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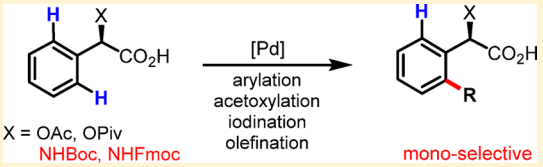
Monoselective *o*-C−H Functionalizations of Mandelic Acid and α-Phenylglycine

Navid Dastbaravardeh, Tetsuya Toba, Marcus E. Farmer, and Jin-Quan Yu*

Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, California 92037, United States

Supporting Information

ABSTRACT: Pd-catalyzed C−H functionalization of mandelic acid and α-phenylglycine is reported. We have developed different protocols for the arylation, iodination, acetoxylation, and olefination of these substrates based on two different (Pd(II)/Pd(IV) and Pd(II)/Pd(0)) catalytic cycles. Four crucial features of these protocols are advantageous for practical applications. First, the α-hydroxyl and amino groups are protected with simple protecting groups such as acetates (Ac, Piv) and carbamates (Boc, Fmoc), respectively. Second, these protocols do not involve installation and removal of a directing group. Third, monoselectivity is accomplished. Fourth, no epimerization occurs at the vulnerable α-chiral centers.



1. INTRODUCTION

The selective, direct C−H functionalization of organic substrates by transition metal catalysts is a very attractive method for structural elaboration. Despite the impressive success in this area, one of the major challenges for these transformations remains the requirement to control site selectivity in molecules that contain multiple C−H bonds. Directed C−H functionalization has proven to be a reliable and powerful approach to utilize existing functional groups in a molecule to predictably guide C−H cleavage at a particular site.[1] However, a number of limitations have prevented practical applications of these directed C−H reactions. First, existing functional groups are often modified to provide improved interactions with transition metal catalysts to promote catalytic C−H activation reactions. Second, reactions are often not compatible with coordinating functional groups. For example, the ubiquitous amino group needs to be specifically protected as phthalimide. The practical carbamate (Boc, Fmoc) protecting groups generally inhibit C−H activation reactions. Third, the formation of a mixture of mono- and di-*o*-C−H functionalization products is also a persistent problem facing the majority of directed C−H activation reactions.[2] Therefore, development of catalysts, conditions, and directing groups to overcome these limitations is of central importance in the field. To achieve optimum efficiency in synthesis, the use of existing functional groups on a molecule of interest to direct C−H activation is most desirable. In this context, our group has been focused on the development of catalytic systems that utilize carboxylic acids and alcohols to direct C−H functionalization reactions.[3] Not only are these functional groups commonly found in natural products and drug molecules, they are easily manipulated into a range of other functional groups making them highly versatile synthetic handles. In the long run, the development of a diverse range of directed C−H activation transformations based on existing functionality in a substrate will continue to grow and enhance the synthetic utility of these emerging methods.

We are especially interested in the diversification of naturally occurring chiral compounds, aiming to expand the synthetic utility of these readily available molecules as chiral synthons in asymmetric synthesis. A number of naturally occurring chiral carboxylic acids are readily available; however, there are only a few reports concerning the use of free carboxylic acids to direct C−H functionalization events in the literature,[4] and the majority of these established protocols are based on the derivatization of simple benzoic acid derivatives which do not contain chiral centers.[5] Other scaffolds such as phenylacetic acid, a major class of synthetically versatile substrates, have been significantly less investigated.[3c,d,6] Recently, our group made strides on this front with the discovery that mono-N-protected amino acid ligands could accelerate the Pd(II)/Pd(0) catalytic cycle and demonstrated this reaction on phenylacetic acids, albeit limited to olefination and cross-coupling via Pd(II)/Pd(0) redox catalysis.[6c] These ligand-accelerated reactions set the stage for us to further investigate whether C−H activation methods can be modified to directly functionalize enantiomerically pure α-substituted phenylacetic acid substrates such as mandelic acid and α-phenylglycine.

We anticipate the key challenge is to achieve compatibility with α-functional groups protected with commonly used carbamates and acetates. If successful, rapid transformation of these readily available building blocks into diverse enantiomerically pure chiral synthons is feasible for asymmetric synthesis. Notably, these scaffolds can already be found in many pharmaceutical drugs (e.g., homatropine,[7] cyclandelate,[8] cefalexin,[9] clopidogrel[7]), and the ability to directly derivatize them may lead to further medicinal investigation of these classes of compounds. Furthermore, we envisioned that by

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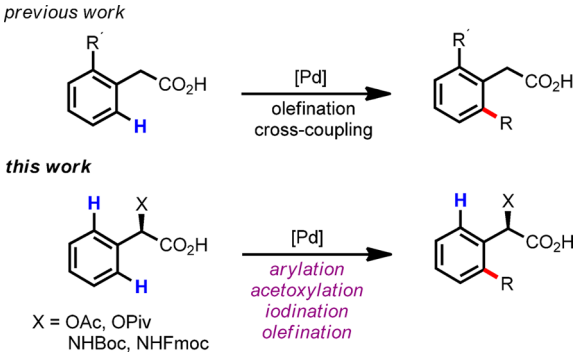


investigating the Pd(II)/Pd(IV) catalytic cycle in addition to previously reported Pd(II)/Pd(0) catalysis,[10] new transformations would be achievable with this class of substrates ranging from C−C to C−X bond formations.

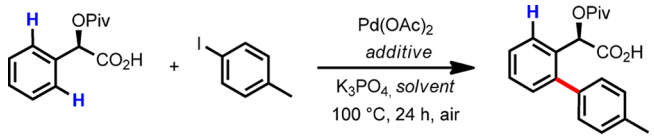
Herein, we describe a variety of *o*-C−H functionalizations of mandelic acid and α-phenylglycine derivatives based on two complementary catalytic cycles, namely Pd(II)/Pd(IV) and Pd(II)/Pd(0) catalysis. The α-amino groups in the substrates for C−H activation are protected with synthetically amenable carbamate (Boc, Fmoc). Notably, to the best of our knowledge, the Boc- and Fmoc-protected α-amino groups have not been shown to be compatible in carboxylate-directed C−H activations prior to this publication.[3c] Importantly, monoselectivity is achieved in all reactions through either optimizing conditions or choosing an appropriate ligand.

2. RESULTS AND DISCUSSION

Pd(II)/Pd(IV) Arylation of Mandelic Acid. Our initial efforts toward the direct arylation of α-substituted phenylacetic acids focused on different Pd(II)/Pd(IV) protocols previously utilized in our lab[11] and other groups.[12] Because previously reported conditions are not compatible with phenylacetic acids,[11,12] we proceeded to develop conditions for the direct arylation of pivaloyl-protected mandelic acid **1a** employing aryl iodides. We initiated our optimization studies with 1 equiv of substrate **1a**, 2 equiv of 4-iodotoluene **2a**, 10 mol % of $Pd(OAc)_2$, 2 equiv of AgOAc, 3 equiv of K_3PO_4, and DCE as solvent. The reaction mixture was stirred for 24 h at 100 °C. To our delight, we could detect the desired product **3a** by ^1H NMR analysis, although in a very low yield of 7% (Table 1, entry 1). On the basis of previous results from our group,[11] we expected the solvent to play a crucial role for this transformation. Indeed, after changing the solvent to toluene, AcOH, or MeCN, no product was formed during the reaction, while other solvents such as DMF or *tert*-amylOH showed similar results to DCE (Table 1, entries 2−6). Interestingly, using HFIP (hexafluoroisopropanol) as solvent changed the outcome of the reaction dramatically, and the product was formed in 77% yield (Table 1, entry 7). Previous results have shown that HFIP can play a crucial role in palladium-catalyzed C−H functionalization reactions, particularly when utilizing weakly coordinating directing groups. Next, we investigated the influence of the additive by testing different silver and copper salts. Among the investigated additives, the initially used AgOAc showed the best activity, while Ag_2CO_3, Ag_2O, and $Cu(OAc)_2$ did not show good reactivity (Table 1, entries 8−10). The absence of AgOAc decreased the conversion significantly, supporting our hypothesis that this additive is crucial in regenerating the catalytically active palladium species from palladium iodides that may be formed after C−C reductive elimination from Pd(IV) after the oxidative addition of Pd(II) to an aryl iodide (Table 1, entry 11).[10] The requirement for silver acetate is consistent with the Pd(II)/(IV) catalytic cycle.[12] It is unlikely that the Pd(0)/Pd(II) catalytic cycle can operate under atmospheric air and in the presence of silver acetate, as these conditions are known to oxidize Pd(0) to Pd(II) and prevent oxidative addition of Pd(0) with ArI, which is the initiating step of the Pd(0)/Pd(II) catalytic cycle. Furthermore, acetates can facilitate the C−H bond activation step via promoting a CMD (concerted metalation deprotonation) mechanism,[13] which may explain why KOAc performed the best among the tested bases (see SI). The reaction does not require any ligand, and the addition of pyridine and amino acid ligands decreased the yield slightly (see SI). Moreover, this reaction is not air and moisture sensitive and can be carried out under air with high yield, further contributing to this reaction's operational simplicity. Finally, we could increase the yield to 90% by decreasing the reaction temperature to 80 °C (Table 1, entry 12). We were pleased to discover that no epimerization occurred and that the product could be obtained with 98% ee.

This reaction also works efficiently with simple protecting groups such as acetates (Table 2, entries 1 and 2), while *tert*-butyl or benzyl protecting groups gave lower conversion (Table

Table 1. Optimization of the Reaction Conditions[a,b]



1a 2a 3a

entry	solvent	additive	yield (%)[b]	entry	solvent	additive	yield (%)[b]
1	DCE	AgOAc	7	7	HFIP	AgOAc	77
2	MeCN	AgOAc	0	8	HFIP	Ag_2CO_3	30
3	toluene	AgOAc	0	9	HFIP	$Cu(OAc)_2$	8
4	DMF	AgOAc	10	10	HFIP	Ag_2O	6
5	AcOH	AgOAc	0	11	HFIP	-	17
6	*tert*-amylOH	AgOAc	9	12	HFIP	AgOAc	90 (89)[c,d,e]

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), additive (0.2 mmol), K_3PO_4 (0.3 mmol), solvent (1 mL), air, 100 °C, 24 h. [b]Yield determined by ^1H NMR analysis of crude reaction mixture using CH_2Br_2 as internal standard. [c]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (0.005 mmol), AgOAc (0.2 mmol), KOAc (0.3 mmol), HFIP (1 mL), air, 80 °C, 24 h. [d]Yield of **3a** after chromatographic purification. [e]98% ee, determined by chiral HPLC.

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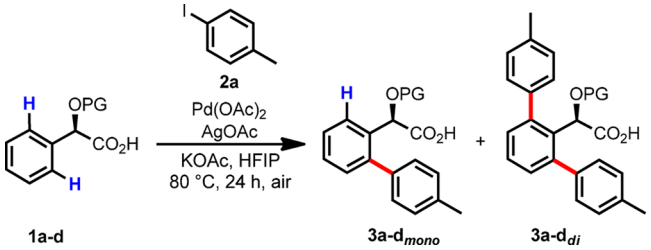
Table 2. Investigation of Protecting Groups for Arylation of Mandelic Acid[a,b]

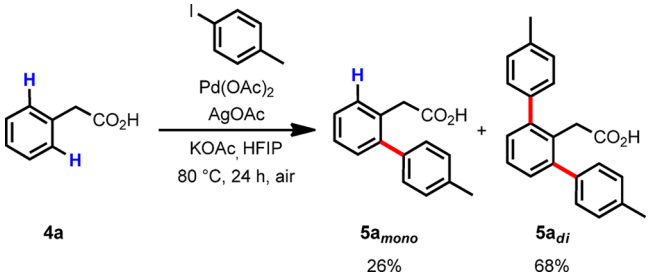


entry	PG	mono:di[b]	yield (%)[b]
1	Piv	>20:1	90 (88)[c]
2	Ac	>20:1	90 (87)[c]
3	*t*Bu	>20:1	13
4	Bn	>20:1	48

[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (0.005 mmol), AgOAc (0.2 mmol), KOAc (0.3 mmol), HFIP (1 mL), air, 80 °C, 24 h. [b]Determined by ^1H NMR analysis of crude reaction mixture. [c]Yields of **3** after chromatographic purification.

2, entries 3 and 4). Notably, we could exclusively obtain the monoarylated product $\mathbf{3}_{mono}$ and no diarylated $\mathbf{3}_{di}$ product was formed under these conditions. We assume that the α-substituent exerts an influence on the selectivity by inhibiting the second C−H bond insertion due to steric effects. In contrast to the observed monoselectivity, arylation of unsubstituted phenylacetic acid with 4-iodotoluene afforded mostly the diarylated product $\mathbf{5a}_{di}$ (Scheme 1).

Scheme 1. Arylation of Phenylacetic Acid 4a



With this newly established arylation protocol, the scope of aryl iodide derivatives was examined. We found this catalytic method to be compatible with arene donors carrying a variety of different functional groups including alkyls (**3a**, **3e**), electron-withdrawing groups such as trifluoromethyl (**3f**), esters (**3g**, **3h**), ketones (**3i**), and aldehydes (**3j**) (Table 3). Phosphonates (**3k**) and acetates (**3l**) also worked well, while strong electron-donating groups such as methoxy (**3m**) or coordinating substituents such as nitro (**3n**) were less tolerated. Sterically demanding ortho-substituted aryls (e.g., 2-Me, 2-Cl) gave no conversion, but meta-substituted aryls (**3e**, **3h**, **3l**) showed good conversion and yields. Halides (**3o**, **3q**, **3r**) are also tolerated and can be used for further synthetic elaborations. Notably, no product was observed from C−H/C−Br coupling in the preparation of **3o** and simple aryl bromides are not effective coupling partners for this reaction. Next, we probed the mandelic acid substrate scope. The best results were obtained with electron-withdrawing substituents such as chloride (**3q** and **3r**) and trifluoromethyl (**3s**), while electron-rich substrates (e.g., 4-OMe) showed significant decarboxylation which was not observed with the simple phenylacetic acid substrate. It is worth noting here that protected α-phenylglycine derivatives (e.g., NHBoc, NHPiv, NPhth) were not appropriate for the present reaction, most likely since the nitrogen coordinates too strong to the palladium catalyst and thus inhibits the catalytic reactivity.

Acetoxylation and Iodination of Mandelic Acid. These findings prompted us to investigate other Pd(II)/Pd(IV)-catalyzed reactions. We were pleased to discover that addition of stoichiometric amounts of $PhI(OAc)_2$ led to the ortho-acetoxylated product **6a**.[14] Further fine-tuning of the protocol was attempted in order to optimize this reaction. The reaction could be performed at 50 °C and delivered product **6a** in 63% yield with 98% ee (Scheme 2). Additionally, we were interested in the iodination of substrate **1a**,[15] enabling easy access to halogenated mandelic acid derivatives which could be used for further C−C and C−N coupling reactions. We have previously developed several Pd-catalyzed C−H iodination protocols using inexpensive molecular iodine as reagent.[16] Hence, we were interested if this approach could also be applicable in this case. Gratifyingly, we found that the addition of iodine to the reaction conditions formed product **7a** in 51% yield and 98% ee.

Pd(II)/Pd(0) Olefination Reaction of Mandelic Acid. While the Pd(II)/Pd(IV) catalysis worked well with the mandelic acid substrate **1a**, poor reactivity was observed with Boc-protected α-phenylglycine under these conditions. In 2010,[6c] our group reported a ligand-accelerated Pd(II)-catalyzed C−H olefination[17] protocol for phenylacetic acids. By using amino acid ligands in conjunction with O_2[18] as a stoichiometric reoxidant, phenylacetic acid substrates could be coupled efficiently with terminal olefins in short reaction times. Our studies showed that monoprotected amino acids (MPAA) offer dramatic improvements in substrate scope, reaction rate, and catalyst lifetime. We anticipated this protocol to also be suitable for the olefination of pivaloyl-protected mandelic acid **1a**. Indeed, the reaction of 1 equiv of **1a** with 2 equiv of ethyl acrylate **8a**, 5 mol % $Pd(OAc)_2$, 15 mol % Ac-Gly-OH, 2 equiv of $KHCO_3$, and *tert*-amylOH as solvent led to full conversion within 2 h. When carrying out this experiment without Ac-Gly-OH, only traces of the product **9a** were formed, supporting our previously reported results. Consistent with our earlier observation,[6d] we obtained a mixture of mono- and di-ortho-olefinated product in a ratio of 2:1, respectively (Table 4, entry 1). It is of note that in this reaction, unlike the arylation, strong inherent bias for monoselectivity in the absence of ligands was not observed, which we attribute to a difference in sterics between aryl and olefinated products. Interestingly, changing the protecting group to *tert*-butyl led to even more diortho-olefinated product (Table 4, entry 3), while other protecting groups such as acetyl and benzyl showed reactivity similar to that of pivaloyl (Table 4, entries 2 and 4).

Our efforts to achieve the monoselectivity of the olefination of mandelic acid **1a** centered on the identification of an optimal ligand in terms of selectivity and reaction rate. On one hand, our previous ligandless conditions[6c] provided monoselectivity but did not afford sufficient reactivity with challenging substrates such as mandelic acid. On the other hand, MPAA ligands can accelerate both mono- and diolefination, and it is crucial to identify an appropriate ligand that can specifically accelerate the mono-olefination through a substrate−ligand match.[6d] Thus, we sought to identify the most efficient ligand backbones by examining a set of commercially available N-

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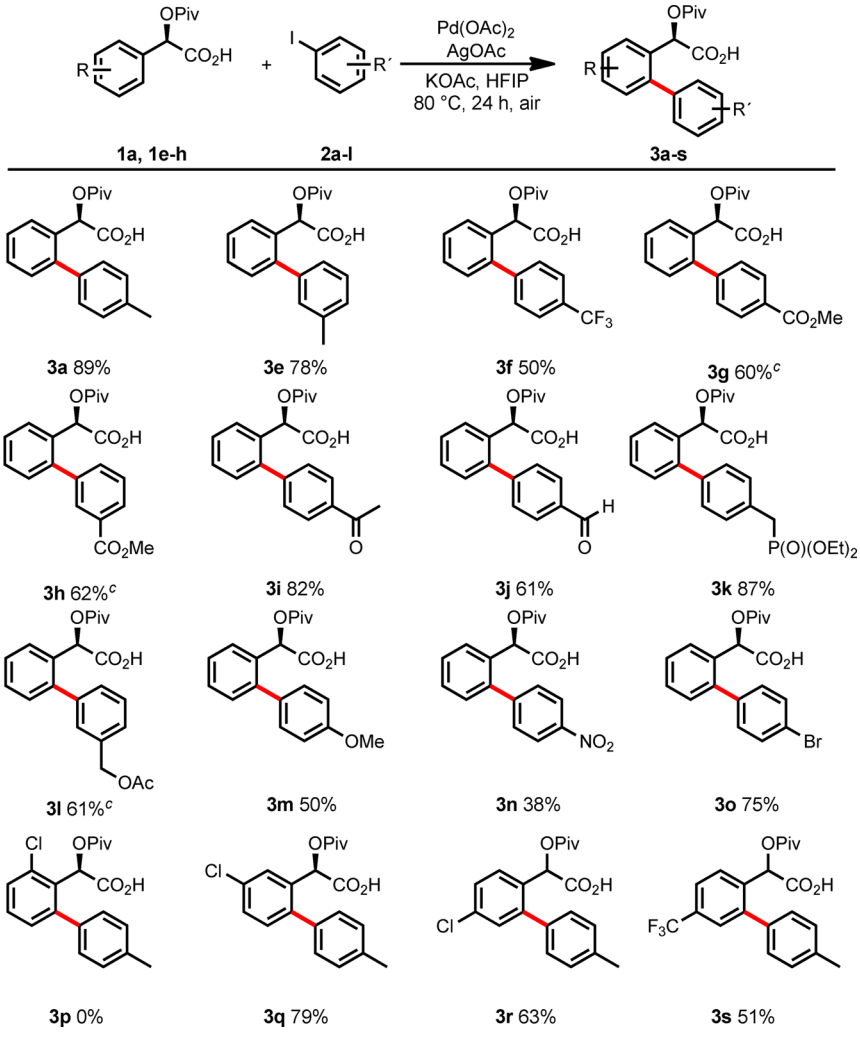
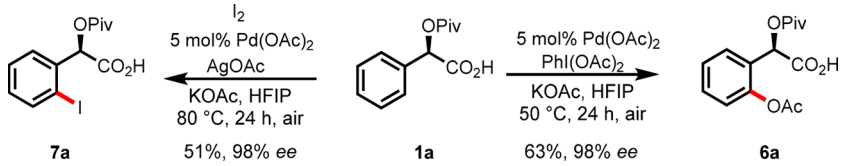
Table 3. Scope of Arylation Reaction[a,b]



[a]Reaction conditions: **1** (0.1 mmol), 2 (0.2 mmol), $Pd(OAc)_2$ (0.005 mmol), AgOAc (0.2 mmol), KOAc (0.3 mmol), HFIP (1 mL), air, 80 °C, 24 h. [b]Yields after chromatographic purification. [c]The product was isolated as the corresponding methyl ester (see SI).

Scheme 2. Iodination and Acetoxylation of Mandelic Acid 1a



protected amino acids (Table 5). To increase operational simplicity, as well as safety, we decided to perform the reactions under 1 atm of air instead of 1 atm O_2. The results indicate a direct correlation between the conversion and the ratio of $\mathbf{9a}_{mono}$:$\mathbf{9a}_{di}$. The higher the conversion, the more diolefinated product is formed. Among the tested amino acids, Ac-Tle-OH and Ac-Leu-OH showed the best reactivity (Table 5, entries 6 and 7). The mono-olefinated product $\mathbf{9a}_{mono}$ could be isolated in 71% yield and 98% ee using Ac-Tle-OH. The ratio of $\mathbf{9a}_{mono}$:$\mathbf{9a}_{di}$ could be pushed toward the diolefinated product by performing the reaction under 1 atm O_2 (Table 5, entry 10). Subsequently, product $\mathbf{9a}_{di}$ was obtained in 82% yield by increasing the reaction temperature and extending the reaction time (Table 5, entry 11). This reaction showed, in general, good reactivity under air which makes it attractive for industrial large scale synthesis.

We next sought to examine the scope of the olefin coupling partner by subjecting various terminal olefins and 3-chloro-substituted mandelic acid **1e** to the reaction conditions. It was decided to use Ac-Leu-OH as a ligand because this amino acid is less expensive than Ac-Tle-OH and no diolefinated product is formed due to the sterically bulky group in the meta-position of substrate **1e**. In accordance with our earlier observations,[6d] this reaction works the best for the installation of the electron-withdrawing olefins such as acrylates (**9f–h**), styrenes (**9i–k**), and phosphonates (**9l**) (Table 6). Efforts to carry out the reaction with vinyl-sulfones, -sulfonates, and -nitriles were unsuccessful. Moreover, nonactivated terminal olefins such as *n*-hexene or *n*-butyl vinyl ether displayed low conversion.

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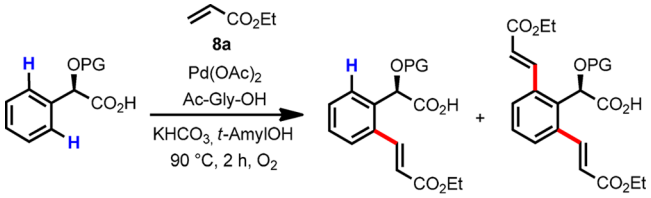
Table 4. Investigation of Protecting Groups for Olefination of Mandelic Acid[a,b]

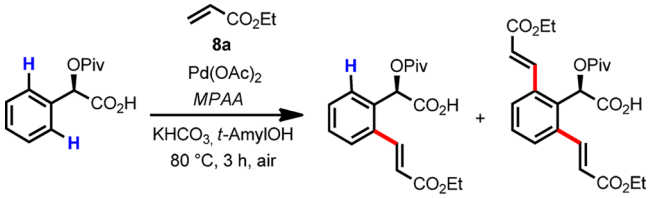


1a-d 9a-d$_{mono}$ 9a-d$_{di}$

		conv (%)[b]			
entry	PG	no ligand	Ac-Gly-OH	mono:di[b]	yield (%)[c]
1	Piv	traces	99	2:1	63
2	Ac	traces	91	2:1	45
3	*t*Bu	traces	99	1:5	n.i.[d]
4	Bn	traces	99	2:1	62

[a]Reaction conditions: **1** (0.1 mmol), **8a** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), Ac-Gly-OH (15 mol %), $KHCO_3$ (0.2 mmol), *tert*-amylOH (0.5 mL), O_2 (1 atm), 90 °C, 2 h. [b]Determined by ^1H NMR analysis of crude reaction mixture. [c]Yields of $\mathbf{9}_{mono}$ after chromatographic purification. [d]n.i. = not isolated.

Table 5. Ligand-Controlled Mono- and Diselective Ortho-Olefination[a,b]



1a 9a$_{mono}$ 9a$_{di}$

entry	MPAA	1a	9a$_{mono}$	9a$_{di}$
1	-	98	traces	0
2	Ac-Gly-OH	45	49	traces
3	Ac-Val-OH	42	50	5
4	Ac-Phe-OH	35	55	8
5	Ac-Ile-OH	52	45	traces
6	Ac-Tle-OH	17	72 (71)[c,d]	8
7	Ac-Leu-OH	16	66	14
8	Boc-Leu-OH	56	41	traces
9	Bz-Leu-OH	84	14	0
10[e]	Ac-Leu-OH	0	65	33
11[f]	Ac-Leu-OH	0	9	85 (82)[g]

[a]Reaction conditions: **1a** (0.1 mmol), **8a** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), MPAA (15 mol %), $KHCO_3$ (0.2 mmol), *t*-AmylOH (0.5 mL), air, 80 °C, 3 h. [b]Conversion determined by ^1H NMR analysis of crude reaction mixture. [c]Yield of $\mathbf{9a}_{mono}$ after chromatographic purification. [d]98% ee, determined by chiral HPLC. [e]O_2 (1 atm). [f]O_2 (1 atm), 90 °C, 6h. [g]Yield of $\mathbf{9a}_{di}$ after chromatographic purification.

Different substituents on the mandelic acid substrate revealed that meta (**9e**) and para (**9n** and **9o**) substituents resulted in good yield while ortho substituents (**9m**) showed lower conversion. In general, electron-withdrawing substituents worked better while an electron-donating group decreases the yield due to partial decarboxylation (**9p**). Ac-Gly-OH was used as ligand for the synthesis of racemic substrates **9n**−**p** in order to avoid any match/mismatch effects between substrate and ligand.

Pd(II)/Pd(0) Olefination of α-Phenylglycine. We were pleased to find that this catalytic system is not restricted to mandelic acid but also α-phenylglycine[19] derivatives were suitable substrates (Table 7) which was not the case for the previous arylation protocol. NHBoc-protected α-phenylglycine showed the best result and reacted even in the absence of Ac-Gly-OH with good monoselectivity (Table 7, entry 1), which is not surprising considering the fact that NHBoc-protected α-phenylglycine can work as a MPAA type ligand and substrate simultaneously. Phthalimide and Fmoc have also been used as protecting groups albeit less effectively when compared to Boc (Table 7, entries 2 and 3). The NHAc-protected α-phenylglycine gave only low conversion (Table 7, entry 4). Presumably, the stronger coordination of the NHAc-group to palladium is prohibiting the C−H insertion step. Interestingly, all α-phenylglycine substrates formed the mono-ortho-olefinated product $\mathbf{11}_{mono}$ exclusively which we attribute to the steric hindrance of the NHPG.

A number of olefins reacted in a similar manner with the *N*-Boc-protected α-phenylglycine **10a** (Table 8). The ortho-olefinated α-phenylglycine **11a** could be isolated in 88% yield and 99% ee. To the best of our knowledge, this is the first protocol for the palladium-catalyzed direct functionalization of *N*-Boc-protected amino acids.

We further demonstrated the scalability of both methods by conducting experiments on larger scale and prepared over 1 g of the products. As expected, the reaction works smoothly on gram-scale, and products **3a** and **11a** were isolated in 84% and 74% yield, respectively (Scheme 3). Importantly, the olefination of α-phenylglycine **1g** was conducted under atmospheric air. In an attempt to lower the catalyst loading, we attempted the same reactions on 0.5 mmol scale, each with 2.5 mol % $Pd(OAc)_2$. In the case of the olefination of Boc-protected α-phenylglycine, the ^1H NMR yield was 59% and in the case of the arylation of pivaloyl-protected mandelic acid, the yield was 43% by ^1H NMR.

3. CONCLUSION

In conclusion, we have developed diverse and high yielding *o*-C−H functionalizations of readily available, enantiomerically pure pivaloyl-protected mandelic acid. Ortho-olefination of Boc-protected α-phenylglycine has also been achieved for the first time in this work. The installation of a directing group is not needed for these reactions, and monoselectivity is achieved by optimizing conditions or choosing a MPAA ligand. As a consequence, we expect these methodologies will be rapidly adopted to prepare diverse, chiral phenyl acetic acid derivatives for use in synthesis and medicinal chemistry.

4. EXPERIMENTAL SECTION

General Procedure for the Arylation of Mandelic Acid (Table 3). An 8 mL vial with a fully covered solid Teflon-lined screw cap equipped with a magnetic stir bar was charged with the substrate (0.1 mmol, 1.0 equiv), ArI (0.2 mmol, 2.0 equiv), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 5 mol %), AgOAc (33 mg, 0.2 mmol, 2.0 equiv), KOAc (29 mg, 0.3 mmol, 3.0 equiv), and HFIP (1 mL). The vial was closed and stirred at 80 °C for 24 h. The reaction vessel was then cooled to rt. A 1.0 N HCl solution (1 mL) was then added, and the mixture was extracted with Et_2O (3 × 3 mL). The organic layers were combined, filtered through a pad of Celite 545, and concentrated in vacuo. The resulting residue was purified by preparative TLC using 2:1 hexanes:EtOAc (with 1% HOAc) as the eluent.

General Procedure for the Acetoxylation of Mandelic Acid (Scheme 2). An 8 mL vial with fully covered solid Teflon lined screw

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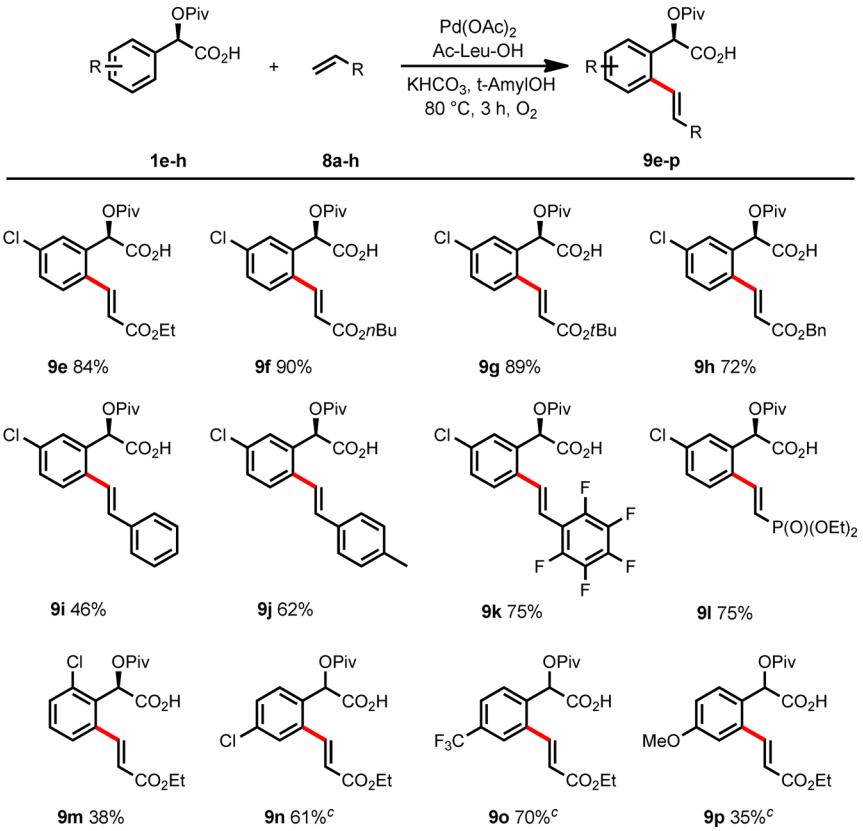
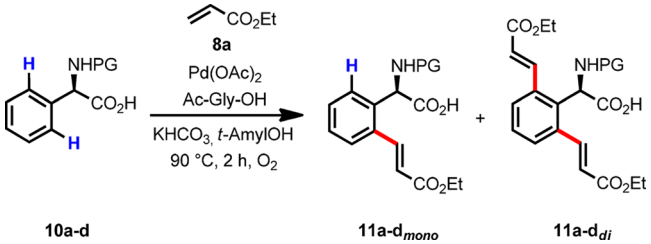
Table 6. Scope of Olefination Reaction of Mandelic Acid[a,b]



[a]Reaction conditions: **1** (0.1 mmol), **8** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), Ac-Leu-OH (15 mol %), $KHCO_3$ (0.2 mmol), *tert*-amylOH (0.5 mL), O_2 (1 atm), 80 °C, 3 h. [b]Yields after chromatographic purification. [c]Ac-Gly-OH instead of Ac-Leu-OH.

Table 7. Investigation of Protecting Groups for α-Phenylglycine[a,b]



		conv (%)[b]			
entry	PG	no ligand	Ac-Gly-OH	mono:di[b]	yield (%)[c]
1	Boc	68	85	>20:1	80
2	Phth	traces	76	>20:1	73
3	Fmoc	traces	72	>20:1	67
4	Ac	0	10	>20:1	n.i.[d]

[a]Reaction conditions: **10** (0.1 mmol), **8a** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), Ac-Gly-OH (15 mol %), $KHCO_3$ (0.2 mmol), *tert*-amylOH (0.5 mL), O_2 (1 atm), 90 °C, 2 h. [b]Determined by ^1H NMR analysis of crude reaction mixture. [c]Yields of $\mathbf{11}_{mono}$ after chromatographic purification. [d]n.i. = not isolated.

cap equipped with a magnetic stir bar was charged with the substrate (0.1 mmol, 1.0 equiv), $PhI(OAc)_2$ (64 mg, 0.2 mmol, 2.0 equiv), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 5 mol %), KOAc (29 mg, 0.3 mmol, 3.0 equiv) and HFIP (1 mL). The vial was closed and stirred at 50 °C for 24 h. The reaction vessel was then cooled to rt. A 1.0 N HCl solution (1 mL) was then added, and the mixture was extracted with Et_2O (3 × 3 mL). The organic layers were combined, filtered through a pad of Celite 545 and concentrated in vacuo. The resulting residue was purified by preparative TLC using 2:1 hexanes:EtOAc (with 1% HOAc) as the eluent.

General Procedure for the Iodination of Mandelic Acid (Scheme 2). An 8 mL vial with fully covered solid Teflon-lined screw cap equipped with a magnetic stir bar was charged with the substrate (0.1 mmol, 1.0 equiv), I_2 (51 mg, 0.2 mmol, 2.0 equiv), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 5 mol %), AgOAc (33 mg, 0.2 mmol, 2.0 equiv), KOAc (29 mg, 0.3 mmol, 3.0 equiv), and HFIP (1 mL). The vial was closed and stirred at 50 °C for 24 h. The reaction vessel was then cooled to rt. A 1.0 N HCl solution (1 mL) was then added, and the mixture was extracted with Et_2O (3 × 3 mL). The organic layers were combined, filtered through a pad of Celite 545, and concentrated in vacuo. The resulting residue was purified by preparative TLC using 2:1 hexanes:EtOAc (with 1% HOAc) as the eluent.

General Procedure for the Olefination of Mandelic Acid and α-Phenylglycine (Tables 6 and 8). An 8 mL vial with septum screw cap equipped with a magnetic stir bar was charged with the substrate (0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 5 mol %), Ac-Leu-OH (2.6 mg, 0.015 mmol, 15 mol %), and $KHCO_3$ (20 mg, 0.2 mmol, 2.0 equiv). The vial was evacuated and flushed with O_2 (three times, CAUTION! The reaction is run in a sealed vessel at elevated temperature under a 1 atm O_2 environment. Though no incidents have been encountered in the submitters' laboratory, it is nonetheless recommended that a blast shield be used while heating in larger scale). After adding dry *tert*-amylOH (0.5 mL) and the olefin coupling partner (0.2 mmol, 2.0 mmol) to the reaction mixture, the vial was closed with a fully covered solid Teflon lined cap and stirred at 80 °C for 3 h. The reaction vessel was then cooled to rt. A 1.0 N HCl solution (1 mL) was then added, and the mixture was extracted with Et_2O (3 × 3 mL). The organic layers were combined, filtered through a pad of Celite 545, and concentrated in vacuo. The resulting residue was purified by preparative TLC using 2:1 hexanes:EtOAc (with 1% HOAc) as the eluent.

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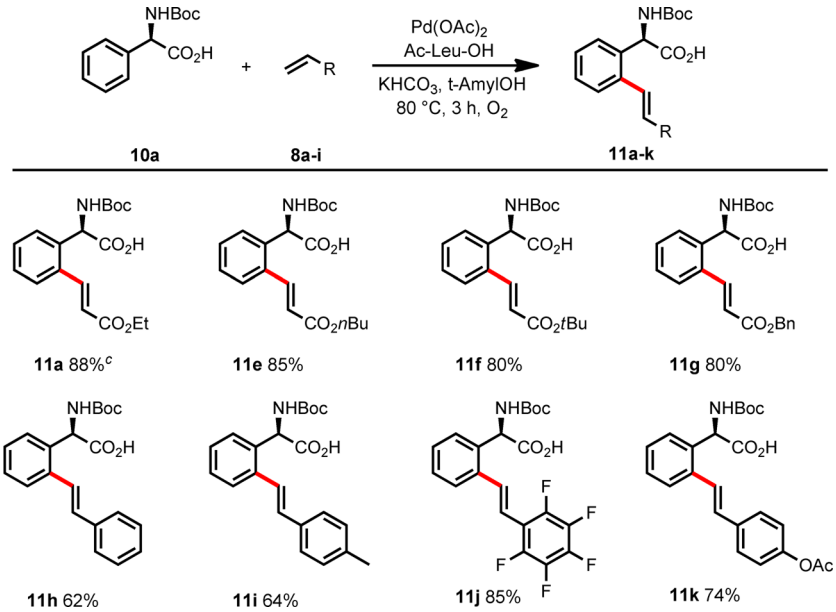
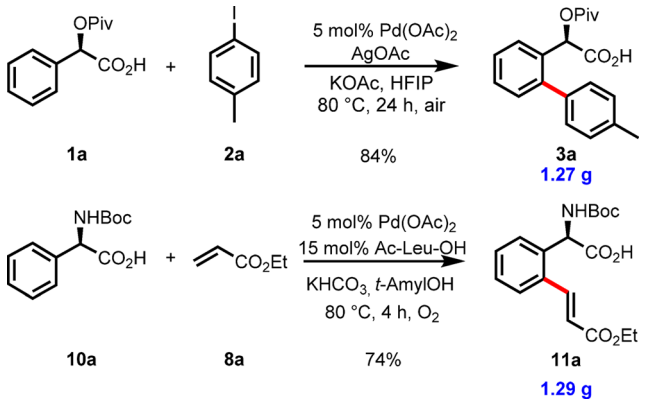
Table 8. Scope of Olefination Reaction of α-Phenylglycine[a,b]



[a]Reaction conditions: **10a** (0.1 mmol), **8** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), Ac-Leu-OH (15 mol %), $KHCO_3$ (0.2 mmol), *tert*-amylOH (0.5 mL), O_2 (1 atm), 80 °C, 3 h. [b]Yields after chromatographic purification. [c]99% ee, determined by chiral HPLC.

Scheme 3. Gram-Scale Synthesis



■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization of new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04324.

■ AUTHOR INFORMATION

Corresponding Author

*yu200@scripps.edu

Notes

The authors declare no competing financial interest.

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