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Directed, Palladium(II)-Catalyzed Intermolecular Aminohydroxylation of Alkenes Using a Mild Oxidation System

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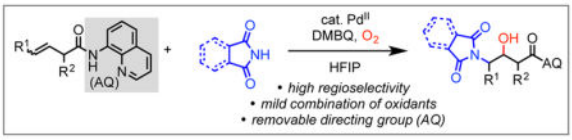
Abstract

A palladium(II)-catalyzed β,γ-aminohydroxylation reaction of non-conjugated alkenyl carbonyl compounds has been developed. This reaction utilizes a cleavable bidentate directing group to achieve regioselective aminopalladation. The resulting chelation-stabilized alkylpalladium(II) intermediate is then hydroxylated using oxygen/2,6-dimethylbenzoquinone in HFIP as the mild oxidation system. Under optimized conditions, various nucleophiles and alkene substrates are capable of delivering good yields and high diastereoselectivity of the aminohydroxylated product.

Graphical Abstract



Since its discovery in 1996 by Sharpless and coworkers,[1] catalytic aminohydroxylation of alkenes has been recognized as a powerful tool in synthetic chemistry to enable expedient access to 1,2-amino alcohols, including those embedded in bioactive compounds.[2] Since then, significant effort has been devoted to expanding the scope of the coupling partners[3] and achieving analogous aminooxygenation reactivity using palladium,[4,5] copper,[6] iron,[7] platinum,[8] and nonmetal[9] catalysts to replace osmium. In particular, the past two decades have witnessed significant advancements in the area of palladium(II)-catalyzed aminooxygenation. Mechanistically, such reactions generally require rapid interception of the reactive aminopalladated alkylpalladium(II) species with a strong oxidant to facilitate C–O reductive elimination from a high-valent intermediate. Intramolecular palladium(II)-

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

Experiment details, spectra data, copies of ^{1}H and ^{13}C NMR spectra, and X-ray crystallographic data. These materials are available free of charge via the Internet at http://pubs.acs.org.

catalyzed aminohydroxylations have generally tolerated a broader scope of oxidants than intermolecular variants. Examples of the former category have been reported with hypervalent iodine,[4a] copper chloride,[4b] hydrogen peroxide/acetic acid,[4c] oxygen/acetic acid,[4d] and nitrogen dioxide from copper(II) nitrate trihydrate[4e] (Scheme 1A). On the other hand, the latter category, has only been described with hypervalent iodine oxidants to the best of our knowledge (Scheme 1B).[5] Though efficacious, these strong oxidants are disadvantageous in terms of functional group compatibility and atom economy. The goal of the present study was to develop an intermolecular alkene 1,2-aminooxygenation reaction using a mild oxidation system by taking advantage of a substrate directivity approach.

Our group has previously developed a series of intermolecular alkene hydrofunctionalization and 1,2-difunctionalization reactions by utilizing a bidentate directing group to govern regioselectivity in the Wacker-type nucleometallation step and also to stabilize the resulting alkylpalladium(II) species for downstream elementary steps.[10,11] Based on this precedent, we questioned whether these intermediates would be sufficiently long-lived to react with weaker electrophilic O-atom sources. We were particularly interested in accessing aminooxygenated products bearing free OH groups directly, as such reactions are historically less precedented.

To initiate our investigation, we considered 3-butenoic acid masked as its 8-aminoquinoline (AQ) amide (**1a**) as the model substrate, phthalimide as nitrogen nucleophile, hexafluoroisopropanol (HFIP) as solvent, and 2,6-dimethylbenzoquinone (DMBQ) as oxidant under air at 100 °C (Table 1). We were excited to find that these conditions yielded 43% of the aminohydroxylated product. Upon screening oxidant (entry 1–3), acid/base (entry 4–7), solvent (entry 8–10), and temperature (entries 1, 11, and 12), we found that our first attempt gave the highest yield. We then performed control experiments in an attempt to identify the oxygen atom source in the system (entries 13 and 14) and found that no product was detected when the reaction was run under nitrogen atmosphere. This led us to speculate that oxygen in the air was the oxygen source and an essential component of the catalytic cycle. Therefore, we continued to optimize the equivalents of DMBQ (entry 15–18) under oxygen atmosphere, and we found that 2 equiv DMBQ yielded 80% product (entry 17).[12]

Having identified optimal conditions, we next investigated the scope of this Pd(II)-catalyzed alkene aminohydroxylation reaction. First, nitrogen nucleophiles were tested with alkene substrate **1a**. Similar to earlier work,[5] we found that cyclic imide nucleophiles with structures similar to phthalimide were compatible coupling partners (**3a–3e**). However, several other nitrogen nucleophiles that had previously been proven to be competent in related reactions,[10a,10d,10e] including saccharin, carbazole, isatin, glutarimide, and thalidomide, were incompatible under these reaction conditions (see Supporting Information). We also attempted selected 1,3-dicarbonyl carbon nucleophiles, but no carbohydroxylated product was observed in these cases. The nucleophile scope for this transformation is much more restricted than that of our other palladium(II)-catalyzed difunctionalization reactions, and at this stage we are unclear on the underlying origin of this phenomenon. One possibility is that after nucleopalladation, a carbonyl group on the phthalimide coordinates to the palladium as a third ligand,[10b,10f] thereby tuning the steric

and electronic environment around the palladium to enable coordination and reaction with the active O-atom electrophile (e.g., O_2).

Subsequently, we examined the scope of non-conjugated alkene substrates with phthalimide **2a** as the nucleophile. An array of α-substituted terminal alkene substrates performed well under the reaction conditions, leading to formation of a single diastereomer in all cases (**3f**–**3k**).[10c] The transformation, however, was found to be sensitive to steric hinderance at the α-position. In particular, attempts to react alkenes with a bulky α-isopropyl group or α, α-*gem*-dimethyl substitution led only to recovered starting material. We were pleased to find that an internal 1,2-dialkyl alkene also worked to some extent in this reaction (**3l**), though it required longer reaction time, higher catalyst loading, and elevated temperature. More sterically congested internal alkenes did not yield the desired product. Interestingly, this reaction also gave small quantities of product when an alternative non-conjugated alkene substrate class was used, namely homoallyl amines masked by a picolinamide bidentate directing group (**3m**). Several other bidentate directing groups were also tested, but none were effective in this reaction (see Supplementary Information).

To demonstrate the practical utility and operational simplicity of this palladium(II)-catalyzed alkene aminohydroxylation method, we performed the reaction on 2.0-mmol scale with alkene substrate **1a** and 1.0-mmol scale with **1f** using phthalimide (**2a**) as nucleophile. In both cases, reaction performance was consistent with that of smaller scale reactions, providing 75% and 82% yields, respectively (Scheme 2).

Several downstream manipulations of the aminohydroxylated product were next performed (Scheme 3). To cleave the AQ directing group, the free hydroxy group was first protected with a *tert*-butyldimethylsilyl (TBS) group, and the AQ was then hydrolyzed in two steps, affording the deprotected carboxylic acid product **4** in quantitative yield.[10d] The AQ directing group could also be transformed in one step to ester derivative **5** via nickel-catalyzed methanolysis.[14] Moreover, after phthalimide deprotection the resulting primary amine was found to undergo cyclization to cleave the directing group and form β-hydroxy-γ-lactam derivative **6**.[10d,10e] We discovered, perhaps unsurprisingly, that this β-hydroxy AQ amide motif is quite susceptible to elimination upon activation; for instance, heating the mesyl-protected alcohol in triethylamine gave 96% of protected trans-4-aminocrotonic acid **7**,[15] which is a potent agonist of GABA(A) and GABA(C) receptors.[16]

Finally, we sought to elucidate the mechanism of this palldium(II)-catalyzed intermolecular aminohydroxylation reaction. We first considered a mechanism in which alkene hydroamination[10a] was followed by directed C(sp^3)–H oxidation. However, this pathway was ruled out because the putative hydroaminated intermediate was found to be unreactive in C(sp^3)–H oxidation under the reaction conditions (Scheme 4A). This indicated that a general reactivity paradigm involving reaction of an aminopalladated intermediate with an O-atom electrophile was operative. We then turned to isotopic labeling experiments to investigate the source of the hydroxy group in the final product. To eliminate the possibility of labeled oxygen sources being exchanged with the oxygen atoms in the inorganic base of $KHCO_3$, reactions were conducted under modified conditions using potassium phthalimate as nucleophile; under these conditions standard product **3a** was isolated in 65% yield after 44

hours (Scheme 4B, entry 1). We next ran the reaction under $^{18}O_2$ atmosphere and observed 26% yield of 70% singly labeled product, and 18% doubly labeled product according to MS (entry 3).[17] On the other hand, using $^{16}O_2$ atmosphere and doping in 1 equiv of $H_2{}^{18}O$ led to high yield but only 12% ^{18}O incorporation (entry 4). The high amount of oxygen incorporation with $^{18}O_2$ atmosphere but not with $H_2{}^{18}O$ is consistent with a mechanism in which the OH in the product originates primarily from O_2. This finding also agrees with our initial observation that the reaction does not take place under nitrogen atmosphere (Table 1, entry 13). Additional labeling experiments with $H_2{}^{18}O$ have established that O-atom exchange between water and the carbonyl groups of the product takes place under the reaction conditions. This pathway is likely responsible for the detection of singly labeled product in the case of entry 3 and doubly labeled product in the case of entry 2 (see Supplementary Information).

At this stage, we are uncertain whether O_2 reacts directly to oxidize the alkylpalladium(II) intermediate to a Pd(III) or Pd(IV) species[18] or whether O_2 is first converted in situ to a reactive oxygen species, such as a peroxide.[4c,4d] The combination of hydrogen peroxide and DMBQ under nitrogen atmosphere under standard conditions was found to provide 37% of the aminohydroxylated product (Scheme 4C, entry 1), indicating that H_2O_2 is a competent oxidant. Other peroxides, such as DTBP, were ineffective under similar conditions, unless used in the presence of oxygen (see Supplementary Information). Based on the results described above, we propose the mechanism shown in Scheme 5, where the oxygen atom in the product is introduced from oxygen atmosphere (Scheme 5).

In conclusion, we have developed a palladium(II)-catalyzed intermolecular aminohydroxylation reaction of non-conjugated alkenes bearing a removable 8-aminoquinoline directing group with DMBQ/O_2/HFIP as the oxidant. This reaction has allowed us to achieve intermolecular β,γ-selective aminooxygenation of 3-butenoic acid derivatives, using oxygen as the OH source. The reaction proceeded smoothly with a range of phthalimide-type nucleophiles and various substituted alkene substrates. The reaction was amenable to scale up, and the 8-aminoquinoline directing group could be easily removed via hydrolysis to provide bioactive compounds. Future investigations will focus on characterizing the reactive O-atom electrophile and elucidating the mechanistic details of the oxidation and C–O reductive elimination steps. Additionally, subsequent studies will seek to and expand the nucleophile and electrophile scope of this approach to alkene difunctionalization. These results will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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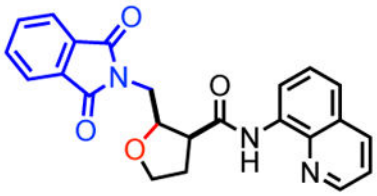
12. See Supplementary Information for other unsuccessful oxidant screens.
13. Benzyl-deprotected byproduct **3k′** was also formed in 13% yield.



(±)-**3k'**, 13%
d.r. > 20:1

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17. This reaction was performed in an autoclave rather than in the standard reaction vessel (Schleck tube, which was charged with O_2 using a balloon). The autoclave was used in this case in order to minimize the volume of $^{18}O_2$ that is wasted during the reaction setup. See the Supporting Information for an experimental procedure. We believe that the lower yield with the autoclave is due to difference in the optimized experimental setup, as the yield of an identical reaction in the autoclave under $^{16}O_2$ atmosphere was 33%.
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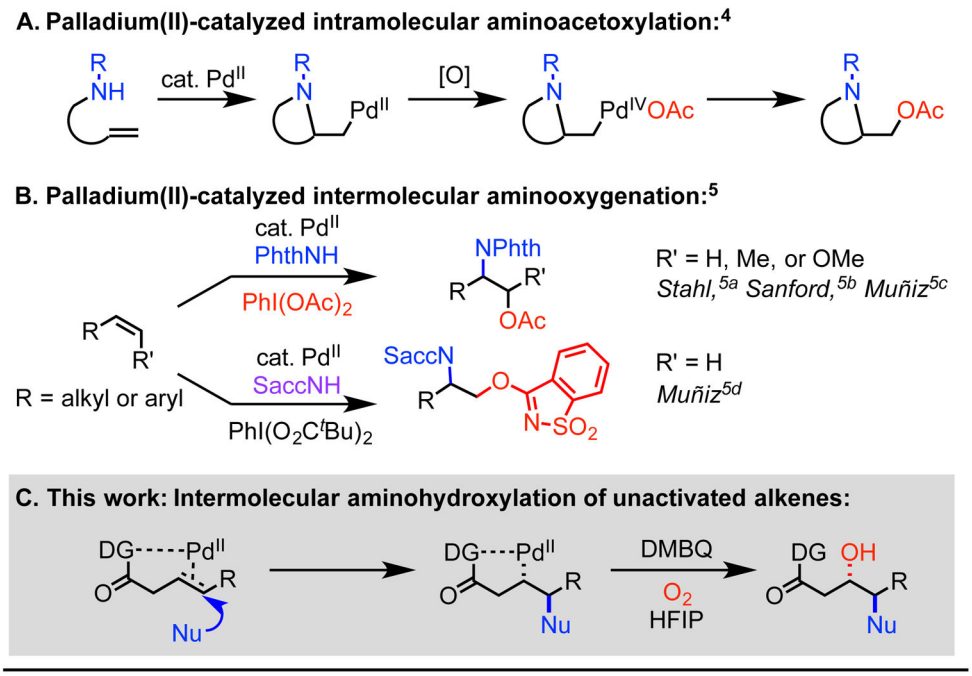
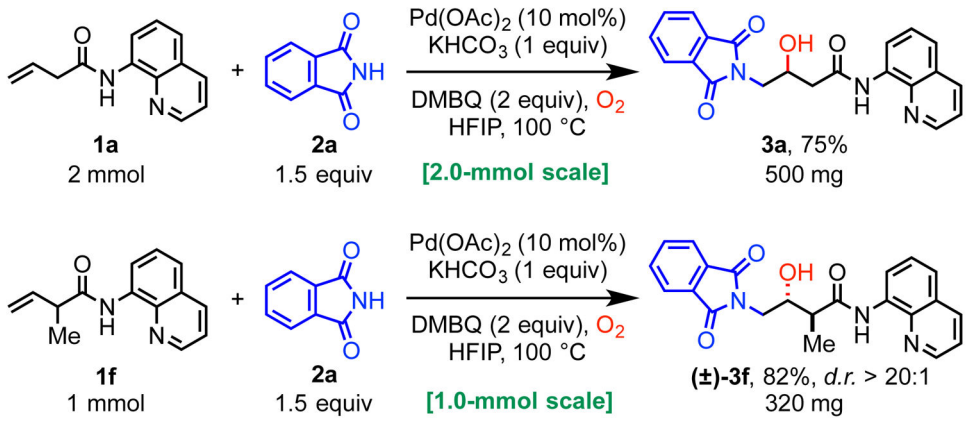
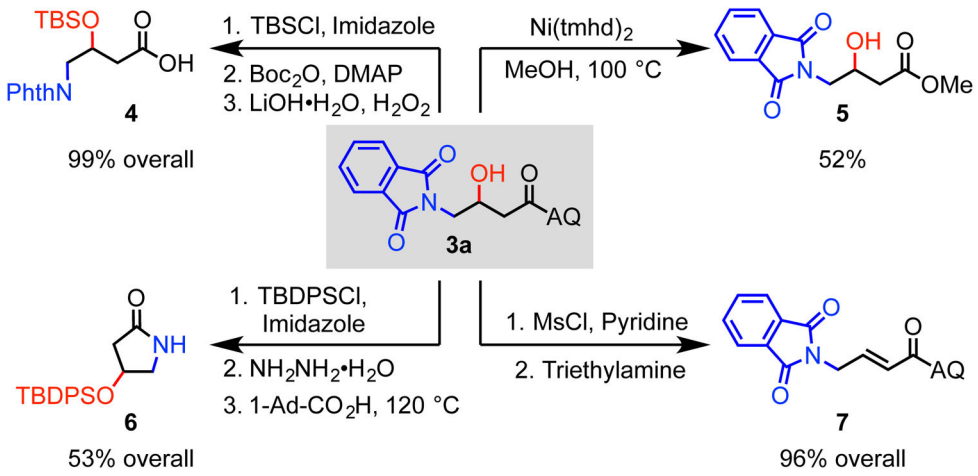


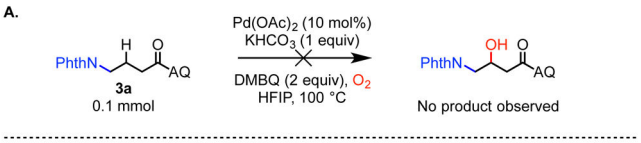
Scheme 1.
Background and Project Synopsis

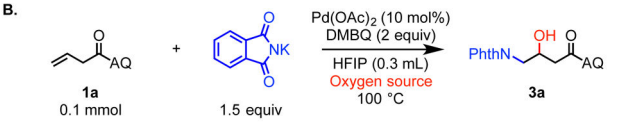


Scheme 2.
Aminohydroxylation Scale-Up

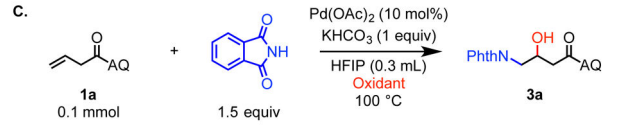


Scheme 3.
Product Deprotection and Diversification





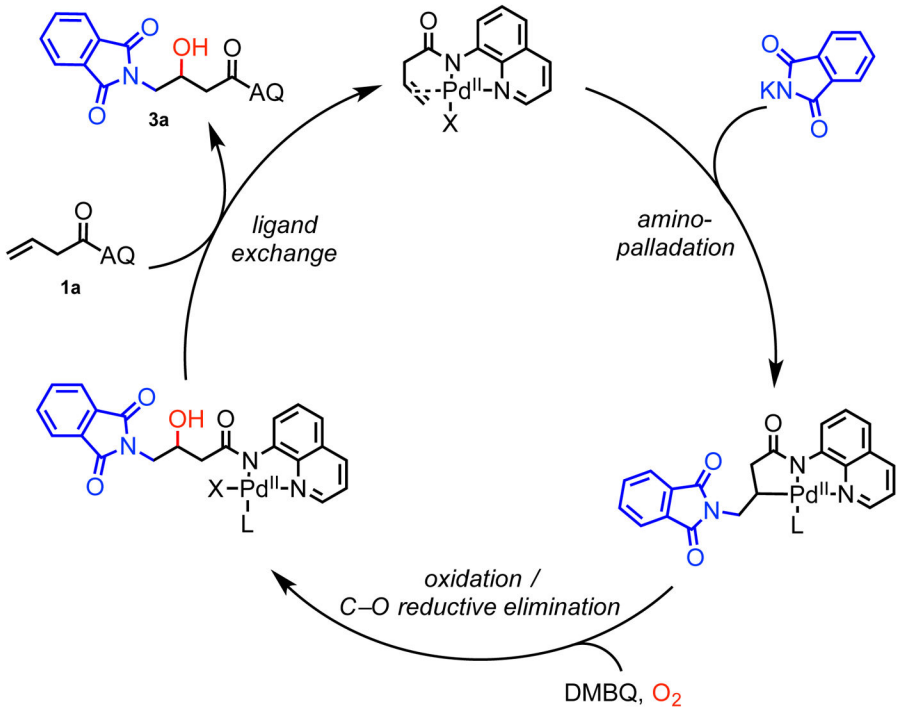
Entry	Oxygen source	Time	^{18}O Incorporation[a]		Yield
1	$^{16}O_2$	44 h	0 %	(0 %)	65 %
2[b]	$^{18}O_2$	44 h	70 %	(18 %)	26 %
3	1 equiv $H_2{}^{18}O$, $^{16}O_2$	44 h	12 %	(0 %)	73 %



Entry	Oxidant	Atmosphere	1a	3a
1	2 equiv DMBQ + 2 equiv H_2O_2	N_2	39 %[c]	37 %
2	2 equiv H_2O_2	N_2	15 %[c]	N.D.
3	2 equiv H_2O_2	Air	16 %[c]	10 %[c]

Scheme 4. Mechanistic Studies

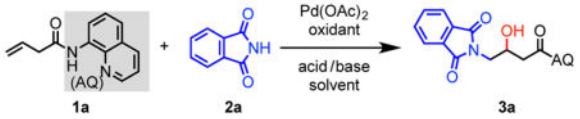
[a] Percentages in parenthesis indicate the amount of doubly labeled product. [b] Reactions run using an autoclave (see footnote 16). [c] The percentage refers to yields determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-triisopropylbenzene as internal standard.



Scheme 5.
Proposed Labeling Mechanism

Table 1

Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	acid / base	oxidant	atmosphere	solvent	yield[b]
1	$KHCO_3$	DMBQ	air	HFIP	(59)
2	$KHCO_3$	benzoquinone	air	HFIP	(34)
3	$KHCO_3$	dimethoxybenzoquinone	air	HFIP	(7)
4	AcOH	DMBQ	air	HFIP	n.d.
5[c]	$KHCO_3$	DMBQ	air	HFIP	(40)
6	K_2HPO_4	DMBQ	air	HFIP	(42)
7	$^{i}Pr_2NEt$	DMBQ	air	HFIP	(30)
8	$KHCO_3$	DMBQ	air	^{t}AmylOH	(10)
9	$KHCO_3$	DMBQ	air	DMF	(5)
10	$KHCO_3$	DMBQ	air	dioxane	(10)
11[d]	$KHCO_3$	DMBQ	air	HFIP	(12)
12[e]	$KHCO_3$	DMBQ	air	HFIP	(14)
13[f]	$KHCO_3$	DMBQ	air	HFIP	(23)
14	$KHCO_3$	DMBQ	N_2	HFIP	n.d.
15	$KHCO_3$	DMBQ	O_2	HFIP	65
16	$KHCO_3$	DMBQ (0.5 equiv)	O_2	HFIP	50
17	**$KHCO_3$**	**DMBQ (2.0 equiv)**	**O_2**	**HFIP**	**80**
18	$KHCO_3$	DMBQ (3.0 equiv)	O_2	HFIP	73

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (1.5 equiv), $Pd(OAc)_2$ (10 mol %), oxidant (1.5 equiv), base (1 equiv), solvent (0.2 mL), 100 °C, 12–16 h.

[b]Isolated yield. Values in parentheses represent yields determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-triisopropylbenzene as internal standard.

[c]$KHCO_3$ (0.5 equiv).

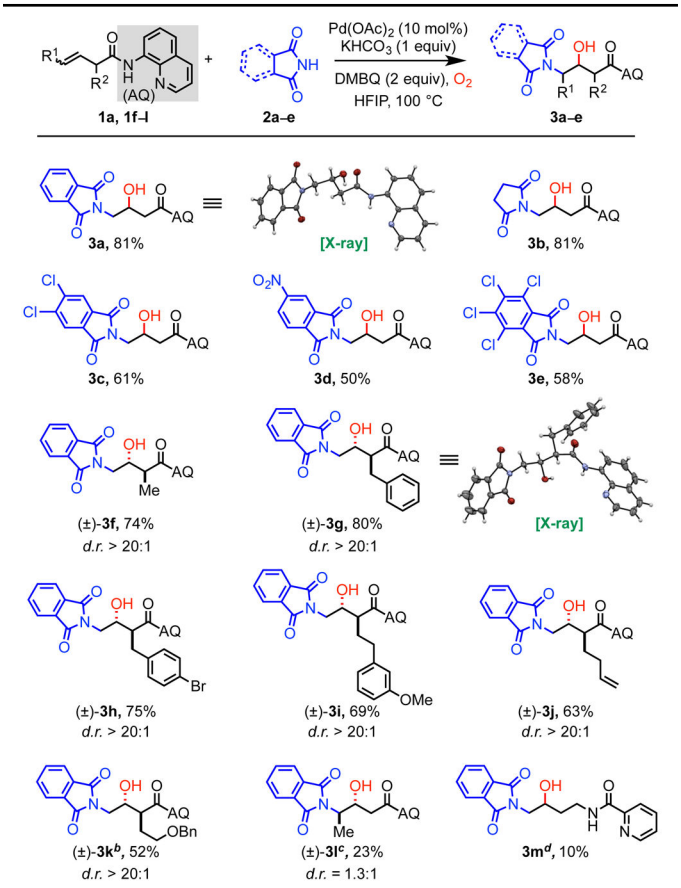
[d] 120 °C.

[e] 80 °C.

[f] 4Å molecular sieves as additive.

Table 2

Reaction Substrate Scope.[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (1.5 equiv), $Pd(OAc)_2$ (10 mol %), DMBQ (2 equiv), K_2CO_3 (1 equiv), HFIP (0.2 mL), 100 °C, O_2 (1 atm), 12–16 h. Percentages refer to isolated yields.

[b]Intramolecular cyclized compound was also recovered (see footnote 13).

[c]$Pd(OAc)_2$ (15 mol%), 120 °C, 2 d.

[d]*N*-(but-3-en-1-yl)picolinamide was used as the alkene.