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Utility of Organoboron Reagents in Arylation of Cyclopropanols via Chelated Pd(II) Catalysis: Chemoselective Access to β-Aryl Ketones

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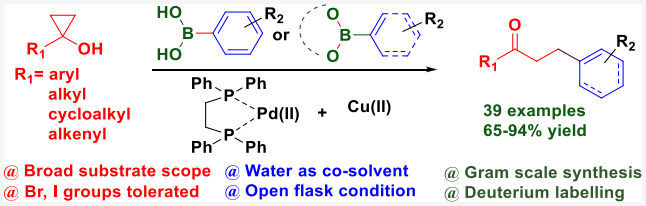
ABSTRACT: Organoborane reagents were investigated as coupling partners to cyclopropanol-derived β-ketone enolates in the presence of a chelated Pd(II) catalyst. Efficient coupling of a range of electronically and sterically diverse cyclopropanols and aryl/alkenyl boronic derivatives (39 examples, 65−94% yield) could be achieved with the generation of synthetically important β-aryl ketone intermediates in a chemoselective fashion. This reactivity paradigm, which broadens the scope of aryl donor partners to homoenolates, allows open-flask conditions, water as a cosolvent, and preparation of halogen-bearing β-aryl ketones that are distinct from previous methods. This chelated Pd(II) catalysis appears to be different from the Pd(0) pathway, as evident from deuterium scrambling studies that could reveal differentiating protonolysis of an α-keto carbopalladium complex in the terminal step.



INTRODUCTION

Because of the unique function of cyclopropanols as precursors of ketone homoenolates, there has been an emerging interest in the cyclopropanol-derived formation of new C−C, C−N, C−O, C−S, and C−X (X = halogen) bonds in recent years.[1,2] They can serve as a structurally distinct class of umpolung three-carbon synthons or β-aryl carbonyl equivalents that could provide fast access to diverse and valuable organic molecules via unusual retrosynthetic disconnection approaches.[3] This synthetic versatility of cyclopropanols has led to the development of several protocols for facile access from a variety of readily available starting materials.[4] Notably, cyclopropanols can be readily prepared from carboxylic esters via the Kulinkovich reaction, involving $Ti(O^iPr)_4$-catalyzed cross-coupling with ethyl Grignard reagents.[4]

In a seminal and elegant work, silyl-protected cyclopropanols were shown to couple to an aryl electrophile (aryl triflate) by Nakamura and Kuwajima, involving Pd(0)-catalyzed β-arylation of cyclopropanol-derived ketone homoenolates.[5] Subsequently, Molander et al. demonstrated that potassium trifluoroboratohomoenolates could readily undergo Pd(0)-promoted Suzuki−Miyaura arylation, leading to facile access of β-functionalized carbonyl derivatives.[6] Recently, it was shown that protection-free cyclopropanols could also undergo Pd(0)-mediated C−C bond formation under mild conditions with aryl halides via cyclopropanol-derived ketone or aldehyde homoenolates (Scheme 1).[7−10] However, the observation of a mixture of products in certain cases arising out of the formation of the competitive β-elimination byproduct may constitute as a potential limiting factor from the chemoselectivity perspective. Moreover, these studies do not offer a preparative scope to synthesize halogen-appended (specifically, Br and I) β-aryl aldehydes or ketones. This lack of generality assumes significance in the context of tactical applications of halogen functionality on an aromatic ring by medicinal chemists for late-stage diversification in the lead optimization phase in a library synthesis mode through well-known C−C and C−X (X = N, O, S) cross-couplings, for example, Suzuki, Buchwald−Hartwig, and Ullmann protocols. Nevertheless, reported Pd(0)-catalyzed reactions, which require inert atmospheric conditions to prevent the oxidation of Pd(0) by molecular oxygen, do not provide the advantage of performing reactions under open-flask conditions. Also, the feasibility of using water as an environmentally friendly solvent or cosolvent has not been disclosed in the arylation of cyclopropanols.

These constraining factors encouraged us to search for an alternative disconnection approach, which would potentially replace the oxidative addition of an aryl halide or triflate bond to a Pd(0) complex with an equivalent yet different protocol. Accordingly, we contemplated making use of a transmetalation approach, which would allow the generation of the ArPd(II) addition product, from a Pd(II) center and an organometallic reagent in order to promote a selective process in which the halogen functionality is sustained (Scheme 2).

This strategy relied on the precedence of transmetalation-based intermolecular Pd(II)-catalyzed oxidative Heck coupling of olefins with organometallic reagents, which has recently

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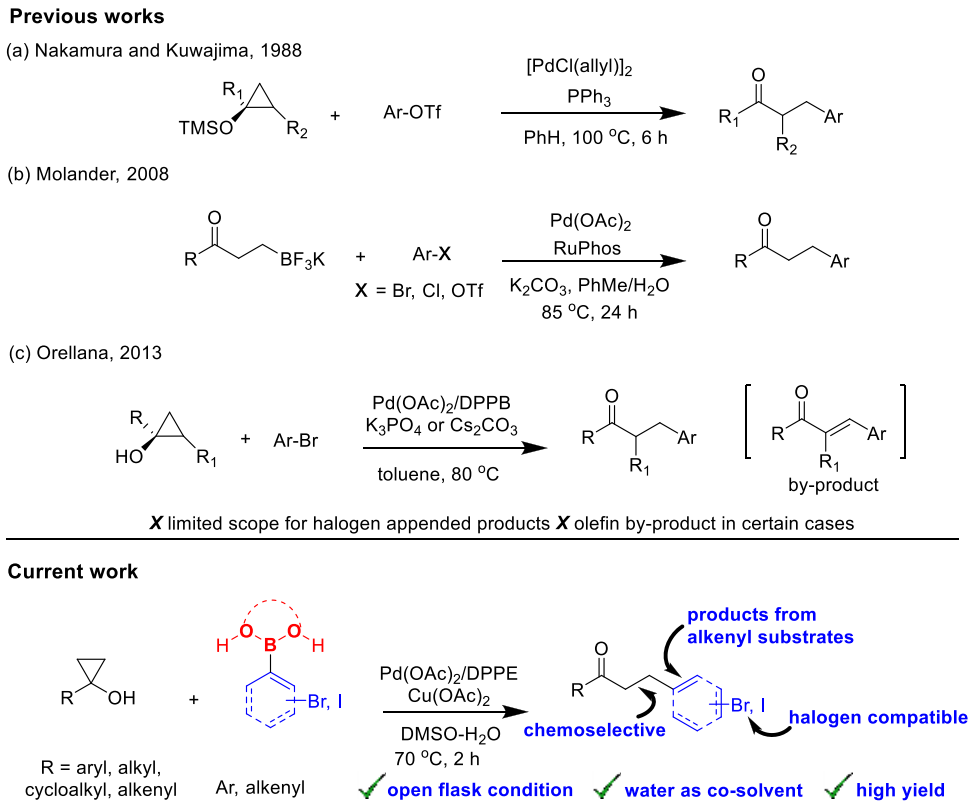
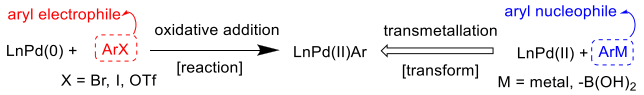
Scheme 1. Comparison of the Present Methodology with Previous Work



Scheme 2. An Antithetic Approach That Would Impart Aryl Nucleophiles as Synthons



emerged as one of the most reliable and efficient methods for C−C bond formation.[11−14] One of the elegant features of this chemistry is the exploitation of organoboronic acids or their derivatives as the powerful arylation resources that are readily available with wide commercial supply, easy to synthesize, relatively less toxic, and mostly stable to air and moisture. Importantly, the catalytic transition metal-mediated or metal-free direct C−H borylation of a range of substrates (for example, arenes and heteroarenes) has greatly expanded the synthetic scope of this class of reagents.[15] We earlier reported direct C−H functionalization of quinones via a radical strategy using arylborornic acids and cyclopropanols that delivered arylated quinones,[16] and γ-carbonyl quinones,[17] respectively. As an extension of our research interest in exploiting cyclopropanols as synthetically useful three-carbon homoeno-

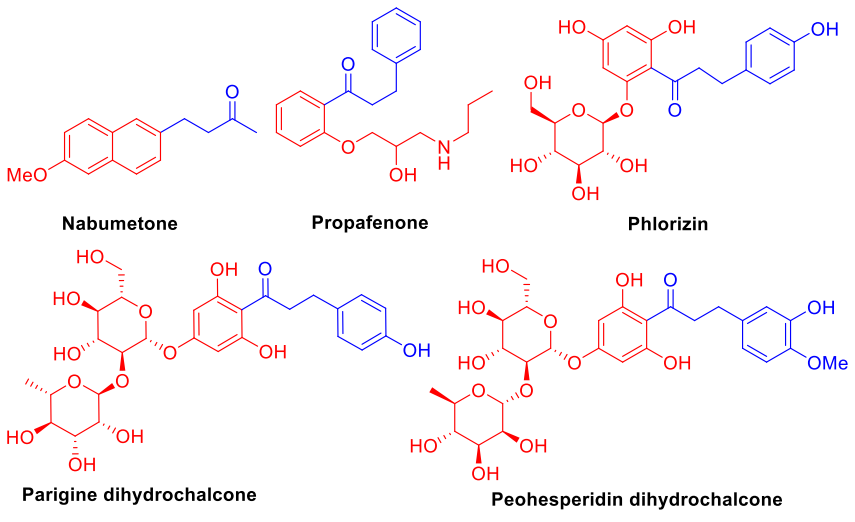


Figure 1. Select examples of pharmaceutically important β-aryl ketone derivatives.

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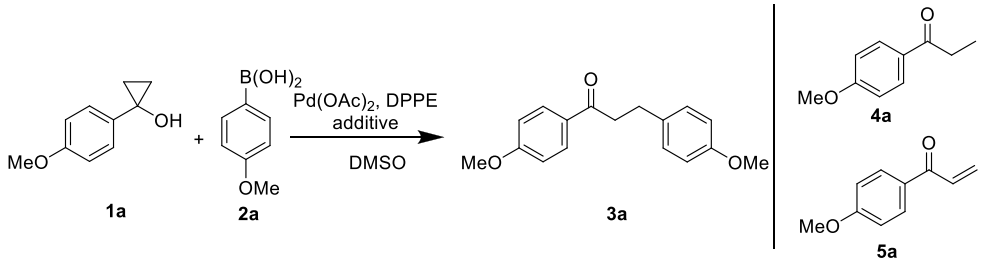
Table 1. Screening of Reaction Conditions to Identify an Efficient Protocol[a]



entry	Pd source	ligand	solvent	additive (equiv)	air/O_2	% yield (**3a**)[b]
1	$Pd(OAc)_2$	DPPE	DMSO	none	O_2	49
2	$Pd(OAc)_2$	DPPE	DMSO	CuCl (0.2)	O_2	58
3	$Pd(OAc)_2$	DPPE	DMSO	CuBr (0.2)	O_2	44
4	$Pd(OAc)_2$	DPPE	DMSO	CuCl (0.2) + KOAc (1.0)	O_2	57
5	$Pd(OAc)_2$	DPPE	DMSO	CuCl (1.0)	O_2	73
6	$Pd(OAc)_2$	DPPE	DMSO	CuCl (1.5)	O_2	78
7	$Pd(OAc)_2$	DPPE	DMSO	CuCl (2.0)	O_2	83
8	$Pd(OAc)_2$	DPPE	DMSO	CuCl (3.0)	O_2	85
9	$Pd(OAc)_2$	DPPE	DMSO	$Cu(OAc)_2$ (3.0)	O_2	93
10	$Pd(OAc)_2$	DPPE	DMSO	$Cu(OAc)_2$ (3.0)	open air	91
11	$Pd(OAc)_2$	DPPE	DMSO	$Cu(OAc)_2$ (3.0)	open air	93
12	$Pd(OAc)_2$	DPPE	DMSO	$Cu(OAc)_2$ (2.0)	open air	94
13	$Pd(OAc)_2$	DPPE	DMSO + H_2O[c]	$Cu(OAc)_2$ (2.0)	open air	93
14	$Pd(OAc)_2$	neocuproine	DMSO + H_2O[c]	$Cu(OAc)_2$ (2.0)	open air	32
15	$Pd(OAc)_2$	bipyridyl	DMSO + H_2O[c]	$Cu(OAc)_2$ (2.0)	open air	47
16	$Pd(OAc)_2$	DPPE	dioxane + H_2O[c]	$Cu(OAc)_2$ (2.0)	open air	70
17	$Pd(OAc)_2$	DPPE	toluene + H_2O[c]	$Cu(OAc)_2$ (2.0)	open air	59
18	$PdCl_2$	DPPE	DMSO + H_2O[c]	$Cu(OAc)_2$ (2.0)	open air	88
19	$PdCl_2(MeCN)_2$	DPPE	DMSO + H_2O[c]	$Cu(OAc)_2$ (2.0)	open air	84
20	$Pd_2(dba)_3$	DPPE	DMSO + H_2O[c]	$Cu(OAc)_2$ (2.0)	open air	86
21	$Pd(OAc)_2$	DPPE	DMSO	$Cu(OAc)_2$ (2.0)	O_2	85[d]
22	$Pd(OAc)_2$	DPPE	DMSO	$Cu(OAc)_2$ (2.0)	O_2	87[e]
23	$Pd(OAc)_2$	DPPE	DMSO	$Cu(OAc)_2$ (2.0)	O_2	60[f]

[a]Until otherwise stated, the reactions were carried out with **1a** (1 equiv), **2a** (entries 1−10, 3.0 equiv; entry 11, 2.5 equiv; entries 12−20, 2.0 equiv), Pd source (entries 1−10, 0.2 equiv; entries 11−20, 0.1 equiv), ligand (0.2 equiv), and an additive in DMSO solvent (3.0 mL) under an oxygen atmosphere using an O_2 balloon or open-air atmosphere at 70 °C for 2 h. [b]Isolated yields [c]DMSO (2.5 mL) + H_2O (0.5 mL) (ratio 5:1). [d]Reaction temperature: 60 °C. [e]Reaction temperature: 80 °C. [f]1.0 equiv of **2a**.

late synthons and development of synthetic protocols for β-aryl carbonyl derivatives,[13,18] we report for the first time that arylboronic acids can effectively serve as the cross-coupling partners with the cyclopropanol-derived metal homoenolates to generate dihydrochalcones and related analogues in a chemoselective mode. Besides, this high yielding new methodology has afforded selective access to halogen-bearing β-aryl ketones, which were not possible by previously reported arylation of cyclopropanols. Moreover, homoenolates, as reverse-polarity synthons of a Michael acceptor, can be construed as precursors of enones, thereby imparting a general synthetic utility that would represent an alternative to the well-precedented conjugate addition of organometallic reagents, including boronic acids, to unsaturated ketones.[19−21]

The "β-aryl carbonyl" motif that includes the privileged dihydrochalcone moiety is an active area of synthetic interest because of the widespread prevalence in natural products of medicinal importance and occurrence in the structures of marketed drugs (Figure 1).[22−29] Applications of β-aryl alkyl carbonyl compounds as useful starting points/intermediates in (a) pharmaceutical chemistry to generate diverse scaffolds and/or drug-like compounds and (b) agricultural chemistry are well-documented. Reflecting the importance of β-aryl alkyl carbonyl derivatives, various synthetic methodologies have recently been reported.[30−35] This is illustrated in our recent report that offers mild and regioselective access to β-aryl aldehydes and ketones, from readily accessible allyl alcohols via a ligated Pd(II)-mediated arylative isomerization approach.[13,18] The present methodology, which is an addition to the compendium of existing methodologies, attempts to broaden the scope of starting materials, especially organoboronic derivatives. Importantly, carboxylic esters, which can be converted to β-aryl ketones via sequential application of the titanium-promoted cyclopropanation and palladium-mediated arylation, can further expand the substrate scope and utility in organic synthesis.

RESULTS AND DISCUSSION

The 1,1-disubstituted cyclopropanol **1a** and 4-methoxyphenylboronic acid **2a** were selected as the model substrates to test our hypothesis. While keeping $Pd(OAc)_2$ as the source of transition metal, bis(diphenylphosphino)ethane (DPPE) as the chelating ligand, and DMSO as the solvent, our initial study focused on the impact of additives under an oxygen atmosphere (balloon) at 70 °C (Table 1). To our delight,

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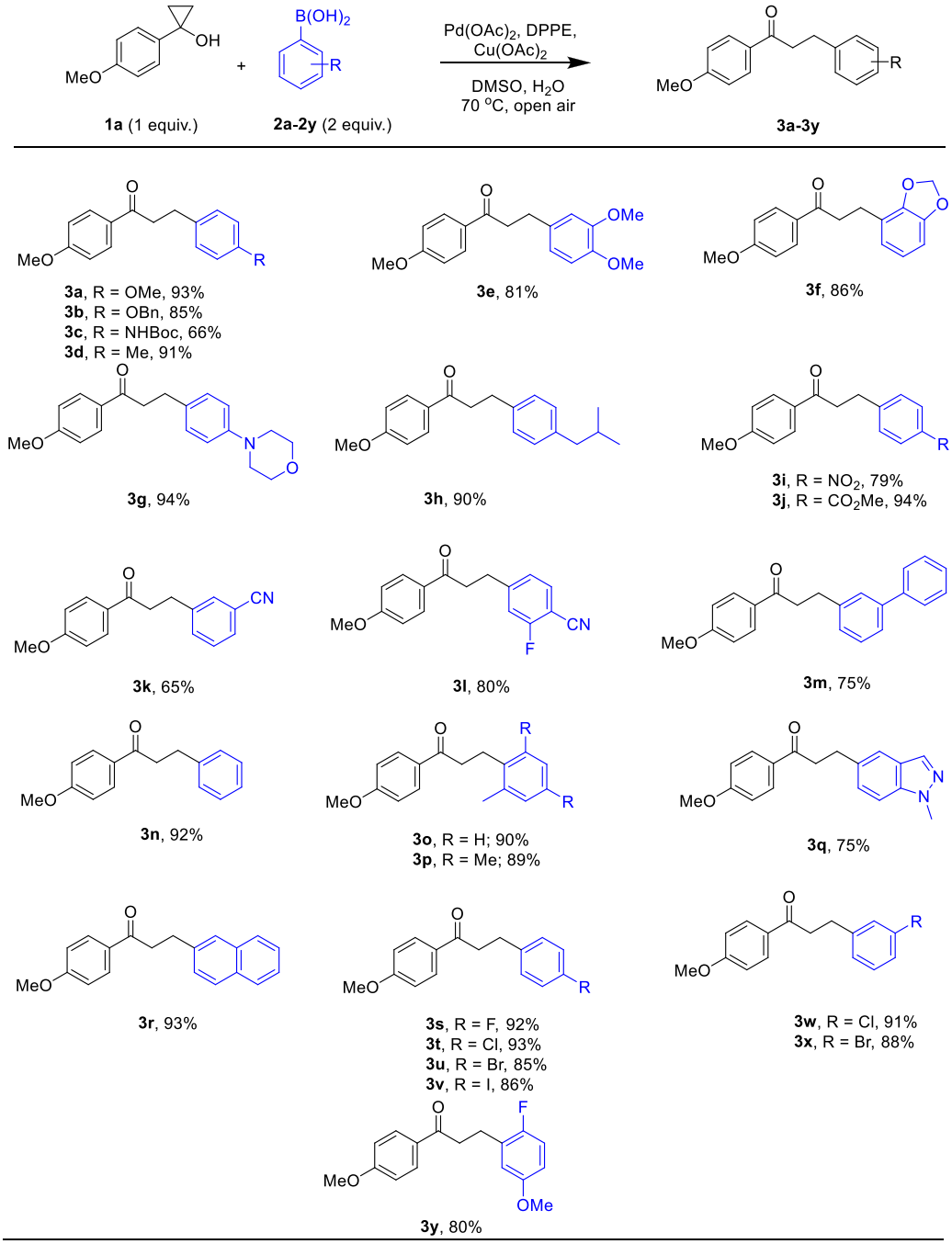
Scheme 3. Preparative Scope of the Coupling of Cyclopropanol 1a with Diverse Arylboronic Acids That Vary in Electronic and Steric Properties



we were able to observe a 49% yield of the desired product **3a** in the absence of any additive, a profile that offered the hope to further enhance the productivity by suppressing the formation of ring-opened byproduct **4a** or **5a** (entry 1). The addition of 0.2 equiv of CuCl resulted in a slight improvement in the yield (58%, entry 2). This prompted an investigation of another copper salt, such as CuBr (entry 3), which resulted in a slightly lower yield. However, a gradual increase in the amount of CuCl was associated with a corresponding proportional yield enhancement, eventually achieving an 85% yield in the presence of 3.0 equiv of CuCl (entries 4−8). Replacement of CuCl (3.0 equiv) with $Cu(OAc)_2$ (3.0 equiv) was found to be beneficial to augment the yield further to 93%, which was consistent with the reaction profile with an almost complete suppression of formation of byproducts **4a** and **5a** (entry 9). However, 4,4′-dimethoxy-1,1′-biphenyl was observed as a byproduct in small amounts (~5% yield), which could be attributed to Pd(II)-mediated homocoupling of **2a**.[36] Having optimized the reaction yield to a satisfactory extent, attempts were made to fine-tune reaction parameters on practical considerations, for example, the feasibility of replacing dioxygen gas with the atmospheric air in an open-vessel fashion from the perspective of safety and cost factors. Gratifyingly, the yield was found to be sustainable even upon switching to open air (entry 10). Optimization of the stoichiometry of the coupling partner **2a**, Pd(II) catalyst, and

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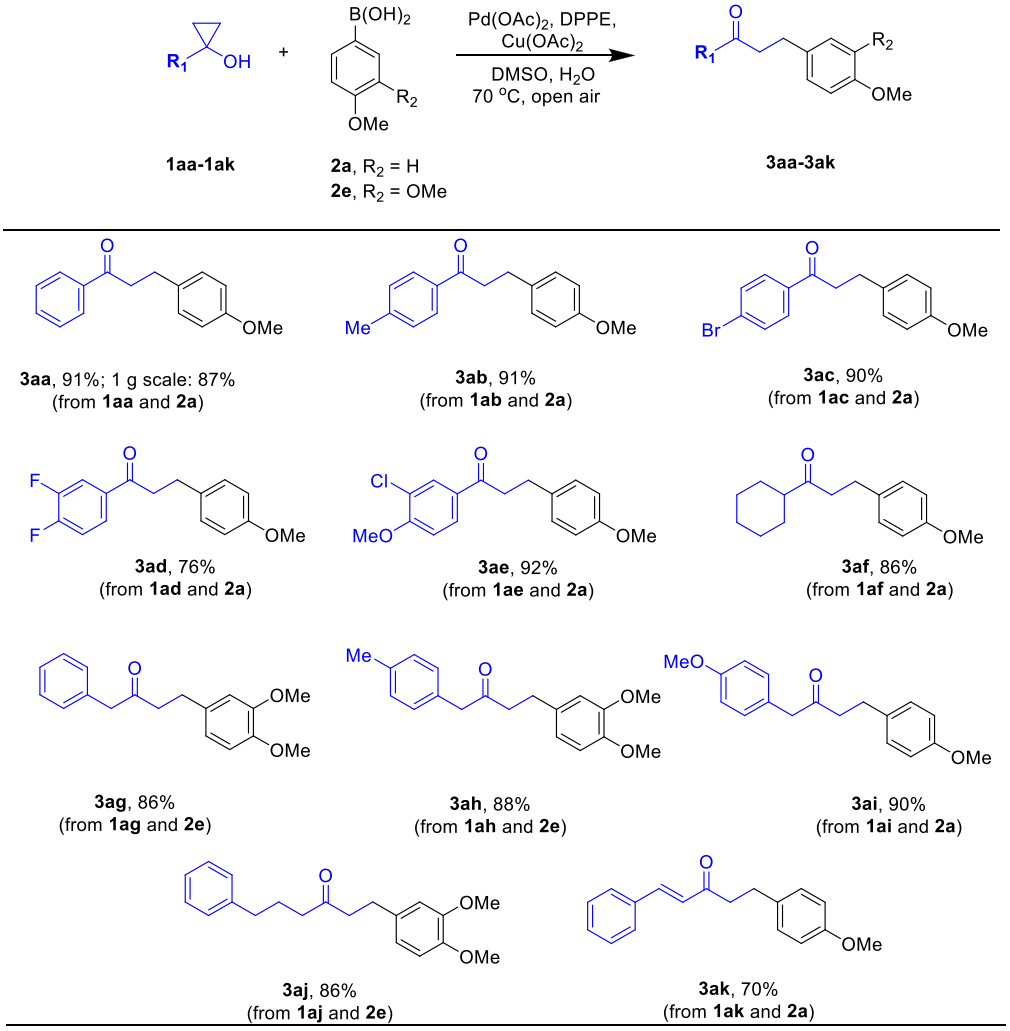
Scheme 4. Preparative Scope of Cyclopropanols Bearing 1-Aryl, 1-Alkyl, 1-Cyclohexyl, and 1-Alkenyl Substituents



Cu(II) salt was next explored as part of an effort to increase the catalytic efficiency of the transformation (entries 11 and 12).

It was observed that the amounts of arylboronic acid (by 33%), $Pd(OAc)_2$ (by 50%), and $Cu(OAc)_2$ (by 33%) could all be substantially reduced without any significant impact on the yield, resulting in the identification of a further efficient condition (entry 12). Remarkably, the product **3a** was obtained in a similar yield (93%) even after blending DMSO with water (0.5 mL), a green solvent, in a 5:1 ratio (entry 13) in an attempt to enhance the eco-friendly character. A limited ligand screening was undertaken involving the replacement of the bidentate phosphine ligand DPPE by nitrogen-coordinating ligands, neocuproine, and bipyridyl, which are known to be less prone to Pd(II)-catalyzed oxidation in the presence of O_2 (entries 14 and 15). However, the nitrogenous ligands were found to be less efficient with a significant reduction in the yield.[12] Solvent screening indicated that the polar aprotic solvent DMSO was found to be more efficient than less-polar solvents like dioxane and toluene (entries 16 and 17). While the role of DMSO in promoting efficient catalysis in the present reaction is not understood, it seems likely that DMSO also serves as a ligand for Pd(II). Sulfoxides, which can bind to metals in two ways through either sulfur or oxygen, are known to be efficient ligands in transition metal-mediated catalysis.[37] Especially, catalyst systems containing both Pd^{II} and DMSO have been proven to be effective in promoting a wide range of synthetic transformations.[38] Replacement of $Pd(OAc)_2$ with different precatalysts like $PdCl_2$, $PdCl_2(MeCN)_2$, and $Pd_2(dba)_3$ was also investigated (entries 18−20). These catalysts were also found to be effective (84−88% yield), although they were slightly inferior to $Pd(OAc)_2$. The reaction was monitored by both LCMS and TLC from 15 min to 2 h at 70 °C. We could observe that the reaction required almost 2 h for the complete consumption of the starting material. The effect of temperature was studied with a minimal variation in the range of 70 ± 10 °C (entries 21 and 22). We could observe that 70 °C was found to provide a better yield than other temperatures (60 or 80 °C). The product yield was reduced to 60% with the increased formation of ring-opening byproduct **4a** in the presence of 1 equiv of **2a** (entry 23). Thus, use of cyclopropanol (1.0 equiv), arylboronic acid (2.0 equiv), $PdOAc_2$ (0.1 equiv), $Cu(OAc)_2$ (2.0 equiv), and DPPE (0.2 equiv) in DMSO−H_2O (5:1 ratio) under the open-air atmosphere at 70 °C was identified as the standard protocol to investigate the substrate scope of both cyclopropanols and organoboronic derivatives.

We began the preparative experiments by investigating the scope of the transmetalation coupling partner with twenty-five different arylboronic acids with a variation in electronic and/or steric characteristics, and the results are summarized in Scheme

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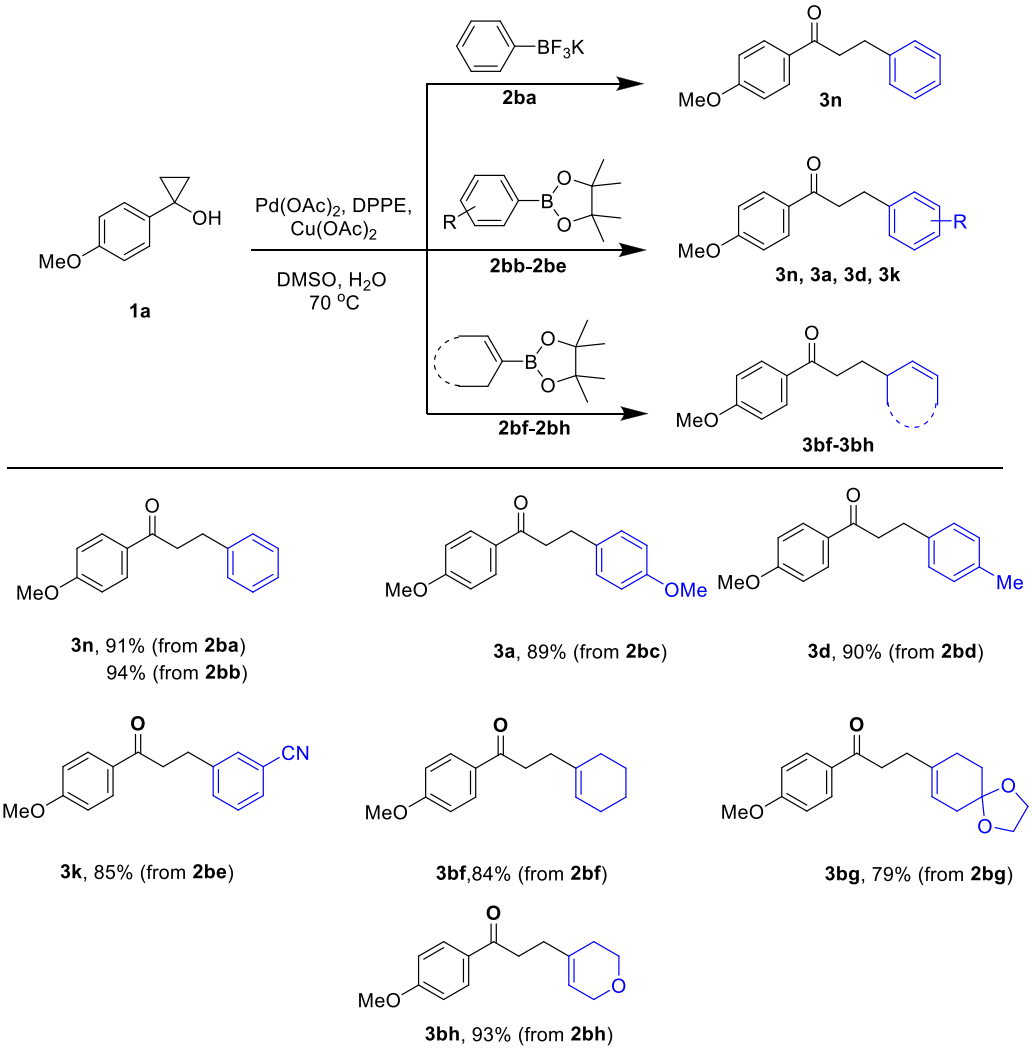
Scheme 5. Preparative Scope of Boronic Acid Head Group Variation and Alkenyl Boronic Esters



3. The arylboronic acids, bearing electron-donating alkyl, alkoxy, and amine functionalities, were found to couple efficiently to obtain the corresponding products with the yields in the range of 66−94% (examples **3a**−**3h**). Interestingly, the coupling of **1a** with arylboronic acids, bearing electron-withdrawing NO_2, CN, CO_2Me, and Ph groups, also took place equally well and provided good to excellent yields (65−94%; examples **3i**−**3m**). These results are especially encouraging, placed in the context of the reported sluggish nature of insertion of electron-poor aryl groups in chelation-controlled cationic Pd(II)-mediated transformations.[11,12] Thus, the absence of significant disparity in reactivity between the electronically distinct boron systems indicates the wide applicability of the reaction. The simple and electronically neutral phenylboronic acid (example **3n**) also gave a superior yield (92%).

A high level of productivity was even achieved upon coupling of sterically demanding arylboronic acids with either 1 or 2 *ortho*-methyl substitutions, as exemplified in the case of **3o** and **3p**. These results imply an improved performance of the present system over the cross-coupling of sterically demanding aryl halides bearing 2 *ortho*-methyl substituents with reduced yields, attributed to the sluggish oxidative addition step that was responsible for an increased and unproductive formation of ring-opened byproduct.[7] Heteroaryl and fused aromatic systems, for example, indazole and 2-naphthyl, were also found to react with **1a** in high yields (examples **3q**−**3r**). Coupling of halogen-bearing arylboronic acids delivered the corresponding dihydrochalcone products (examples **3s**−**3y**) in very high yields (80−93%), indicating that the reaction outcome was undeterred by the presence of highly susceptible Br and I functionalities. The reactions, as exemplified by **3t**−**3x**, were found to be chemoselective with the absence of concomitant generation of byproducts from the putative Pd(0) catalysis that would involve oxidative addition across Ar−Br and Ar−I bonds. Moreover, this reaction profile seems to suggest a mechanism that does not involve the generation of $L_nPd(0)$ as a means of the reductive elimination step.

The preparative scope of the cyclopropyl coupling partner was next investigated by varying the substitutions on the phenyl group, keeping either **2a** or **2e** as the arylboronic acid (Scheme 4). The coupling reactions in the case of examples **3aa**−**3ae** afforded high yields (76−92%). The chemoselective reaction profile was evident in the example **3ac**, supporting further the compatibility of oxidative-addition-susceptible

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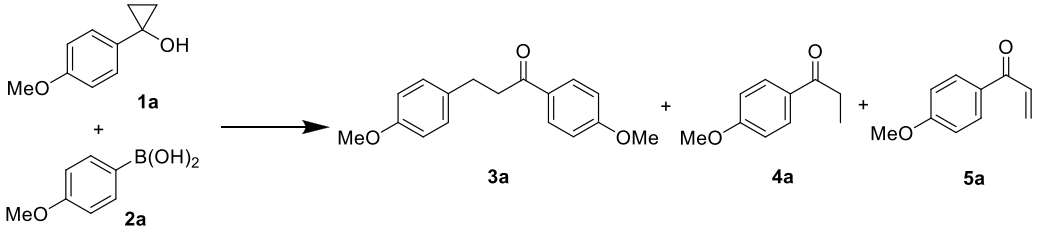
Table 2. Controlled Reactions to Investigate the Mechanistic Aspects of the Catalysis[a]



entry	$Pd(OAc)_2$	$Cu(OAc)_2$	LiCl[b]	atm.	% yield (3a)[c]	% yield (4a)[c]	% yield (5a)[c]
1	yes	no	no	open air	45	40	0
2	no	yes	no	open air	0	0	81
3	yes	yes	yes	open air	24	43	0
4	yes	yes	no	N_2	90	0	0

[a]The standard condition was modified as per the table. [b]3.0 equiv. [c]Isolated yields.

halogen functionalities irrespective of their presence in either the cyclopropanol (**3ac**) or organoboronic counterpart [Scheme 3: **3u**, **3v**, and **3x** (see **2u**, **2v** and **2x** in the supporting information)]. The cyclopropanols, which have been employed in the above preparative examples, bear an aryl group at 1-position of cyclopropanol. In an attempt to expand the scope of the ketone homoenolates, the effect of replacing the 1-aryl substitution with cycloalkyl, aralkyl, and aralkenyl groups was investigated (examples **3af**–**3ak**). Swapping the phenyl group (**3aa**) with the cyclohexyl group (**3af**) or inserting the alkyl substitution like methyl and propyl spacers between the aryl and cyclopropyl ring (**3ag**–**3aj**) had no deleterious impact on the productivity outcome, although this structural modification involved a change of electronic character (sp^2 to sp^3) of the attachment point at the cyclopropyl ring. Arylation of cyclopropanol (**3ak**), bearing a styrenyl moiety with a double bond, was also found to provide an acceptable yield with a chemoselective coupling that was not associated with the oxidative Heck arylation at the olefinic bond. In order to determine the practical utility of this methodology, a large-scale reaction, illustrated with the cyclopropanol, for example, **3aa**, was performed (1 g scale), which was found to furnish an almost comparable yield to that of the small-scale reaction.

To expand the scope of borane warheads of arylboronic nucleophiles, organoboronic esters and organotrifluoroborate salts (also known as Molander's salts) were considered (Scheme 5). While boronic acids can pose challenges with cumbersome purification, less stability, and uncertain stoichiometry due to the possibility of trimerization to the corresponding boroxine, organoboronic esters, and organotrifluoroborate variants appear to have better advantages than boronic acids like known stoichiometry, insensitivity to air and moisture and/or ease of storage as crystalline solids.[39,40] The organoboronate esters can be readily accessed using a number of methods, for example, iridium(I)-catalyzed C–H activation of arenes with bis(pinacolato)diboron (Pin_2B_2)[41] and transmetalation from reactive organometallics.

In a representative trial reaction, simple phenylboronic acid (**2n**) was replaced with either potassium phenyltrifluoroborate (**2ba**) or phenylboronic acid pinacol ester (**2bb**) for coupling with the cyclopropanol **1a** (example **3n**). Like phenylboronic acid, these surrogates were also found to efficiently couple, and the yields were only slightly lower than that of coupling with **2n**.

These results encouraged us to investigate the scope of organoboronic esters containing both aryl and alkenyl moieties, and the results are summarized in Scheme 5. Alkenyl boron reagents have been emerging as versatile and important synthons in organic synthesis.[42,43] Substituted alkenyl boronic esters are known for a variety of synthetic applications that include facile metal-catalyzed transformations to obtain a series of functionalities like C–C, C–O, C–N, and C–X (X = F, Cl, Br, and I), the synthesis of tri- and tetra-substituted alkenes via the Suzuki coupling, the total synthesis of natural products, and the generation of medicinally useful agents. Coupling of **1a** with select substituted arylboronic esters was also found to be efficient with the yields that were either similar (examples **3a**, **3d**, and **3n**) or improved (example **3k**) when compared to that of the corresponding arylboronic acids. An intramolecular cross-coupling of cyclopropanols and alkenyl halides or triflates as part of a seven-membered ring annulation has been disclosed by Cha et al.[44] Surprisingly, the intermolecular variant of coupling cyclopropanols with the alkenyl partners (halides, triflates, or alkenyl boronic acid derivatives) has received meager attention. Hence, there exists an opportunity to expand the scope for alkenyl partners in an attempt to access aryl pent-4-en-1-one systems. The investigated olefinic boronic ester derivatives afforded β-substituted ethyl ketone derivatives with good yields in the range of 79–93% (examples **3bf**–**3bh**) with no significant impact of variation in the cyclic moiety, for example, carbocyclic (cyclohexenyl) or heterocyclic (dihydropyranyl) groups.

Overall, the examples discussed above support the generality of the transformation with the compatibility of various functionalities like OBn, Boc, ester, halogens (Br and I), nitrile, ketal, and olefin. In contrast to the reported propensity of palladium homoenolates to undergo degradation to the corresponding enone byproducts via β-hydride elimination in few cases,[7] the formation of such byproducts was not observed in our examples, indicating the suppression of occurrence of the associated side-reaction pathway.

While a probable mechanism in the case of Pd(0)-catalyzed cross-coupling of cylcopropanols and aryl halides has been postulated, the catalytic pathway based on detailed mechanistic studies remains to be fully understood.[2,7,8,10] This stimulated us to gain insights into the mechanistic aspects of the catalytic cycle that involved an alternate Pd(II) system as the active catalyst with an arylboronic acid as the surrogate of an aryl halide. Accordingly, controlled experiments were carried out

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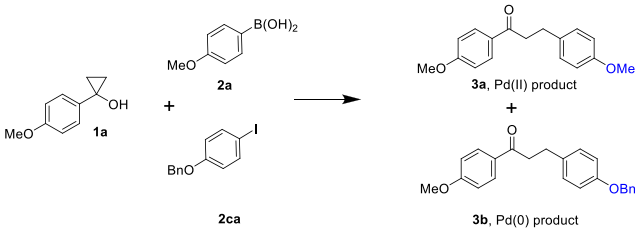
Table 3. Competitive Experiments to Glean Insight into the Involvement of the Pd(0) Complex, Involving Oxidative Addition of an Aryl Iodide[a]



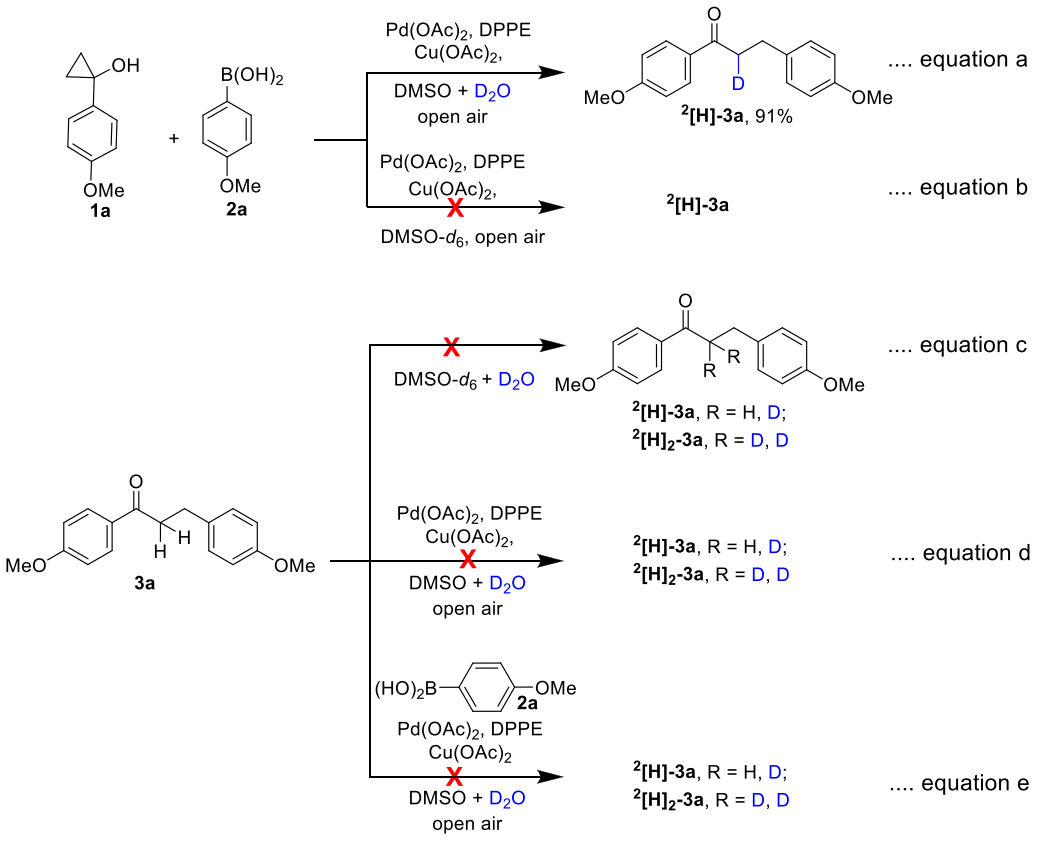
entry	base[b]	% yield (3a)[c]	% yield (3b)[c]
1	none	71	0
2	Et_3N	61	8
3	K_2CO_3	34	30

[a]Standard conditions were applied except that **2a** and **2ca** (1.0 equiv of each) were used in a 1:1 ratio. [b]3.0 equiv. [c]Isolated yields.

that have been depicted in Table 2, Table 3, Scheme 6, and Scheme 7. Following submission of the model substrates **1a** and **2a** to the standard condition in the absence of $Cu(OAc)_2$, it was observed that the desired product **3a** could still be obtained (Table 2, entry 1). However, the yield of the desired product was reduced, a profile that can be attributed to an almost equal propensity to the concurrent formation of ring-opening protonolysis byproduct **4a**. This result indicates that Pd(II) is capable of opening the cyclopropanol and subsequently promoting C−C bond formation to deliver **3a** in a manner that is independent of Cu(II). At the same time, the Pd(II) ketone homoenolate intermediate is subject to an alternative pathway that would involve competitive protonolysis, thereby constituting a suboptimal system. In the absence of Pd(II), Cu(II) is capable of opening the cyclopropanol, resulting in the formation of β-hydride elimination product **5a** but could not promote C−C bond formation between **5a** and **2a** further (Table 2, entry 2). Reactions of Cu(II) salts with cyclopropanol substrates to generate enone derivatives like **5a** via β-hydride elimination of the corresponding Cu(II) ketone homoenolates have been well-documented.[45−47] Unlike Pd(II) species, the Cu(II) ketone homoenolate is not susceptible to protonolysis of the side reaction, thereby promoting selective β-hydride elimination. Although the cyclopropyl ring-opening process can be Cu(II)-mediated, catalytic Pd(II) would still be required to promote the C−C bond formation between **5a** and **2a** to obtain **3a** (see later: Scheme 7). Additionally, it may be inferred that Cu(II) plays the primary role in the ring-opening step of the catalytic cycle under a standard protocol (Table 1, entry 13) with the suppression of Pd(II)-mediated ring cleavage. This is consistent with the negligible formation of **4a**, a major byproduct in the Pd(II)-promoted catalytic pathway.

The palladium(II) catalysis, which involves arylboronic acids containing nonmetal-coordinating electropositive transmetalation handles (e.g., $-B(OH)_2$), has previously been proposed to proceed via a cationic manifold in the presence of a bidentate ligand and another ligand (for example, $^{-}OCOCF_3$, ^{-}OAc, or a

Scheme 6. Controlled Experiments to Study the Incorporation of Deuterium or H/D Exchange



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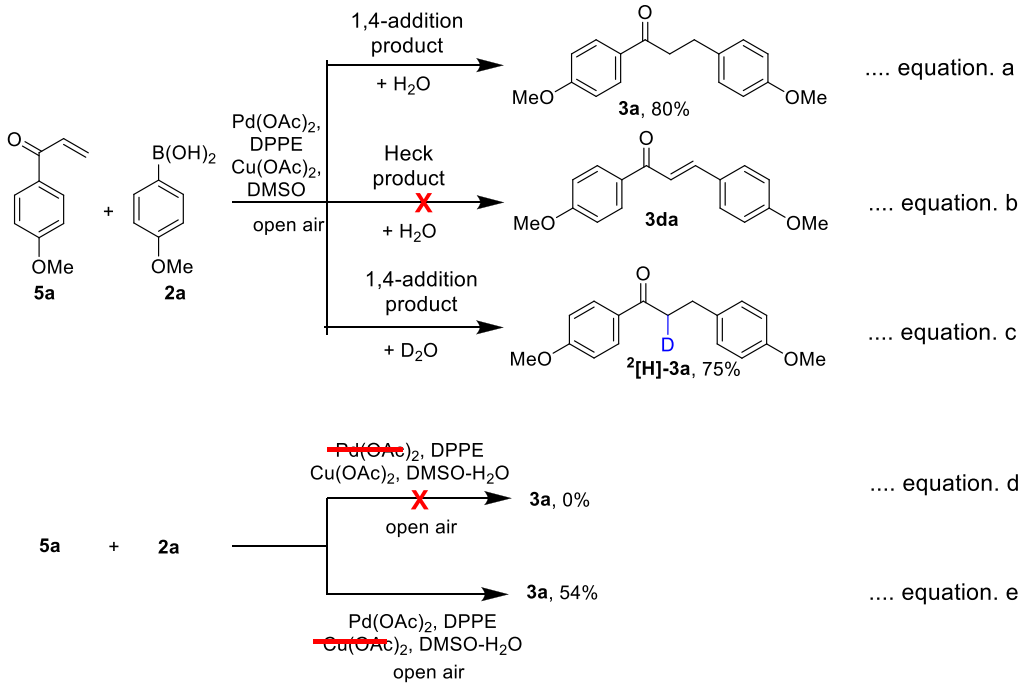
Scheme 7. Controlled Experiments to Study the Arylative Insertion of β-Hydride Elimination Intermediate 5a



solvent) that can readily dissociate.[11,48] Experimentally, mechanistic studies involving ESI-MS-(+) analysis of reaction mixtures of bidentate ligand (for example, neocuproine and dppp) controlled Pd(II)-catalyzed arylation of olefins could reveal the involvement of cationic organopalladium intermediates during the course of the reaction.[49,50] Additionally, the addition of the chloride ion to cationic palladium complexes has been shown to substantially reduce the reaction rate with olefins in the Heck−Mizoroki cross-coupling due to the formation of neutral palladium chloride species.[51] In the reported Pd(0)-catalyzed β-arylation of homoenolates, silyl-protected cyclopropanols have been shown to undergo coupling with a cationic arylpalladium complex catalytically generated from the oxidative addition of an aryl triflate.[5] Moreover, the addition of stoichiometric LiCl or tetra-*n*-butylammonium bromide to the reaction mixture was found to almost completely inhibit the catalysis. In order to verify the cationic nature of the arylation of the ketone homoenolate in the present protocol, a neutral aryl-palladium(II) catalysis was contemplated with the addition of LiCl (3.0 equiv) into the reaction mixture. This additive resulted in a dramatic reduction in the reaction rate with a substantial drop in the yield of **3a** from 93% to 24% after 2 h, indicating the suppression of the reaction rate of arylation following the shift from cationic to the neutral pathway (Table 2, entry 3). The chemoselectivity was also destroyed, as apparent from the concomitant generation of **4a** with approximately a 2:1 ratio to the arylation product **3a**, an observation that could be attributed to the high tendency of palladium keto homoenolate species under neutral Pd(II) conditions to undergo the protonolysis side reaction before arylative insertion.

Because the standard reaction was conducted under the open-flask condition, a controlled experiment was undertaken under an inert atmosphere of N_2 gas to study the influence of dioxygen gas as an oxidant. Dioxygen would be expected to positively impact the catalytic turn over, if the catalytic cycle would involve the steps that generate Pd(0) and require Pd(0) to be oxidized back to the active catalyst Pd(II). However, the reaction yield was not altered significantly, suggesting that molecular oxygen does not play a major role in the catalytic system (Table 2, entry 4). This result is largely consistent with deuterium incorporation studies (*vide infra*) that reveal protonolysis in the final step of the catalytic cycle, leading to the regeneration of active Pd(II), a mechanistic profile that does not require an oxidant for catalytic turn over.

Next, an intermolecular competition experiment between the aryl nucleophile **2a** and the aryl electrophile **2ca** for coupling with **1a** was studied to further understand the kinetic and mechanistic aspects behind $L_nPd(II)$ and $L_nPd(0)$ (Table 3). Pd(0) species can be expected to form from Pd(II) ketone homoenolates in the reaction system through the operative mechanisms like (a) β-hydride elimination to generate the corresponding unsaturated ketone **5a**[19,52] and (b) reductive elimination of the organopalladium complex upon arylative insertion to generate **3a**. Under the standard conditions, the formation of the arylboronic acid-derived product (**3a**) was only observed with no concomitant formation of Heck-type product **3b** (entry 1). This result, which is consistent with the observed chemoselectivity in the preparative examples, does not seem to support the possibility of either the presence or involvement of Pd(0) in the reaction system. To gain further insight, we also investigated the reaction profile after adding a base into the reaction mixture. Among multiple roles that a base can play in the catalysis, it can promote the selective reduction of Pd(II) to Pd(0) or recycling of the Pd(0) complex from the hydridopalladium(II) intermediate derived via β-hydride elimination, thereby allowing accumulation of Pd(0) species that is conducive to open alternative reaction pathways like oxidative addition of aryl halides. The product **3b** was obtained in 7:1 and 1:1 ratios, respectively, in the presence of the organic base Et_3N (Table 3, entry 2) and the inorganic base K_2CO_3 (Table 3, entry 3). The formation of an

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aryl halide-based product was thus possible only upon modifying the pH of the reaction via the addition of a base that is conducive to the generation of Pd(0). Overall, these results suggest that the possibility of the involvement of Pd(0) in the catalytic cycle is limited, an assumption that is in concordance with other experimental observations (for example, protonolysis in the final step of catalysis and the limited role of oxygen) that does not support the generation of Pd(0).

In order to understand whether the catalytic cycle would encompass a protonolysis step in the presence of a proton source, the possibility of deuterium incorporation was investigated by subjecting the substrate **1a** to standard reaction conditions by replacing H_2O with D_2O as a cosolvent (Scheme 6, equation a). Interestingly, this resulted in the H/D exchange of one of the two methylene protons at the α-position to the carbonyl of dihydrochalcone **3a** with the preferred formation of the **3a**-*d* compound in the absence of the formation of the normal product **3a**. In order to understand whether DMSO can act as a protic source beyond its role as the solvent, a reaction was conducted by replacing DMSO with DMSO-d_6 in the absence of D_2O (Scheme 6, equation b). However, no deuterium incorporation was observed, ruling out the possibility of DMSO acting as a proton donor.

Analysis of ketone **3a** by ^{1}H NMR spectroscopy following a 24 h equilibration with DMSO-d_6 and D_2O did not show either mono- or dideuterium incorporation at the α-position of the carbonyl, suggesting that the normal product **3a** is not capable of H/D exchange with D_2O (Scheme 6, equation c). As a further step, the product **3a** itself was subjected to the standard catalytic conditions for 3 h in the absence (Scheme 6, equation d) or presence of boronic acid **2a** (Scheme 6, equation e). These later two experiments were designed to investigate the role of boronic acid as a strong Bronsted acid in promoting either the incorporation of deuterium or H/D exchange. However, **3a** did not undergo any deuterium incorporation, suggesting that the end product expelled from the catalytic cycle was not susceptible to H/D exchange under reaction conditions. On the basis of these key observations, it can be suggested that incorporation of deuterium at the carbon atom α to the ketone occurs as an inherent part of the catalytic cycle, which is presumably an outcome of protonolysis of the carbopalladium(II) complex in the final step of the catalysis with the release of the parent and active Pd(II) catalyst. Furthermore, the deuterium incorporation eliminates the possibility of reductive elimination as the final step of the catalytic cycle and generation of Pd(0) species.

The Cu(II)-promoted formation of vinyl ketone **5a** (see Table 2, entry 2) stimulated an interest to probe whether the generated enone would undergo arylative insertion with the arylboronic reagent (Scheme 7). As discussed previously, the formation of vinyl ketones by Cu(II)-mediated ring opening of hydroxycyclopropanes, involving the generation of metal keto enolates and subsequent β-hydride elimination, is well-precedented.[45,47,53] In this direction, vinyl ketone **5a** was isolated following treatment of the cyclopropanol **1a** with $Cu(OAc)_2$ and was then subjected to the standard condition. Interestingly, this reaction furnished the 1,4-addition product **3a** (Scheme 7, equation a) but did not provide the Heck-type vinylation product (equation b), suggesting an absence of the β-hydride elimination mechanistic pathway. Additionally, the coupling of **5a** and **2a** was conducted under standard conditions by replacing H_2O with D_2O that afforded an end product with the characteristic deuterium installation at the α-position to the carbonyl of dihydrochalcone **3a** (Scheme 7, equation c). These observations lend support to the generation and protonolysis of an α-keto carbopalladium complex (for example, see **G** in Figure 2) in line with the mechanism of the

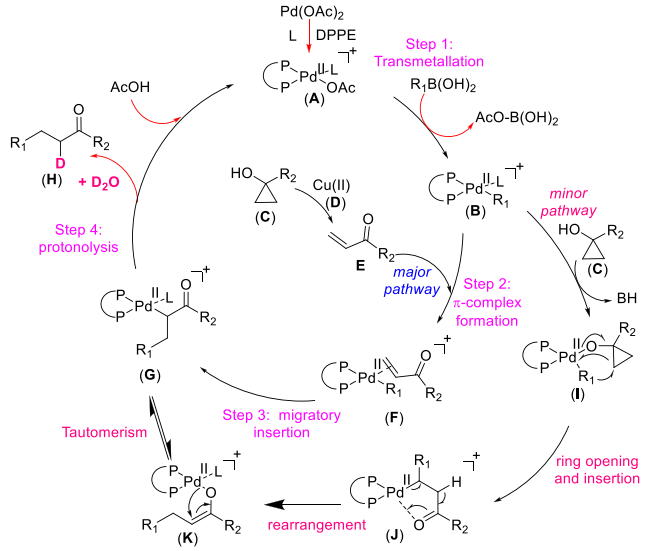

Figure 2. Proposed mechanism for cationic Pd(II)-assisted C−C cross-coupling of cyclopropanol with organoboronic acid.

well-precedented conjugate addition of organoboronic acids to α,β-unsaturated ketones.[20] Two additional experiments were designed to examine the metal-catalyzed conjugate addition process in the presence of only Pd(II) or only Cu(II) to gain an understanding of the metal that could be responsible for the C−C bond-forming step. The product **3a** was not obtained with Cu(II) salt alone in the absence of a Pd(II) source (Scheme 7, equation d). In contrast, **3a** could be obtained in the presence of Pd(II) even after excluding Cu(II) salt, albeit in a modest yield (Scheme 7, equation e). These observations corroborate with the earlier findings (Table 2, entries 1 and 2) that Pd(II), but not Cu(II), is responsible for the C−C bond formation step.

On the basis of observations from the controlled experiments, the proposed catalytic cycle that can be analogous to the palladium(II)-catalyzed conjugate addition of organoboronic acids to an enone involves key steps of transmetalation, insertion, and hydrolytic carbon-Pd bond cleavage, as illustrated in Figure 2.[54] This involves the generation of the cationic aryl/alkenylpalladium(II) complex (**B**) in the foremost step of the putative catalytic cycle, resulting from transmetalation of the aryl/alkenyl organoborane reagent with the DPPE-chelated palladium(II) complex (**A**).[3,11,49,50] The vinyl ketone intermediate (**E**) is generated by Cu(II)-mediated ring opening of hydroxycyclopropane (**C**), involving the generation of copper keto enolate and subsequent β-hydride elimination.[45−47] Subsequently, the vinyl ketone substrate **E** coordinates to the metal center of the Pd(II)-aryl/alkenyl species through the vacant site to form the olefin-Pd π-complex (**F**). Migratory insertion of the aryl/alkenyl group from the metal center into the olefinic bond via syn addition results in the generation of α-keto carbopalladium complex **G**.[20] This species undergoes protonolysis in the presence of a proton source to liberate β-arylethyl ketone product (**H**) and the

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active catalyst **A** that can initiate the next catalytic cycle. As discussed earlier, experimental observation of the insertion of the deuterium atom at the α-methylene position to the keto group of **3a** in the presence of D_2O under standard condition supports the protonolysis event of the α-keto carbopalladium complex **G** (Scheme 6). In the Pd(0)-promoted cross-coupling of cyclopropanol-derived homoenolates, it is hypothesized that the reductive elimination of an arylpalladium(II) homoenolate constitutes the final step of the catalytic process in order to furnish the arylated ketone product and active Pd(0) species.[1,3] In contrast to the Pd(0) mechanism, our mechanistic studies reveal a differentiated catalytic cycle for the cationic Pd(II) pathway that would require the arylpalladium(II) homoenolate to undergo the carbopalladation and protonolysis after the migratory insertion of the aryl moiety, corroborated by the deuterium incorporation studies.

In line with entry 1 in Table 2, a minor pathway may involve the role of the palladium complex alone with the initial steps of the catalytic cycle that are expected to be similar to that of previously reported direct arylation of siloxycyclopropanes by the aryl triflate via cationic arylpalladium complex.[4,5] It seems likely that the initial step involves the coordination of the cyclopropanol substrate **C** to the palladium(II) intermediate (**B**) to generate the cyclopropyloxypalladium(II) intermediate, which subsequently undergoes C−C bond cleavage of the highly strained cyclopropyl ring and aryl/alkenyl insertion to provide the metal ketone homoenolate **J**. This intermediate rearranges to provide the enol-coordinated palladium(II) intermediate **K**. This later species can undergo tautomeric equilibrium with carbo-palladium intermediate **G** in the solution state with high susceptibility of these tautomers for hydrolytic cleavage. The C-bound tautomer **G** is subjected to protonolysis in the presence of a protic source like water to selectively deliver the 1,4-addition product **H** without the formation of the competitive Heck-type coupling product via β-hydride elimination.[55]

CONCLUSION

In conclusion, we took advantage of widely available organoboronic reagents as the new and efficient coupling partners to the homoenolate equivalents for forging C−C bonds. The design strategy relied on the selective engagement of these aryl agents with electrophilic Pd(II) over Pd(0), thereby exploiting the mechanistic differences in the catalysis between these Pd systems to promote chemoselectivity. Preparative capabilities over a range of structurally diverse aryl and alkenyl boronic acids/esters and substituted cyclopropanols indicate the broad scope of this new methodology. Importantly, this protocol has paved the way for new substrate classes like halogen-appended dihydrochalcones, which cannot be accessed by previously reported methods. Furthermore, it has been demonstrated that this operationally simple reaction can be performed under open-flask conditions with water as the green cosolvent and is capable of producing β-aryl ketones on the gram scale. The deuterium incorporation studies, which were conducted as part of a mechanistic investigation to gain insight into the catalytic pathway of cationic Pd(II), provided critical information on the occurrence of α-keto carbopalladation and subsequent protonolysis in the terminal step. Further investigations for (a) optimizing the catalytic efficiency of the reaction in terms of the stoichiometry of $Cu(OAc)_2$ and $ArB(OH)_2$, (b) expanding the scope of this transformation to 1,2-disubstituted cyclopropanols, cyclobutanols, and cyclopentanols as substrates, and (c) developing applications toward the synthesis of natural products, are currently under progress in these laboratories.

EXPERIMENTAL SECTION

Materials and General Methods. All anhydrous reactions were performed under an atmosphere of N_2 or Ar gas with magnetic stirring. Reagents and solvents were purchased from commercial suppliers and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC). TLC was performed using E. Merck precoated silica plates (60F-254) with a 0.25 mm thickness and visualized using short-wave UV light or developing agents ($KMnO_4$, phosphomolybdic acid, or *p*-anisaldehyde). Purifications were performed using flash column chromatography with 60−120 mesh silica gel as the stationary phase and a gradient of ethyl acetate in petroleum ether as the mobile phase.

Known compounds were characterized by comparing their ^{1}H NMR spectra to the previously reported data. New compounds were characterized by ^{1}H NMR, ^{13}C NMR, and MS, and copies of ^{1}H and ^{13}C NMR spectra have been included at the end of the Supporting Information. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker 300 and 400 MHz instruments. ^{1}H NMR chemical shifts are reported in ppm (δ) relative to the internal standard tetramethylsilane (TMS, δ 0.00 ppm). ^{13}C NMR chemical shifts are reported in ppm with respect to solvent resonance as the internal standard ($CDCl_3$ at 77.0 ppm). NMR data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), multiplet (m), and broad singlet (br. s)], coupling constant [Hz], and integration). For LC/MS characterization of the purified compounds, reversed-phase analytical HPLC/MS experiments were performed on an Agilent 1200 Series system coupled with a single quadrupole instrument using the electrospray ionization (ESI) method or Waters Aquity system coupled with a Waters Micromass SQ mass spectrometer. High-resolution mass spectrometry (HRMS) data were obtained from an Orbitrap (Thermofisher) mass spectrometer using a heated ESI method in positive or negative ion detection mode.

Experimental Procedures. *General Procedure for the Synthesis of Cyclopropanols via the Kulinkovich Reaction.* To a solution of ester (25 mmol, 1 equiv) and titanium tetraisopropoxide (35 mmol, 1.4 equiv) in anhydrous THF (25 mL; 1 M solution) was added dropwise 1 M solution of ethylmagnesium bromide in THF (70 mmol, 2.8 equiv) over 30 min at 0 °C. The reaction mixture was stirred at room temperature for 14 h. Then the solution was cooled to 0 °C and slowly quenched with ice water. The precipitate was filtered and washed with ethyl acetate. The filtrate was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under a vacuum to afford the residue. The crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether to afford the product.

*1-(3,4-Difluorophenyl)cyclopropan-1-ol (**1ad**).* Following a 5.0 g (29 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 10:90) to afford the title product as a light yellow oil (3.9 g, 79%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.19−7.05 (m, 2H), 7.02−6.93 (m, 1H), 2.47−2.22 (br s., 1H), 1.32−1.25 (m, 2H), 1.05−0.97 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.8 (dd, J_{C-F} = 130 Hz, 13 Hz), 148.4 (dd, J_{C-F} = 129 Hz, 13 Hz), 141.6 (d, J_{C-F} = 8 Hz), 120.1 (dd, J_{C-F} = 7, 3 Hz), 117.0 (d, J_{C-F} = 17 Hz), 113.9 (d, J_{C-F} = 19 Hz), 56.0, 18.1; HRMS (ESI/Orbitrap) *m*/*z* [M + H]$^+$ calcd for $C_9H_9F_2O$ 171.0616, found 171.0658.

*1-(3-Chloro-4-methoxyphenyl)cyclopropan-1-ol (**1ae**).* Following a 5.0 g (25 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 15:85) to afford the title product as a colorless oil (3.6 g, 73%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 0.34 (d, *J* = 2.3 Hz, 1H), 7.19 (dd, *J* = 2.3, 8.6 Hz, 1H), 6.89 (d, *J* =

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8.5 Hz, 1H), 3.90 (s, 3H), 2.48 (br. s, 1H), 1.27−1.21 (m, 2H), 1.03−0.96 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.7, 137.4, 127.1, 124.2, 122.4, 112.0, 56.2, 17.2; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{10}H_{12}ClO_2$ 199.0520, found 199.0560.

General Procedure for the Reaction of Cyclopropanols with Organoboronic Acids, Organoboronic Esters, or Organotrifluoroborates. A mixture containing cyclopropanol (1 mmol, 1 equiv), organoboronic acid (2 mmol, 2 equiv)/organoboronic acid pinacol ester (2 mmol, 2 equiv)/potassium organotrifluoroborate (2 mmol, 2 equiv), $Pd(OAc)_2$ (0.1 mmol, 0.1 equiv), $Cu(OAc)_2$ (2 mmol, 2 equiv), and DPPE (0.2 mmol, 0.2 equiv) in a solvent mixture (0.33 M solution) of DMSO (2.5 mL) and water (0.5 mL) was stirred at 70 °C in an oil bath for 2 h under open air. The reaction mixture was monitored by TLC. After completion of the reaction, the mixture was partitioned between ethyl acetate and water (note that, if there was no separation of layers, the mixture was filtered through a Celite bed, and the bed was washed with ethyl acetate). After filtration, the separation of layers was observed). The organic layer was washed with water and brine solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to get the crude product, which was purified by column chromatography.

*1,3-Bis(4-methoxyphenyl)propan-1-one (**3a**).*[56] Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 15:85) to afford the title product as an off-white solid (306 mg, 93%): ^1H NMR (400 MHz, chloroform-*d*) δ 8.03−7.94 (m, 2H), 7.26−7.17 (m, 2H), 6.98−6.92 (m, 2H), 6.90−6.84 (m, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 3.32−3.20 (m, 2H), 3.11−2.99 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.0, 163.5, 158.0, 133.5, 130.3, 130.1, 130.1, 129.3, 114.0, 113.7, 55.5, 55.3, 40.4, 29.5; LCMS (ES) m/z 271.3 $[M + H]^+$

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*1,3-Bis(4-methoxyphenyl)propan-1-one-2-d (^{2}[H]-**3a**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, while using 2.5 mL of DMSO and 0.5 mL of D_2O (0.33 M solution), the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 15:85) to afford the title product as an off-white solid (301 mg, 91%): ^1H NMR (400 MHz, chloroform-*d*) δ 8.01−7.92 (m, 2H), 7.22−7.16 (m, 2H), 6.99−6.90 (m, 2H), 6.90−6.66 (m, 2H), 3.89 (s, 3H), 3.70 (s, 3H), 3.27−3.16 (m, 1H), 3.05−2.98 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.0, 163.4, 158.0, 133.5, 130.3, 130.0, 129.4, 113.9, 113.7, 55.5, 55.3, 40.4, 40.2, 40.0, 29.5; LCMS (ES) m/z 272.3 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{17}H_{18}DO_3$ 272.1391, found 272.1386.

*3-(4-(Benzyloxy)phenyl)-1-(4-methoxyphenyl)propan-1-one (**3b**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 15:85) to afford the title product as an off-white solid (358 mg, 85%): ^1H NMR (400 MHz, chloroform-*d*) δ 7.99−7.93 (m, 2H), 7.51−7.31 (m, 5H), 7.23−7.16 (m, 2H), 7.00−6.89 (m, 4H), 5.06 (s, 2H), 3.88 (s, 3H), 3.28−3.19 (m, 2H), 3.07−2.98 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.0, 163.4, 157.2, 137.2, 133.8, 130.3, 130.0, 129.4, 128.6, 127.9, 127.5, 114.9, 113.7, 70.1, 55.5, 40.5, 29.5; LCMS (ES) m/z 347.3 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{23}H_{23}O_3$ 347.1642, found 347.1633.

*tert-Butyl (4-(3-(4-Methoxyphenyl)-3-oxopropyl)phenyl)-carbamate (**3c**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 15:85) to afford the title product as an off-white solid (286 mg, yield: 66%): ^1H NMR (400 MHz, chloroform-*d*) δ 7.97−7.91 (m, 2H), 7.32−7.25 (m, 2H), 7.18 (d, J = 8.5 Hz, 2H), 6.96−6.90 (m, 2H), 6.43 (br s, 1H), 3.87 (s, 3H), 3.25−3.17 (m, 2H), 3.05−2.97 (m, 2H), 1.52 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.9, 163.4, 153.5, 136.4, 136.2, 130.3, 128.9, 118.9, 113.7, 80.1, 55.4, 40.2, 29.7, 28.3; LCMS (ES) m/z 300.1 [M-*tert*-butyl]$^+$; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{21}H_{26}NO_4$ 356.1856, found 356.1847.

*1-(4-Methoxyphenyl)-3-(p-tolyl)propan-1-one (**3d**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 10:90) to afford the title product as an off-white solid (282 mg, yield: 91%): ^1H NMR (400 MHz, chloroform-*d*) δ 8.00−7.91 (m, 2H), 7.15 (q, J = 8.1 Hz, 4H), 6.98−6.90 (m, 2H), 3.88 (s, 3H), 3.29−3.20 (m, 2H), 3.08−2.99 (m, 2H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.9, 163.4, 138.4, 135.6, 130.3, 130.0, 129.2, 128.3, 113.7, 55.5, 40.3, 29.9, 21.0; LCMS (ES) m/z 255.3 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{17}H_{19}O_2$ 255.1380, found 255.1387.

*3-(3,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)propan-1-one (**3e**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 20:80) to afford the title product as an off-white solid (296 mg, yield: 81%): ^1H NMR (400 MHz, chloroform-*d*) δ 7.94−7.92 (m, 2H), 6.92−6.90 (m, 2H), 6.78−6.76 (m, 3H), 3.85 (s, 9H), 3.23−3.3.19 (m, 2H), 3.01- 2.97 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.9, 163.5, 148.9, 147.5, 134.1, 130.3, 130.0, 120.2, 113.7, 111.9, 111.4, 56.0, 55.9, 55.5, 40.4, 30.0; LCMS (ES) m/z 301.3 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{18}H_{21}O_4$ 301.1434, found 301.1444.

*3-(Benzo[d][1,3]dioxol-5-yl)-1-(4-methoxyphenyl)propan-1-one (**3f**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 15:85) to afford the title product as a light brown solid (298 mg, yield: 86%): ^1H NMR (400 MHz, chloroform-*d*) δ 7.97−7.94 (m, 2H), 6.95−6.92 (m, 2H), 6.77−6.72 (m, 3H), 5.93 (s, 2H), 3.88 (s, 3H), 3.24−3.19 (m, 2H), 3.01−2.96 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.8, 163.5, 147.6, 145.8, 135.3, 130.3, 130.0, 121.1, 113.7, 108.9, 108.3, 100.8, 55.5, 40.3, 30.1; LCMS (ES) m/z 285.1 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{17}H_{17}O_4$ 285.1121, found 285.1129.

*1-(4-Methoxyphenyl)-3-(4-morpholinophenyl)propan-1-one (**3g**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 15:85) to afford the title product as an off-white solid (372 mg, yield: 94%): ^1H NMR (400 MHz, chloroform-*d*) δ 8.00−7.90 (m, 2H), 7.18 (d, J = 8.3 Hz, 2H), 6.96−6.90 (m, 2H), 6.90−6.84 (m, 2H), 3.91−3.83 (m, 7H), 3.27−3.17 (m, 2H), 3.17−3.10 (m, 4H), 3.10−2.90 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.0, 163.4, 150.0, 130.8, 130.3, 130.1, 129.1, 116.1, 113.7, 66.9, 55.5, 49.7, 40.3, 29.5; LCMS (ES) m/z 326.1 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{20}H_{24}NO_3$ 326.1751, found 326.1751.

*3-(4-Isobutylphenyl)-1-(4-methoxyphenyl)propan-1-one (**3h**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 15:85) to afford the title product as an off-white solid (327 mg, yield: 90%): ^1H NMR (400 MHz, chloroform-*d*) δ 7.99−7.93 (m, 2H), 7.17 (d, J = 7.8 Hz, 2H), 7.12−7.06 (m, 2H), 6.97−6.91 (m, 2H), 3.90 (s, 3H), 3.28−3.22 (m, 2H), 3.07−3.00 (m, 2H), 2.46 (d, J = 7.1 Hz, 2H), 1.85 (dquin, J = 13.5, 6.8 Hz, 1H), 0.91 (d, J = 6.6 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.0, 163.4, 139.4, 138.6, 130.3, 130.0, 129.2, 128.1, 113.7, 55.4, 45.0, 40.2, 30.2, 30.0, 22.4; LCMS (ES) m/z 297.2 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{20}H_{25}O_2$ 297.1849, found 297.1848.

*1-(4-Methoxyphenyl)-3-(4-nitrophenyl)propan-1-one (**3i**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 20:80) to afford the title product as a yellow solid (275 mg, yield: 79%): ^1H NMR (400 MHz, chloroform-*d*) δ 8.19−8.13 (m, 2H), 7.98−7.92 (m, 2H), 7.43 (d, J = 8.5 Hz, 2H), 6.98−6.92 (m, 2H), 3.89 (s, 3H), 3.36−3.29 (m, 2H), 3.23−3.15 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.6, 163.7, 149.4, 146.5, 130.3, 129.4, 123.7, 113.9, 55.5, 39.0, 29.9; LCMS (ES) m/z 286.1 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{16}H_{16}NO_4$ 286.1074, found 286.1073.

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*Methyl 4-(3-(4-Methoxyphenyl)-3-oxopropyl)benzoate (**3j**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 15:85) to afford the title product as an off-white solid (342 mg, yield: 94%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.99−7.93 (m, 4H), 7.35−7.28 (m, 2H), 6.95−6.92 (m, 2H), 3.96 (s, 3H), 3.88 (s, 3H), 3.28−3.20 (m, 2H), 3.15−3.12 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.2, 167.0, 163.6, 147.0, 130.3, 129.8, 128.5, 128.1, 127.2, 113.8, 55.5, 52.0, 39.4, 30.2; LCMS (ES) *m*/*z* 299.3 [M + H]$^+$; HRMS (ESI/Orbitrap) *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}O_4$ 299.1278, found 299.1270.

*3-(3-(4-Methoxyphenyl)-3-oxopropyl) benzonitrile (**3k**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 15:85) to afford the title product as an off-white solid (211 mg, yield: 65%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.95 (d, *J* = 9.0 Hz, 2H), 7.57 (s, 1H), 7.55−7.48 (m, 2H), 7.45−7.37 (m, 1H), 6.95 (d, *J* = 9.0 Hz, 2H), 3.89 (s, 3H), 3.33−3.25 (m, 2H), 3.16−3.08 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.8, 163.7, 142.9, 133.2, 132.0, 130.3, 129.9, 129.7, 129.3, 118.9, 113.8, 112.5, 55.5, 39.2, 29.6; LCMS (ES) *m*/*z* 266.3 [M + H]$^+$; HRMS (ESI/Orbitrap) *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}NO_2$ 266.1176, found 266.1180.

*2-Fluoro-4-(3-(4-methoxyphenyl)-3-oxopropyl)benzonitrile (**3l**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 15:85) to afford the title product as an off-white solid (276 mg, yield: 80%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.99−7.90 (m, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.21−7.10 (m, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.34−3.25 (m, 2H), 3.19−3.10 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.4, 163.8, 163.2 (d, J_{C-F} = 250 Hz), 150.6 (d, J_{C-F} = 8 Hz), 133.3, 130.3, 129.5, 125.1, 116.5 (d, J_{C-F} = 15 Hz), 114.1, 113.9, 99.0 (d, J_{C-F} = 16 Hz), 55.5, 38.6, 30.0; LCMS (ES) *m*/*z* 284.2 [M + H]$^+$; HRMS (ESI/Orbitrap) *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{15}FNO_2$ 284.1081, found 284.1074.

*3-([1,1′-Biphenyl]-3-yl)-1-(4-methoxyphenyl) propan-1-one (**3m**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 15:85) to afford the title product as an off-white solid (288 mg, yield: 75%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.98 (d, *J* = 8.8 Hz, 2H), 7.64−7.59 (m, 2H), 7.49−7.34 (m, 6H), 7.31−7.25 (m, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H), 3.37−3.29 (m, 2H), 3.19−3.12 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.8, 163.5, 142.0, 141.5, 141.2, 130.3, 130.0, 128.9, 128.7, 127.4, 127.4, 127.3, 127.2, 125.0, 113.8, 55.5, 40.1, 30.5; LCMS (ES) *m*/*z* 317.1 [M + H]$^+$; HRMS (ESI/Orbitrap) *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{21}O_2$, 317.1536, found 317.1537.

*1-(4-Methoxyphenyl)-3-phenylpropan-1-one (**3n**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 10:90) to afford the title product as an off-white solid (269 mg, yield: 92%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.98 (d, *J* = 7.3 Hz, 2H), 7.62−7.54 (m, 1H), 7.52−7.44 (m, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 3.81 (s, 3H), 3.34−3.26 (m, 2H), 3.08−3.00 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.4, 158.0, 136.9, 133.3, 133.0, 129.3, 128.6, 128.0, 114.0, 55.3, 40.7, 29.3; LCMS (ES) *m*/*z* 241.3 [M + H]$^+$; HRMS (ESI/Orbitrap) *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}O_2$ 241.1223, found 241.1228.

*1-(4-Methoxyphenyl)-3-(o-tolyl)propan-1-one (**3o**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 10:90) to afford the title product as an off-white solid (279 mg, yield: 90%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.00−7.93 (m, 2H), 7.23−7.10 (m, 4H), 6.97−6.90 (m, 2H), 3.88 (s, 3H), 3.25−3.17 (m, 2H), 3.09−3.01 (m, 2H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.0, 163.5, 139.6, 136.0, 130.3, 130.0, 128.7, 126.3, 126.2, 113.8, 55.5, 38.8, 27.7, 19.4; LCMS (ES) *m*/*z* 255.3 [M + H]$^+$; HRMS (ESI/Orbitrap) *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{19}O_2$ 255.1380, found 255.1385

*3-Mesityl-1-(4-methoxyphenyl)propan-1-one (**3p**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 10:90) to afford the title product as an off-white solid (306 mg, yield: 89%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.96 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.89 (s, 2H), 3.88 (s, 3H), 3.12−2.98 (m, 4H), 2.32 (s, 6H), 2.28 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.2, 163.5, 136.1, 135.4, 135.0, 130.3, 130.0, 129.0, 113.8, 55.5, 37.6, 23.9, 20.8, 19.7; LCMS (ES) *m*/*z* 283.3 [M + H]$^+$; HRMS (ESI/Orbitrap) *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{23}O_2$ 283.1693, found 283.1701.

*1-(4-Methoxyphenyl)-3-(1-methyl-1H-indazol-5-yl)propan-1-one (**3q**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 25:75) to afford the title product as a brown solid (269 mg, yield: 75%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.00−7.90 (m, 3H), 7.60 (s, 1H), 7.38−7.30 (m, 2H), 6.97−6.90 (m, 2H), 4.08 (s, 3H), 3.90 (s, 3H), 3.35−3.28 (m, 2H), 3.22−3.15 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.8, 163.5, 138.9, 133.6, 132.2, 130.3, 130.0, 127.7, 124.3, 119.8, 113.7, 108.9, 55.5, 40.5, 35.5, 30.2; LCMS (ES) *m*/*z* 295.3 [M + H]$^+$; HRMS (ESI/Orbitrap) *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}N_2O_2$ 295.1441, found 295.1448.

*1-(4-Methoxyphenyl)-3-(naphthalen-2-yl)propan-1-one (**3r**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 10:90) to afford the title product as an off-white solid (329 mg, yield: 93%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.03−7.95 (m, 2H), 7.87−7.78 (m, 3H), 7.72 (s, 1H), 7.53−7.38 (m, 3H), 6.99−6.92 (m, 2H), 3.89 (s, 3H), 3.42−3.33 (m, 2H), 3.29−3.21 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.8, 163.5, 139.0, 133.7, 132.1, 130.3, 130.0, 128.1, 127.6, 127.5, 127.2, 126.5, 126.0, 125.3, 113.8, 55.5, 40.0, 30.45; LCMS (ES) *m*/*z* 291.0 [M + H]$^+$; HRMS (ESI/Orbitrap) *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{19}O_2$ 291.1380, found 291.1380.

*3-(4-Fluorophenyl)-1-(4-methoxyphenyl)propan-1-one (**3s**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 10:90) to afford the title product as a white solid (291 mg, yield: 92%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.95 (d, *J* = 8.8 Hz, 2H), 7.21 (dd, *J* = 8.4, 5.5 Hz, 2H), 7.04−6.88 (m, 4H), 3.88 (s, 3H), 3.29−3.19 (m, 2H), 3.10−2.99 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.6, 163.5, 161.8 (d, J_{C-F} = 242 Hz), 137.1 (d, J_{C-F} = 3 Hz), 130.3, 129.9, 129.8 (d, J_{C-F} = 7 Hz), 115.2 (d, J_{C-F} = 21 Hz), 113.8, 55.5, 40.1, 29.5; LCMS (ES) *m*/*z* 259.1 [M + H]$^+$; HRMS (ESI/Orbitrap) *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}FO_2$ 259.1129, found 259.1139.

*3-(4-Chlorophenyl)-1-(4-methoxyphenyl)propan-1-one (**3t**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 10:90) to afford the title product as an off-white solid (311 mg, yield: 93%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.99−7.92 (m, 2H), 7.31−7.24 (m, 2H), 7.23−7.17 (m, 2H), 6.99−6.90 (m, 2H), 3.89 (s, 3H), 3.29−3.21 (m, 2H), 3.10−3.01 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.4, 163.5, 139.9, 131.8, 130.3, 129.8, 128.6, 113.8, 55.5, 39.8, 29.6; LCMS (ES) *m*/*z* 275.0 [M + H]$^+$; HRMS (ESI/Orbitrap) *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}ClO_2$ 275.0833, found 275.0829.

*3-(4-Bromophenyl)-1-(4-methoxyphenyl)propan-1-one (**3u**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 10:90) to afford the title product as an off-white solid (332 mg, yield: 85%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.86−7.79 (m, 2H), 7.63−7.58 (m, 2H), 7.20−7.15 (m, 2H), 6.89−6.83 (m, 2H), 3.81 (s, 3H), 3.28−3.21 (m, 2H), 3.05−2.99 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.3, 158.1, 135.6, 133.1, 131.9, 129.6, 129.3, 128.2, 114.0, 55.3, 40.7, 29.2;

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LCMS (ES) m/z 320.1 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{16}H_{16}BrO_2$ 319.0328, found 319.0329.

*3-(4-Iodophenyl)-1-(4-methoxyphenyl)propan-1-one (**3v**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 10:90) to afford the title product as an off-white solid (382 mg, yield: 86%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.96−7.91 (m, 2H), 7.64−7.59 (m, 2H), 7.04−7.00 (m, 2H), 6.96−6.91 (m, 2H), 3.89 (s., 3H), 3.26−3.21 (m, 2H), 3.04−2.99 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.3, 163.5, 141.1, 137.4, 130.5, 130.2, 129.8, 113.7, 91.0, 55.4, 39.6, 29.6; LCMS (ES) m/z 367.1 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{16}H_{16}IO_2$ 367.0189, found 367.0191.

*3-(3-Chlorophenyl)-1-(4-methoxyphenyl)propan-1-one (**3w**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 10:90) to afford the title product as an off-white solid (304 mg, yield: 91%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.01−7.92 (m, 2H), 7.28−7.25 (m, 1H), 7.25−7.14 (m, 3H), 6.99−6.93 (m, 2H), 3.89 (s, 3H), 3.30−3.23 (m, 2H), 3.11−3.01 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.3, 163.6, 143.5, 134.2, 130.3, 130.2, 129.8, 129.8, 128.6, 126.7, 126.3, 113.8, 113.8, 113.7, 55.5, 39.7, 29.9; LCMS (ES) m/z 275.2 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{16}H_{16}ClO_2$ 275.0833, found 275.0833.

*3-(3-Bromophenyl)-1-(4-methoxyphenyl)propan-1-one (**3x**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 10:90) to afford the title product as an off-white solid (341 mg, yield: 88%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.00−7.92 (m, 2H), 7.46−7.40 (m, 1H), 7.35 (dt, J = 7.3, 1.9 Hz, 1H), 7.23−7.15 (m, 2H), 6.98−6.92 (m, 2H), 3.89 (s, 3H), 3.29−3.22 (m, 2H), 3.14−2.97 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.3, 163.6, 143.9, 131.5, 130.5, 130.2, 129.8, 129.2, 128.5, 127.2, 122.5, 113.8, 55.5, 39.7, 29.8; LCMS (ES) m/z 321.0 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{16}H_{16}BrO_2$ 319.0328, found 319.0323.

*3-(2-Fluoro-5-methoxyphenyl)-1-(4-methoxyphenyl)propan-1-one (**3y**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 15:85) to afford the title product as an off-white solid (282 mg, yield: 80%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.99−7.91 (m, 2H), 6.99−6.91 (m, 3H), 6.80 (dd, J = 6.1, 3.2 Hz, 1H), 6.70 (dt, J = 8.9, 3.5 Hz, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.28−3.22 (m, 2H), 3.09−3.01 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.5, 163.5, 155.6, 154.1 (d, J_{C-F} = 153 Hz), 130.3, 129.9, 129.0 (d, J_{C-F} = 23 Hz), 115.9 (d, J_{C-F} = 6 Hz), 115.6 (d, J_{C-F} = 32 Hz), 113.7, 112.5 (d, J_{C-F} = 11 Hz), 55.7, 55.4, 38.5, 24.5, LCMS (ES) m/z 289.3 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{17}H_{18}FO_3$ 289.1234, found 289.1239.

*3-(4-Methoxyphenyl)-1-phenylpropan-1-one (**3aa**).* Following a 200.0 mg (1.5 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 10:90) to afford the title product as an off-white solid (326 mg, yield: 91%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.98 (d, J = 7.3 Hz, 2H), 7.34−7.20 (m, 5H), 6.92 (d, J = 8.5 Hz, 2H), 3.81 (s, 3H), 3.34−3.26 (m, 2H), 3.08−3.00 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.4, 158.0, 136.9, 133.3, 133.0, 129.3 128.6, 128.0, 113.7, 114.0, 55.3, 40.7, 29.3; LCMS (ES) m/z 241.1 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M]^+$ calcd for $C_{16}H_{16}O_2$ 240.1223, found 240.1230.

*3-(4-Methoxyphenyl)-1-(p-tolyl)propan-1-one (**3ab**).* Following a 200.0 mg (1.4 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 10:90) to afford the title product as a white solid (312 mg, yield: 91%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.91−7.86 (m, 2H), 7.27 (d, J = 7.8 Hz, 2H), 7.22−7.17 (m, 2H), 6.89−6.84 (m, 2H), 3.81 (s, 3H), 3.29−3.23 (m, 2H), 3.06−3.00 (m, 2H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.9, 143.7, 134.4, 133.4, 129.3, 129.2, 129.2, 128.1, 113.9, 55.2, 40.5, 29.3, 21.6; LCMS (ES) m/z 255.3 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{17}H_{19}O_2$ 255.1380, found 255.1386.

*1-(4-Bromophenyl)-3-(4-methoxyphenyl)propan-1-one (**3ac**).* Following a 200.0 mg (1.0 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 10:90) to afford the title product as an off-white solid (271 mg, yield: 90%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.98−7.91 (m, 2H), 7.42 (dd, J = 8.2, 1.8 Hz, 2H), 7.17−7.11 (m, 2H), 6.94 (dd, J = 8.7, 1.8 Hz, 2H), 3.90 (s, 3H), 3.28−3.19 (m, 2H), 3.07−2.99 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.4, 163.5, 140.5, 131.5, 130.3, 130.3, 129.8, 128.6, 119.8, 113.8, 55.5, 39.7, 29.6; LCMS (ES) m/z 321.0 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{16}H_{16}BrO_2$ 319.0328, found 319.0329.

*1-(3,4-Difluorophenyl)-3-(4-methoxyphenyl)propan-1-one (**3ad**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 10:90) to afford the title product as an off-white solid (247 mg, yield: 76%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.83−7.76 (m, 1H), 7.76−7.70 (m, 1H), 7.30−7.20 (m, 1H), 7.19−7.14 (m, 2H), 6.89−6.83 (m, 2H), 3.80 (s, 3H), 3.26−3.20 (m, 2H), 3.05−2.98 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.7, 158.0, 153.4 (dd, J_{C-F} = 155, 13 Hz), 150.2 (dd, J_{C-F} = 149, 13 Hz), 133.9 (d, J_{C-F} = 8 Hz), 132.8, 129.2, 124.9 (dd, J_{C-F} = 11, 3 Hz), 117.4 (d, J_{C-F} = 14 Hz), 117.2 (d, J_{C-F} = 12 Hz), 114.0, 55.2, 40.5, 29.1; LCMS (ES) m/z 277.2 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{16}H_{15}F_2O_2$ 277.1035, found 277.1038.

*1-(3-Chloro-4-methoxyphenyl)-3-(4-methoxyphenyl)propan-1-one (**3ae**).* Following a 200.0 mg (1.0 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 15:85) to afford the title product as an off-white solid (282 mg, yield: 92%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.99 (s, 1H), 7.90−7.84 (m, 1H), 7.17 (d, J = 8.8 Hz, 2H), 6.99−6.93 (m, 1H), 6.88−6.80 (m, 2H), 3.97 (s, 3H), 3.82 (s, 3H), 3.24−3.16 (m, 2H), 3.05−2.96 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.0, 158.7, 158.0, 133.2, 130.6, 129.3, 128.4, 122.9, 114.0, 111.3, 56.4, 55.3, 40.4, 29.3; LCMS (ES) m/z 305.2 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + H]^+$ calcd for $C_{17}H_{18}ClO_3$ 305.0939, found 305.0940.

*1-Cyclohexyl-3-(4-methoxyphenyl)propan-1-one (**3af**).* Following a 200.0 mg (1.4 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 10:90) to afford the title product as a colorless oil (302 mg, yield: 86%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.15−7.09 (m, 2H), 6.88−6.81 (m, 2H), 3.80 (s, 3H), 2.88−2.80 (m, 2H), 2.78−2.71 (m, 2H), 2.37−2.27 (m, 1H), 1.87−1.74 (m, 4H), 1.71−1.60 (m, 1H), 1.39−1.13 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 213.3, 158.0, 133.5, 129.3, 113.9, 55.3, 51.0, 42.5, 28.9, 28.4, 25.9, 25.7; LCMS (ES) m/z 247.1 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + Na]^+$ calcd for $C_{16}H_{22}NaO_2$ 269.1512, found 269.1515.

*4-(3,4-Dimethoxyphenyl)-1-phenylbutan-2-one (**3ag**).* Following a 200.0 mg (1.4 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 15:85) to afford the title product as an off-white solid (331 mg, yield: 86%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.41−7.25 (m, 3H), 7.24−7.13 (m, 2H), 6.78 (d, J = 8.0 Hz, 1H), 6.73−6.64 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.68 (s, 2H), 2.91−2.81 (m, 2H), 2.81−2.74 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 207.5, 148.9, 147.4, 134.1, 133.6, 129.4, 128.7, 127.0, 120.1, 111.8, 111.4, 56.0, 55.8, 50.4, 43.7, 29.5; LCMS (ES) m/z 285.1 $[M + H]^+$; HRMS (ESI/Orbitrap) m/z $[M + Na]^+$ calcd for $C_{18}H_{20}NaO_3$ 307.1305, found 307.1313.

*4-(3,4-Dimethoxyphenyl)-1-(p-tolyl)butan-2-one (**3ah**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 20:80) to afford the title product

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as a light yellow solid (324 mg, yield: 88%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.18−7.11 (m, 2H), 7.10−7.04 (m, 2H), 6.82−6.75 (m, 1H), 6.72−6.64 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.64 (s, 2H), 2.87−2.80 (m, 2H), 2.80−2.72 (m, 2H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 207.8, 148.9, 147.4, 136.6, 133.7, 131.0, 129.4, 129.3, 120.1, 111.8, 111.4, 56.0, 55.8, 50.1, 43.6, 29.5, 21.0; LCMS (ES) *m*/*z* 299.1 [M + H]$^+$; HRMS (ESI/Orbitrap) *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{22}NaO_3$ 321.1461, found 321.1470.

*1,4-Bis(4-methoxyphenyl)butan-2-one (**3ai**).* Following a 200.0 mg (1.1 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 15:85) to afford the title product as an off-white solid (287 mg, yield: 90%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.39−7.24 (m, 3H), 7.18 (d, *J* = 7.8 Hz, 2H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.73−6.64 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.68 (s, 2H), 2.89−2.74 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 207.5, 148.9, 147.4, 134.1, 133.6, 129.4, 128.7, 127.0, 120.1, 111.8, 111.4, 56.0, 55.8, 50.4, 43.7, 29.5; LCMS (ES) *m*/*z* 285.1 [M + H]$^+$; HRMS (ESI/Orbitrap) *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{20}NaO_3$ 307.1305, found 307.1312.

*1-(3,4-Dimethoxyphenyl)-6-phenylhexan-3-one (**3aj**).* Following a 200.0 mg (1.1 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 20:80) to afford the title product as an off-white solid (306 mg, yield: 86%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.34−7.27 (m, 2H), 7.24−7.15 (m, 3H), 6.83−6.78 (m, 1H), 6.77−6.71 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 2.90−2.83 (m, 2H), 2.75−2.68 (m, 2H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.42 (t, *J* = 7.4 Hz, 2H), 1.99−1.88 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 209.9, 149.0, 147.5, 141.6, 133.8, 128.5, 128.4, 126.0, 120.2, 111.9, 111.5, 56.0, 55.9, 44.5, 42.2, 35.1, 29.4, 25.2; LCMS (ES) *m*/*z* 313.3 [M + H]$^+$; HRMS (ESI/Orbitrap) *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{24}NaO_3$ 335.1618, found 335.1624.

*(E)-5-(4-Methoxyphenyl)-1-phenylpent-1-en-3-one (**3ak**).* Following a 200.0 mg (1.3 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 15:85) to afford the title product as an off-white solid (234 mg, yield: 70%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.62−7.47 (m, 3H), 7.44−7.35 (m, 3H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.76 (s, 1H), 6.72 (s, 1H), 3.80 (s, 3H), 3.04−2.92 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.5, 158.0, 142.7, 140.1, 134.5, 133.2, 130.5, 129.3, 128.9, 128.3, 126.2, 114.0, 55.3, 42.7, 29.3; LCMS (ES) *m*/*z* 267.2 [M + H]$^+$; HRMS (ESI/Orbitrap) *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}O_2$ 267.1380, found 267.1372.

*3-(Cyclohex-1-en-1-yl)-1-(4-methoxyphenyl)propan-1-one (**3bf**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 10:90) to afford the title product as a white solid (251 mg, yield: 84%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.00−7.95 (m, 2H), 6.99−6.91 (m, 2H), 5.49−5.43 (m, 1H), 3.89 (s, 3H), 3.07−3.01 (m, 2H), 2.37 (t, *J* = 7.8 Hz, 2H), 2.04−1.96 (m, 4H), 1.69−1.54 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.9, 163.3, 136.7, 130.3, 130.2, 121.3, 113.7, 55.5, 36.8, 32.6, 28.5, 25.2, 22.9, 22.5; LCMS (ES) *m*/*z* 245.2 [M + H]$^+$; HRMS (ESI/Orbitrap) *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{21}O_2$ 245.1536, found 245.1530.

*1-(4-Methoxyphenyl)-3-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-propan-1-one (**3bg**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 25:75) to afford the title product as a white solid (290 mg, yield: 79%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.00−7.94 (m, 2H), 6.98−6.93 (m, 2H), 5.41−5.37 (m, 1H), 4.06−3.99 (m, 4H), 3.89 (s, 3H), 3.11−3.03 (m, 2H), 2.55−2.39 (m, 2H), 2.32−2.22 (m, 4H), 1.84−1.77 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.5, 163.4, 136.5, 130.3, 130.0, 118.4, 113.7, 108.0, 64.4, 55.5, 36.6, 35.6, 31.5, 31.1, 27.9; LCMS (ES) *m*/*z* 303.2 [M + H]$^+$; HRMS (ESI/Orbitrap) *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{23}O_4$ 303.1591, found 303.1590.

*3-(3,6-Dihydro-2H-pyran-4-yl)-1-(4-methoxyphenyl)propan-1-one (**3bh**).* Following a 200.0 mg (1.2 mmol, 1 equiv) scale reaction, the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 20:80) to afford the title product as an off-white solid (279 mg, yield: 93%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.02−7.89 (m, 2H), 7.01−6.86 (m, 2H), 5.51−5.42 (m, 1H), 4.11 (d, *J* = 2.3, 4.5 Hz, 2H), 3.92 (s, 3H), 3.84−3.74 (m, 2H), 3.12−2.98 (m, 2H), 2.50−2.36 (m, 2H), 2.14−2.06 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.3, 163.5, 134.7, 130.3, 130.0, 120.0, 113.8, 65.5, 64.3, 55.5, 36.0, 35.9, 35.7, 35.5, 31.4, 28.7; LCMS (ES) *m*/*z* 247.1 [M + H]$^+$; HRMS (ESI/Orbitrap) *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}O_3$ 247.1329, found 247.1329.

Procedure for the Cross-Coupling of 5a with 2a. A mixture containing vinyl ketone **5a** (1 mmol, 1 equiv), **2a** (2 mmol, 2 equiv), $Pd(OAc)_2$ (0.1 mmol, 0.1 equiv), $Cu(OAc)_2$ (2 mmol, 2 equiv), and DPPE (0.2 mmol, 0.2 equiv) in a solvent mixture (0.33 M solution) of DMSO (2.5 mL) and water (0.5 mL) was stirred at 70 °C in an oil bath for 2 h under open air. The reaction mixture was monitored by TLC. After completion of the reaction, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to get the crude product, which was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether (ratio = 15:85) to afford the product **3a** as an off-white solid (263 mg, 80%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00160.

^{1}H NMR and ^{13}C{^{1}H} NMR spectra of new compounds (PDF)

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The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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