]oxazol-2-yl)-3-methylphenyl)malonate (**5q**).* Colorless oil 62 mg, 85% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85−7.80 (m, 1H), 7.58 (ddd, J = 4.7, 2.9, 0.6 Hz, 1H), 7.49−7.44 (m, 2H), 7.42−7.38 (m, 2H), 7.34−7.30 (m, 1H), 4.90 (s, 1H), 4.19 (q, J = 7.1 Hz, 4H), 2.37 (s, 3H), 1.21 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 161.7, 150.8, 141.6, 139.3, 133.9, 130.8, 130.5, 128.2, 127.1, 125.5, 124.7, 120.6, 110.9, 61.9, 55.5, 20.9, 14.1; HRMS (ESI−Orbitrap) calcd for $C_{21}H_{21}NO_5H^+$ [M + H] 368.1492, found 368.1493.

*Tetraethyl 2,2′-(2-(benzo[d]oxazol-2-yl)-5-methyl-1,3-phenylene) dimalonate (**5r**).* White solid 81 mg, mp 116−118 °C, 77% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (ddd, J = 4.0, 2.9, 0.6 Hz, 1H), 7.53 (ddd, J = 4.9, 2.8, 0.6 Hz, 1H), 7.43 (d, J = 0.5 Hz, 2H), 7.42−7.36 (m, 2H), 4.91 (s, 2H), 4.19 (qd, J = 7.1, 1.1 Hz, 8H), 2.45 (s, 3H), 1.21 (t, J = 7.1 Hz, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 160.6, 150.7, 141.5, 141.4, 133.9, 130.3, 125.7, 125.6, 124.8, 120.8, 110.8, 62.0, 55.5, 21.9, 14.0; HRMS (ESI−Orbitrap) calcd for $C_{28}H_{31}NO_9H^+$ [M + H] 526.2072, found 526.2067.

*Diethyl 2-(2-(pyrimidin-2-yl)thiophen-3-yl)malonate (**7a**).* Colorless oil 60 mg, 94% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, J = 4.9 Hz, 2H), 7.40 (d, J = 5.2 Hz, 1H), 7.21 (d, J = 5.3 Hz, 1H), 7.05 (t, J = 4.9 Hz, 1H), 6.46 (s, 1H), 4.21 (qd, J = 7.1, 1.3 Hz, 4H), 1.24 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 161.8, 156.8, 139.1, 134.4, 130.5, 128.3, 118.4, 61.6, 52.3, 14.1; HRMS (ESI−TOF) calcd for $C_{15}H_{16}N_2O_4SNa^+$ [M + Na] 343.0723, found 343.0731.

*Diethyl 2-(1-(pyridin-2-yl)-1H-pyrrol-2-yl)malonate (**7b**).* A mixture of 2-(1*H*-pyrrol-1-yl)pyridine **6b** (0.2 mmol), $[Cp^*RhCl_2]_2$ (1 mg, 2 μmol, 1 mol %), and AgF (1 mg, 10 μmol, 5 mol %) was stirred in EtOH (2 mL) for 1 h under Ar. **2a** (0.24 mmol, 1.2 equiv) was added in one pot, and the solution was kept at 75 °C for 6 h. The mixture was cooled to room temperature, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was then purified by flash column chromatography to give the **7b** as colorless oil, 37 mg, 62% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (ddd, J = 4.9, 1.9, 0.8 Hz, 1H), 7.76 (ddd, J = 8.2, 7.5, 1.9 Hz, 1H), 7.32 (dd, J = 4.8, 4.1 Hz, 1H), 7.14 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H), 7.10 (dd, J = 3.1, 1.7 Hz, 1H), 6.34 (ddd, J = 3.5, 1.7, 0.6 Hz, 1H), 6.31 (t, J = 3.3 Hz, 1H), 5.45 (s, 1H), 4.21 (q, J = 7.1 Hz, 4H), 1.24 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 152.6, 148.1, 138.8, 125.2, 121.1, 120.9, 115.6, 112.3, 110.2, 61.7, 52.7, 14.2; HRMS (ESI−TOF) calcd for $C_{16}H_{18}N_2O_4Na^+$ [M + Na] 325.1164, found 325.1167.

*Diethyl 2-(2-(pyridin-2-yl)thiophen-3-yl)malonate (**7c**).* Following the general procedure and reacted for 48 h. Colorless oil 33 mg, 51% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, J = 4.3 Hz, 1H), 7.68 (dd, J = 7.7, 1.7 Hz, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.32 (d, J = 5.3 Hz, 1H), 7.24 (d, J = 5.2 Hz, 1H), 7.16 (dd, J = 7.0, 5.1 Hz, 1H), 5.84 (s, 1H), 4.22 (tt, J = 7.2, 3.6 Hz, 4H), 1.25 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 152.8, 149.5, 140.2, 136.9, 131.0, 130.3, 125.3, 122.5, 122.0, 61.8, 52.3, 14.2; HRMS (ESI−TOF) calcd for $C_{16}H_{17}NO_4SNa^+$ [M + Na] 342.0776, found 342.0775.

*Diethyl 2-(2-(isoquinolin-1-yl)furan-3-yl)malonate (**7d**).* Colorless oil 69 mg, 98% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 8.7 Hz, 1H), 8.09−8.00 (m, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.75 (dd, J = 8.1, 1.2 Hz, 1H), 7.67 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.57−7.51 (m, 1H), 7.47 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 6.78−6.71 (m, 1H), 6.40 (s, 1H), 4.28 (dd, J = 7.1, 5.5 Hz, 4H), 1.30 (t, J = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 150.1, 149.4, 147.8, 142.5, 136.5, 129.7, 129.4, 127.6, 126.9, 126.3, 118.6, 117.8, 114.0, 61.8, 50.2, 14.2; HRMS (ESI−Orbitrap) calcd for $C_{20}H_{19}NO_5H^+$ [M + H] 354.1336, found 354.1339.

*Tetraethyl 2,2′-(1-(pyridin-2-yl)-1H-pyrrole-2,5-diyl) dimalonate (**7e**).* Followed the procedure of disubstitution. Colorless oil 78 mg, 85% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, J = 4.8, 1.2 Hz, 1H), 7.82 (td, J = 7.7, 1.9 Hz, 1H), 7.36−7.27 (m, 2H), 6.42 (s, 2H), 4.60 (s, 2H), 4.19−4.08 (m, 8H), 1.19 (t, J = 7.1 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 150.3, 149.7, 138.5, 125.3, 123.3, 122.7, 110.5, 61.9, 51.0, 14.0; HRMS (ESI−Orbitrap) calcd for $C_{23}H_{28}N_2O_8H^+$ [M + H] 461.1918, found 461.1912.

*Tetraethyl 2,2′-(1-(4-methylpyridin-2-yl)-1H-pyrrole-2,5-diyl)-dimalonate (**7f**).* Followed the procedure of disubstitution. White solid 84 mg, mp 130−132 °C, 88% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, J = 5.0 Hz, 1H), 7.15−7.12 (m, 1H), 7.10−7.08 (m, 1H), 6.41 (s, 2H), 4.59 (s, 2H), 4.19−4.11 (m, 8H), 2.39 (s, 3H), 1.21 (t, J = 7.1 Hz, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.4, 150.4, 150.2, 149.4, 125.3, 124.3, 123.5, 110.6, 61.9, 51.1, 21.1, 14.1; HRMS (ESI−TOF) calcd for $C_{24}H_{30}N_2O_8Na^+$ [M + Na] 497.1900, found 497.1919.

*Ethyl 2-(2-(1H-pyrazol-1-yl)phenyl)acetate (**8a**).* Colorless oil 33 mg, 71% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74−7.63 (m, 2H), 7.43−7.31 (m, 4H), 6.46−6.37 (m, 1H), 4.07 (q, J = 7.1 Hz, 2H), 3.68 (s, 2H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 140.7, 140.2, 131.8, 131.0, 130.4, 128.6, 128.2, 126.2, 106.5, 60.9, 37.6, 14.2; HRMS (ESI−TOF) calcd for $C_{13}H_{14}N_2O_2Na^+$ [M + Na] 253.0953, found 253.0962.

*Ethyl 2-(3-methyl-2-(pyrimidin-2-yl)phenyl)acetate (**8b**).* Colorless oil 43 mg, 84% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (d, J = 4.9 Hz, 2H), 7.29 (t, J = 7.6 Hz, 1H), 7.26 (t, J = 4.9 Hz, 1H), 7.21 (dd, J = 7.6, 3.6 Hz, 2H), 4.01 (q, J = 7.1 Hz, 2H), 3.49 (s, 2H), 2.15 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 167.7, 157.1, 139.1, 136.4, 132.4, 129.5, 128.8, 128.5, 119.1, 60.7, 39.6, 20.3, 14.2; HRMS (ESI−TOF) calcd for $C_{15}H_{16}N_2O_2Na^+$ [M + Na] 279.1104, found 279.1123.

*Ethyl 2-(2-(pyridin-2-yl)phenyl)acetate (**8c**).* A mixture of 2-phenylpyridine (0.2 mmol), $[Cp^*RhCl_2]_2$ (1 mg, 2 μmol, 1 mol %), and AgF (1 mg, 10 μmol, 5 mol %) was stirred in EtOH (2 mL) for 1h under Ar. **2n** (0.24 mmol, 1.2 equiv) was added in one pot, and the solution was kept at 75 °C for 6 h. The mixture was cooled to room temperature, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was then purified by flash column chromatography to give the **8c** as colorless oil, 24 mg in 49% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 7.75 (td, J = 7.7, 1.8 Hz, 1H), 7.49−7.43 (m, 2H), 7.39−7.34 (m, 3H), 7.24 (ddd, J = 7.6, 4.9, 1.1 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 3.83 (s, 2H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 159.7, 149.0, 140.6, 136.6, 132.7, 131.5, 130.0, 128.7, 127.5, 124.1, 121.9, 60.7, 39.5, 14.3; HRMS (ESI−Orbitrap) calcd for $C_{15}H_{15}NO_2H^+$ [M + H] 242.1176, found 242.1167.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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