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Pd-Catalyzed Monoselective *ortho*-C−H Alkylation of *N*-Quinolyl Benzamides: Evidence for Stereoretentive Coupling of Secondary Alkyl Iodides

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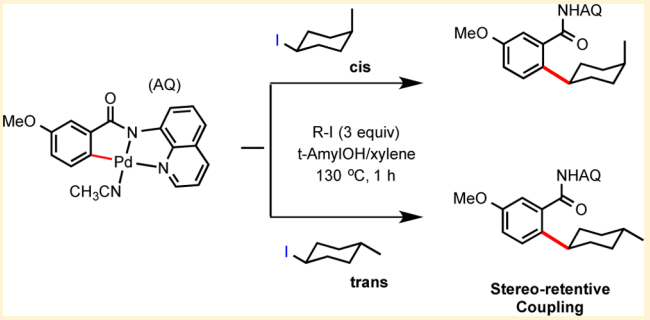
Supporting Information

ABSTRACT: We report a method for the monoselective alkylation of *ortho*-C−H bonds of *N*-quinolyl benzamides with both primary and secondary alkyl halides under palladium catalysis. With promotion by $NaHCO_3$ and $(BnO)_2PO_2H$ or $(PhO)_2PO_2H$, symmetric benzamide substrates can be selectively *ortho*-alkylated to give either mono- or dialkylated products by simply adjusting the amount of $NaHCO_3$ applied. The use of phosphate notably improves the alkylation yield, although it may not be directly involved in C−H palladation or the subsequent functionalization step. Kinetic isotope effect studies indicate that C−H palladation is not the rate-limiting step. Examination of the reactions of an isolated palladacycle intermediate with both *cis*- and *trans*-4-methylcyclohexyl iodides revealed surprising stereoretentive couplings of these alkyl iodides. This evidence strongly suggests that the functionalization of the palladacycle with secondary alkyl iodides proceeds via a rarely precedented concerted oxidative addition pathway.



INTRODUCTION

Metal-catalyzed, directing-group-mediated C−H functionalization is emerging as a powerful synthetic strategy for transforming organic compounds.[1,2] Compared with the increasingly mature area of C−H arylation reactions, synthetically useful protocols for metal-catalyzed C−H alkylation are considerably less common.[3] While various alkyl precursors, including tin[4] and borane-based[5] alkyl reagents, activated alkenes,[6,7] and even alkanes,[8] have been successfully applied in various metal-catalyzed C−H alkylation systems,[9] alkyl halides are particularly attractive due to their accessibility and broad applicability in organic synthesis.[10−13] Among metal catalysts, palladium complexes have demonstrated distinct capability for efficient C−H functionalization, particularly of unactivated $C(sp^3)$−H bonds, under mild reaction conditions.[1f,i] In 1984, Tremont reported the first Pd-catalyzed *ortho*-C−H alkylation of acetanilide with MeI (Scheme 1A).[10a] In 2009, Yu and co-workers reported that simple benzoic acids undergo *ortho*-C−H alkylation with methylene and ethylene dichloride forming 5 or 6-membered lactone products in good yield.[10d] In 2010, Daugulis and co-workers reported Pd-catalyzed aminoquinoline (AQ)[14b] carboxamide-directed alkylation of β $C(sp^2)$−H and $C(sp^3)$−H bonds with primary alkyl halides (Scheme 1A).[14−21] In 2012, our laboratory reported that *N*-benzyl picolinamides (PA) can undergo a similar Pd-catalyzed *ortho*-$C(sp^2)$−H alkylation with primary alkyl halides (eq 1, Scheme 1B).[20a] More recently, we demonstrated that PA[20b] and AQ[20c] auxiliaries can enable efficient Pd-catalyzed alkylation of unactivated and methylene $C(sp^3)$−H bonds with primary alkyl halides. Despite these advances, more development is needed to improve the synthetic utility of Pd-catalyzed C−H alkylation to the level attained by existing metal-catalyzed cross-coupling methods.[22]

Previous studies by the Daugulis group and others have shown that 8-aminoquinoline is an excellent bidentate directing group for Pd-catalyzed C−H functionalization.[19] Mechanistic studies have shown that AQ-directed Pd-catalyzed C−H functionalization can proceed through a $Pd^{II/IV}$ cycle.[14b] However, the details of this catalytic cycle are poorly understood, and the substrate scope of these Pd-catalyzed AQ-directed transformations is often restrictive. For instance, the halide coupling partners in Pd-catalyzed C−H alkylation reactions are limited to more reactive primary alkyl halides; the coupling of secondary alkyl halides is much more challenging, even with more reactive $C(sp^2)$−H bonds.[23] In addition, the monoselective alkylation of *N*-quinolyl benzamides (e.g., compound **1**, eq 5 below) bearing two equivalent *ortho*-C−H bonds has not been achieved.[24,25]

Herein, we report our investigation of Pd-catalyzed *ortho*-C−H alkylation of *N*-quinolyl benzamides with both primary and secondary alkyl halides. Under the promotion of $NaHCO_3$ and organic phosphates, symmetric benzamide substrates can be selectively *ortho*-alkylated to give either mono- or dialkylated products by simply adjusting the amount of $NaHCO_3$ applied. Kinetic isotope effect (KIE) studies indicate that C−H

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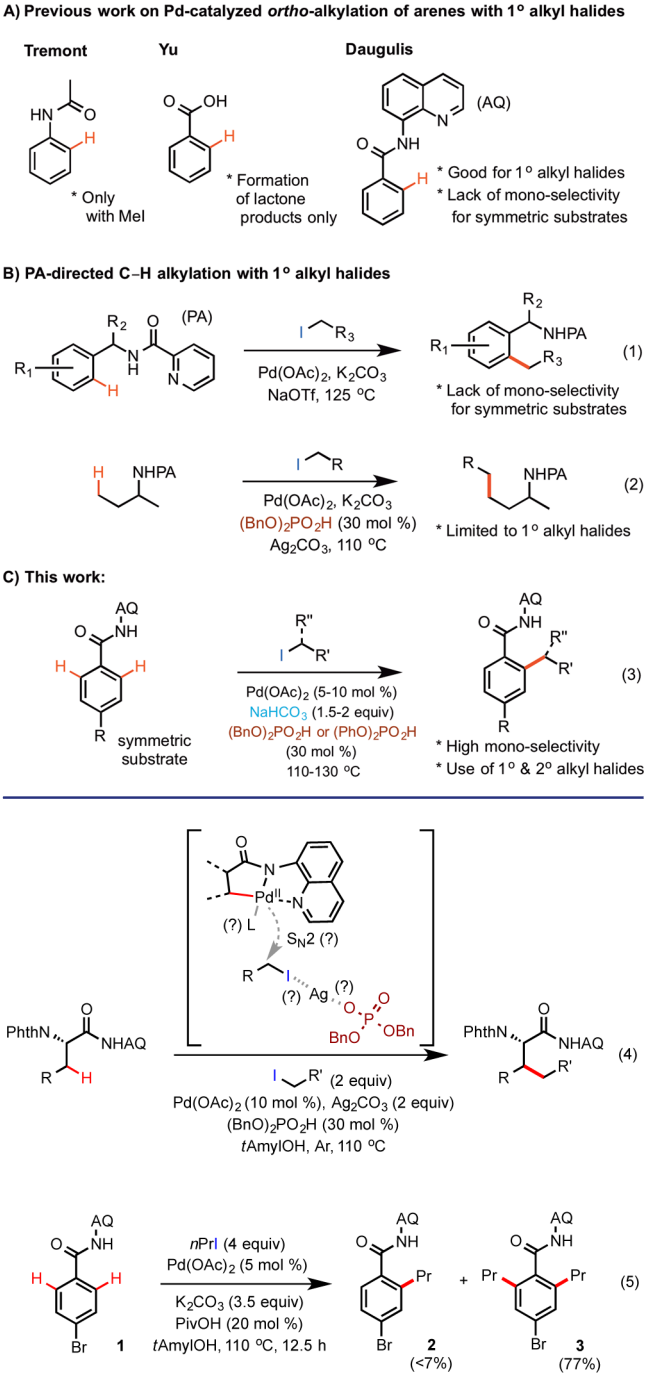
Scheme 1. Pd-Catalyzed C−H Alkylation with Alkyl Halides



palladation is not the rate-limiting step. Surprisingly, reaction of an isolated Pd^{II} palladacycle with both *cis*- and *trans*-3-methylcyclohexyl iodides proceeded with retention of stereochemistry. This strongly suggests that the functionalization of palladacycle with secondary alkyl iodides proceeds via a rarely precedented concerted oxidative addition pathway.

RESULTS AND DISCUSSION

Our interest in this particular AQ-directed *ortho*-C(sp^2)−H alkylation originated from our recent studies of Pd-catalyzed C(sp^3)−H alkylation. In these studies, we discovered that a catalytic amount of dibenzyl phosphate $(BnO)_2PO_2H$ (BP), in combination with Ag salt, served as a uniquely effective promoter in Pd-catalyzed PA- and AQ-directed alkylation of unactivated C(sp^3)−H bonds with primary alkyl halides (eqs 2 and 4).[20b,c] However, we were puzzled by the functional role of phosphate additive due to the complexity of the reaction conditions. Because Ag_2CO_3 was also required in both reaction systems, we suspected that BP might react with Ag_2CO_3 to form a soluble silver phosphate species, thus playing a solid-to-solution phase-transfer role (eq 4). We reasoned that modulating the concentration of Ag^+ in the reaction system might attenuate the reactivity of alkyl halides, which could otherwise undergo competing side reactions such as esterification with OAc^-. Alternatively, BP might serve as a ligand for Pd and facilitate the oxidative addition of alkyl halides.[26,27] It is also possible that phosphate might facilitate the dissociation of Pd^{II} from the bidentate AQ group of alkylated product and accelerate catalyst turnover. To probe the functional role of phosphate, we turned our attention to a less complex reaction system: the *ortho*-C(sp^2)−H alkylation of *N*-quinolyl benzamides, which does not require Ag.

Monoselective *ortho*-C(sp^2)−H alkylation with Primary Alkyl Iodides. Pd-catalyzed *ortho*-C−H alkylation of N-quinolyl benzamides with primary alkyl halides under Ag-free conditions was first reported by Daugulis in 2010.[14b] For example, alkylation of **1** with 4 equiv of *n*PrI gave dialkylated product **3** in good yield (eq 5). However, the *ortho*-C−H alkylation of symmetric arene substrates (e.g., **1**) cannot be stopped at the monoalkylation stage, limiting the transformation's synthetic utility. In our own trials, alkylation of **1** with 1 equiv of *n*PrI under Daugulis's conditions gave a mixture of **2** (25%) and **3** (34%). The second *ortho*-C−H alkylation of symmetric arene substrates, e.g., **1**, should be slightly sterically disfavored relative to the first *ortho*-C−H alkylation. However, this disparity may be too small to allow for effective differentiation and monoselectivity in Pd-catalyzed C−H functionalization systems, especially for sterically less bulky alkyl groups. Furthermore, monoalkylation may alter the electronics of the product and activate it toward further alkylation.[28] Encouraged by the promoting ability of phosphates in Pd-catalyzed C(sp^3)−H alkylation, we wondered whether they might enable monoselective *ortho*-C(sp^2)−H alkylation of benzamides.

As shown in Table 1, we commenced our study of mono C−H alkylation of *N*-quinolyl benzamide **4** with *n*PrI (3 equiv) and 5 mol% of $Pd(OAc)_2$ at 110 °C. Interestingly, unsubstituted substrate **4** appeared to be considerably less reactive toward ortho alkylation than **1** under the original conditions (K_2CO_3/PivOH, see eq 4). Alkylation of **4** proceeded with poor conversion and mainly gave dialkylated product **6** (entry 1). Reaction of **4** under our previously optimized conditions for PA-directed NaOTf-promoted C-(sp^2)−H alkylation also proceeded in low yield (entry 2).[20a] Reaction of **4** under our recently reported conditions for AQ-directed C(sp^3)−H alkylation (2 equiv of Ag_2CO_3 and 30 mol % of BP in *t*AmylOH at 110 °C) gave higher conversion but mainly product **6** (entry 3). Interestingly, use of 2 equiv of Na_2CO_3 or $NaHCO_3$ and 30 mol% of BP gave monoalkylated product **5** in improved yield and selectivity (entries 7, 8). Use of 1:1 mixed solvent of *t*AmylOH (A) and 1,2-dichloroethane (D) gave higher conversion than either solvent individually (entries 8−10). Lowering the amount of $NaHCO_3$ to 1.5 equiv improved the monoselectivity (entry 12). Finally, running the reaction under 1 atm of O_2[29] gave **5** in 81% isolated yield along with 9% of dialkylated product **6** (entry 13).

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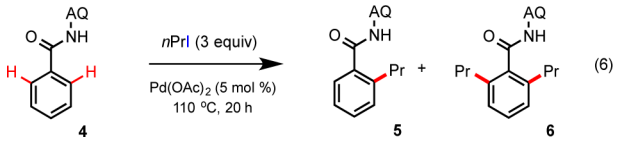
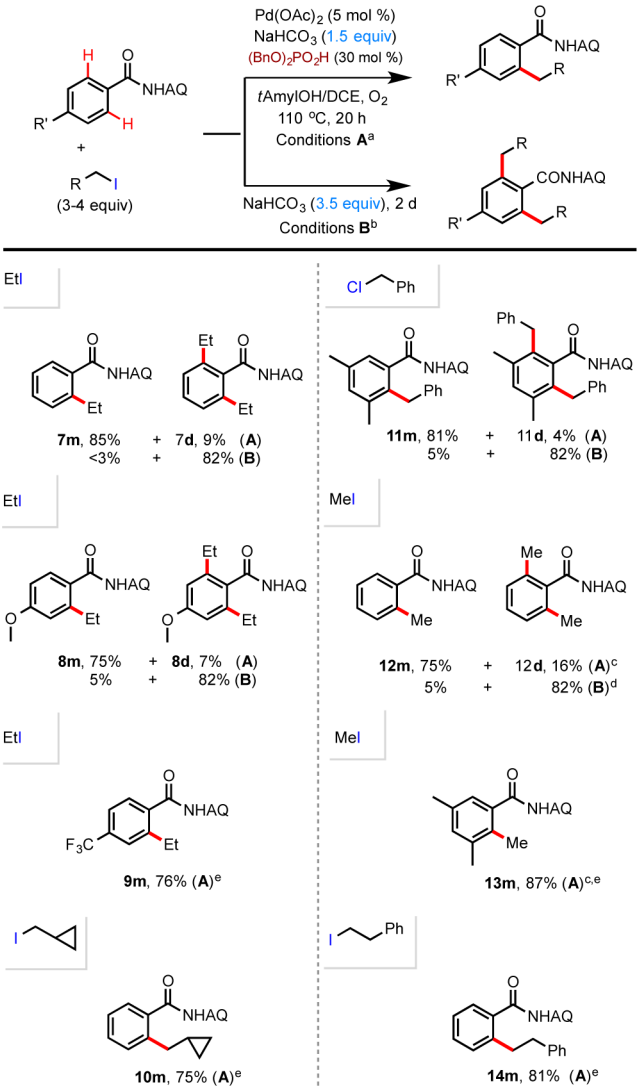
Table 1. Monoselective *ortho*-C−H Alkylation of 4 with nPrI



entry	reagents (equiv)[a]	solvents[b]	yield (%) 5	6
1	PrI (4), K_2CO_3 (3.5), PivOH (0.2), Ar	A	<2	16
2	PrI (3), K_2CO_3 (2), NaOTf (3), O_2	A	4	12
3	PrI (3), Ag_2CO_3 (2), BP (0.3), Ar	A	<2	42
4	PrI (3), Ag_2CO_3 (2), Ar	A	<2	12
5	PrI (3), K_2CO_3 (2), Ar	A	<2	15
6	PrI (3), K_2CO_3 (2), BP (0.3), Ar	A	6	24
7	PrI (3), Na_2CO_3 (2), BP (0.3), Ar	A	48	6
8	PrI (3), $NaHCO_3$ (2), BP (0.3), Ar	A	49	3
9	PrI (3), $NaHCO_3$ (2), BP (0.3), Ar	D	47	2
10	PrI (3), $NaHCO_3$ (2), BP (0.3), Ar	A/D (1:1)	69	12
11	PrI (3), $NaHCO_3$ (2), BP (1), Ar	A/D (1:1)	34	18
12	PrI (3), $NaHCO_3$ (1.5), BP (0.3), Ar	A/D (1:1)	62	6
13	PrI (3), $NaHCO_3$ (1.5), BP (0.3), O_2	A/D (1:1)	84 (81)[d]	9
14	PrI (3), $NaHCO_3$ (1.5), O_2	A/D (1:1)	31	<2
15	PrI (3), BP[c] (0.3), O_2	A/D (1:1)	<2	<2
16	PrI (3), $NaHCO_3$ (1.5), PP[c] (0.3), O_2	A/D (1:1)	76	15
17	PrI (3), $NaHCO_3$ (1.5), BP (0.3), O_2 $PdCl_2$ (5 mol%)[e]	A/D (1:1)	65	2
18	PrI (3), $NaHCO_3$ (1.5), PivOH (0.3), O_2	A/D (1:1)	23	35
19	PrI (3), $NaHCO_3$ (1.5), PivOH (0.3), BP (0.3), O_2	A/D (1:1)	52	22
20	PrI (3), $NaHCO_3$ (1.5), BP (0.3), O_2, TEMPO (1)	A/D (1:1)	25	<2
21[f]	PrI (3), $NaHCO_3$ (3.5), BP (0.3), O_2	A/D (1:1)	13	76
22[f]	PrI (4), $NaHCO_3$ (3.5), BP (0.3), O_2	A/D (1:1)	9	82 (77)[d]

[a]All screening reactions were carried out on a 0.2 mmol scale at 0.1 M concentration; the reaction vial is purged with Ar or O_2 and sealed with PTFE cap. Yields are based on ^{1}H NMR analysis of the crude reaction mixture use 1,2-dichloroethane as an internal standard. [b]A = *t*AmylOH, D = 1,2-dichloroethane. [c]BP = $(BnO)_2PO_2H$, PP = $(PhO)_2PO_2H$. [d]Isolated yield. [e]$PdCl_2$ was used as catalyst. [f]48 h.

Scheme 2. Scope of Symmetric *N*-Quinolyl Benzamides[a]



All reactions were carried out on a 0.2 mmol scale; isolated yields are given. [a]Conditions A, see entry 13 of Table 1. [b]Conditions B, see entry 22 of Table 1. [c]1.1 equiv of MeI was used. [d]2.2 equiv of MeI was used. [e]Dialkylation <5%.

Notably, use of 1.5 equiv of $NaHCO_3$ alone gave 31% yield of **5** with excellent selectivity (entry 14), while the addition of catalytic amount of BP provided a 50% increase in alkylation yield. The use of 30 mol% of BP alone gave no conversion (entry 15) and use of diphenyl phosphate (PP) gave similar results (entry 16). The amount of $NaHCO_3$ present determined the mono- or diselectivity of the reaction. In contrast to the high monoselectivity obtained with 1.5 equiv of $NaHCO_3$ and 30 mol% of BP in entry 13, dialkylated product **6** was the major product when 3.5 equiv of $NaHCO_3$ was applied with 30 mol% of BP for a longer reaction time of 2 days (entry 21). A 77% isolation yield of **6** was obtained with 4 equiv of *n*PrI and a reaction time of 2 days (entry 22). As shown in entry 18, a control experiment using 5 mol% of $PdCl_2$ catalyst also proceeded in good yield and excellent selectivity, indicating that a carboxylate ligand such as OAc is not required for this Pd-catalyzed C−H alkylation.

Next, we examined the scope of this AQ-directed monoselective *ortho*-C−H alkylation of symmetric aryl carboxamides (Scheme 2). A variety of primary alkyl iodides including cyclopropylmethyl iodide afforded the corresponding alkylation products in good yield and monoselectivity under the standard conditions A (1.5 equiv of $NaHCO_3$/30 mol% of BP, see entry 13 of Table 1). No ring-opening side products were formed in the alkylation of **4** with cyclopropylmethyl iodide (see **10m**). Diminished mono/di selectivity was observed for alkylation of **4** with MeI presumably due to its high reactivity and reduced steric bulk (see **12** and **13**). Under the dialkylation conditions B with 3.5 equiv of $NaHCO_3$ for 2 d (see entry 22 of Table 1), dialkylated products were obtained in good yield and selectivity (see **7d**, **8d**, **11d**, **12d**). No N-alkylation side products were formed under the standard *ortho*-C−H alkylation conditions.

Asymmetric benzamides bearing *ortho* or *meta* substituents also undergo selective *ortho*-C−H alkylation with a range of primary alkyl halides under the standard conditions A (Scheme 3). *ortho*-Substituted benzamide substrates with either electron-donating or -withdrawing groups can be alkylated in excellent yield (see **15** and **16**). Alkylation using alkyl bromides proceeds in considerably lower yield (see **18**). No rearranged side products were formed following alkylation with 6-bromohexene. With the exception of benzyl chloride, unactivated alkyl chlorides were unreactive. Alkylation of heteroaromatic

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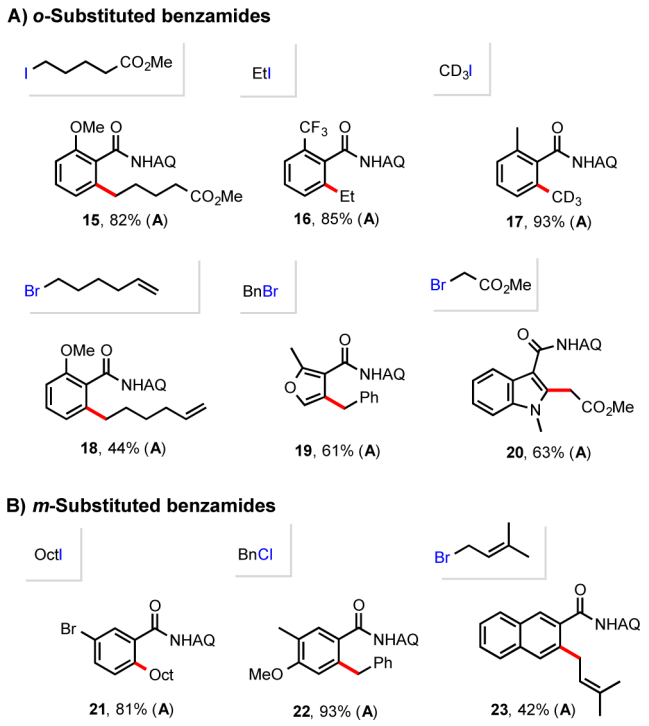
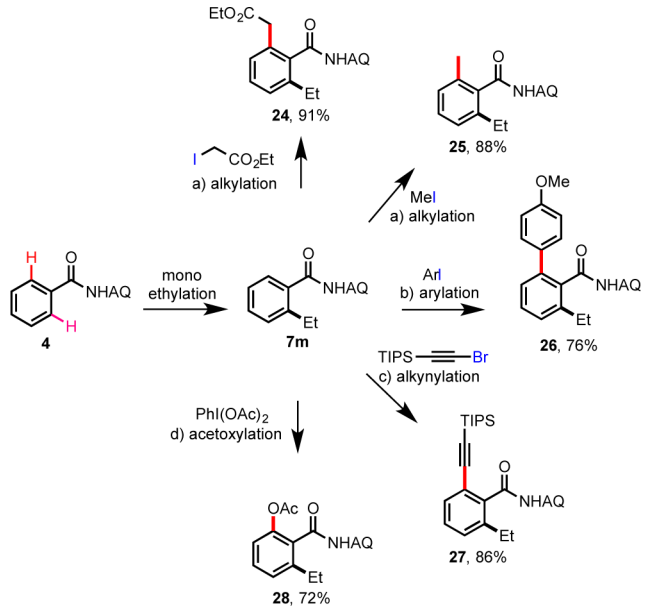
Scheme 3. Substrate Scope of Asymmetric Benzamides and Primary Alkyl Halides[a]



[a]All reactions were carried out on a 0.2 mmol scale under standard conditions A; isolated yields are given.

Scheme 4. Sequential *ortho*-C−H Functionalization of 4[a]



[a]All reactions were carried out on a 0.2 mmol scale; isolated yields are given. Reagents and conditions: (a) $Pd(OAc)_2$, BP (30 mol%), *t*AmylOH/DCE, O_2, 110 °C; (b) $Pd(OAc)_2$, ArI, Ag_2CO_3, *t*AmylOH, Ar, 110 °C; (c) $Pd(OAc)_2$, *o*-phenylbenzoic acid (20 mol%), $KHCO_3$, DCE, Ar, 100 °C; (d) $Pd(OAc)_2$, $PhI(OAc)_2$, AcOH/xylene (1:2), Ar, 110 °C. See Supporting Information for detailed conditions.

substrates such as furan and indole also worked well (see **19** and **20**). As shown in Scheme 3B, *meta*-substituted benzamides were selectively alkylated at their less hindered *ortho* position.

As demonstrated in Scheme 4, the ability to selectively monoalkylate the *ortho*-C−H bonds of symmetric benzamides enables the convenient syntheses of a broad variety of ortho disubstituted benzamides via sequential C−H functionalization. Benzamide **4** was first monoethylated with EtI to give **7m** (Scheme 2). The remaining *ortho*-C−H bond of **7m** was alkylated with α-iodoacetate and MeI to give compounds **24** and **25**, arylated with *p*-methoxyphenyl iodide to give **26**, alkynylated to give **27**, and acetoxylated with $PhI(OAc)_2$ to give **28** in good to excellent yields under optimized Pd-catalyzed conditions.[15]

Monoselective *ortho*-C(sp^2)−H Alkylation with Secondary Alkyl Iodides. Encouraged by the excellent performance of primary alkyl iodides in this AQ-directed BP-promoted monoselective *ortho*-C−H alkylation system, we proceeded to attempt alkylation with secondary alkyl iodides. As shown in Table 2, reaction of benzamide **4** with 3 equiv of *i*PrI with PivOH/K_2CO_3 in *t*AmylOH gave no conversion (entry 1). Reaction under Ag_2CO_3/BP conditions also gave little product **29** (entry 2). Reaction under the standard conditions A with 5 mol% of $Pd(OAc)_2$ gave product **29** in low yield but with excellent monoselectivity (entry 3). Increasing the catalyst loading to 10 mol% gave 23% yield of **29** (entry 4) and increasing the amount of $NaHCO_3$ from 1.5 to 2 equiv gave notably higher conversion (entry 5). Furthermore, use of mixed solvent of *t*AmylOH (A)/xylene (X) improved the yield of **29** to 79% (entry 7). Finally, the use of 30 mol% of diphenyl phosphate (PP) provided 85% isolation yield of **29** (entry 8). Similarly to the reaction of primary alkyl iodides, 42% of product **29** was formed using 2 equiv of $NaHCO_3$ alone (entry 9), while the use of 30 mol% of PP alone gave no conversion (entry 10).

The amount of $NaHCO_3$ present influences the mono- or diselectivity of the reaction. In contrast to the high monoselectivity obtained with 2 equiv of $NaHCO_3$ and 30 mol% of PP, dialkylated product **30** was the major product when 3.5 equiv of $NaHCO_3$ was applied with BP for a prolonged reaction time (2 days, entry 14). A 84% isolated yield of **30** was obtained with 6 equiv of *i*PrI and 3.5 equiv of K_2CO_3 base (entry 15). As shown in entry 13, a control experiment using 10 mol% of $PdCl_2$ catalyst also proceeded in good yield and excellent selectivity, indicating that a carboxylate ligand such as OAc is not required for this Pd-catalyzed C−H alkylation. Compared with PP, addition of 30 mol% of PivOH provides a much less significant improvement (entry 11 vs 9).

As shown in Scheme 5, a broad scope of benzamide substrates is susceptible to monoselective *ortho*-C−H alkylation with secondary alkyl halides using standard conditions C. Compared with primary alkyl iodides, secondary iodides are less reactive and require higher catalyst loading and reaction temperature. Steric hindrance also notably reduces the reactivity of secondary alkyl iodides. For instance, while *i*PrI gave excellent alkylation yields for both symmetric and unsymmetric benzamides, *sec*-butyl iodide and *sec*-pentyl iodide were considerably less reactive (see **36**, **37**, and **38**). Tertiary halides (e.g., *t*BuI) were completely unreactive under these conditions. Interestingly, alkylation with α-methylbenzyl bromide gave excellent yield (see **44**). Similarly to the reactions of primary alkyl halides, the alkylation of *meta*-substituted arene substrates with secondary halides took place selectively at the less hindered ortho position (see **36**). As shown by compounds **33** and **36**, electron-deficient benzamide substrates are considerably less reactive.[30]

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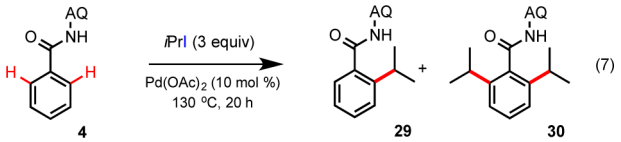
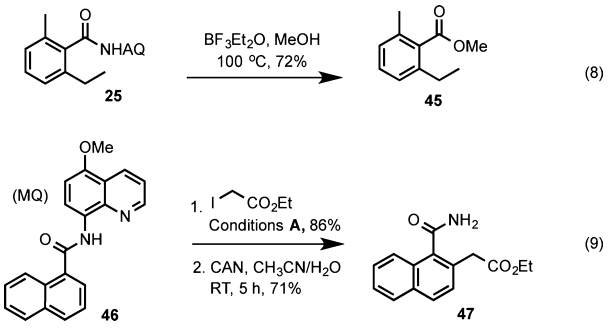
Table 2. Monoselective *ortho*-C−H Alkylation of 4 with iPrI



entry	reagents (equiv)	solvents	yield (%) 29	30
1[a]	K_2CO_3 (3.5), PivOH (0.2), Ar	A	<2	<2
2	Ag_2CO_3 (2), BP (0.3), Ar	A	<2	<2
3[b]	$NaHCO_3$ (1.5), BP (0.3), O_2	A/D (1:1)	15	<2
4	$NaHCO_3$ (1.5), BP (0.3), O_2	A/D (1:1)	23	<2
5	$NaHCO_3$ (2.0), BP (0.3), O_2	A/D (1:1)	62	6
6	$NaHCO_3$ (2.0), BP (0.3), O_2	X[c]	25	<2
7	$NaHCO_3$ (2.0), BP (0.3), O_2	A/X (1:1)	79	7
8	$NaHCO_3$ (2.0), PP[d] (0.3), O_2	A/X (1:1)	89 (85)[e]	7
9	$NaHCO_3$ (2.0), O_2	A/X (1:1)	42	2
10	PP (0.3), O_2	A/X (1:1)	<2	<2
11	$NaHCO_3$ (2.0), PivOH (0.3), O_2	A/X (1:1)	53	5
12	$NaHCO_3$ (2.0), PP (0.3), PivOH (0.3), O_2	A/X (1:1)	75	2
13	$NaHCO_3$ (2), PP (0.3), O_2 $PdCl_2$ (5 mol%)[f]	A/X (1:1)	68	2
14[g]	$NaHCO_3$ (3.5), PP (0.3), O_2	A/X (1:1)	26	65
15[g]	K_2CO_3 (3.5), PP (0.3), O_2	A/X (1:1)	2	88 (84)[e]

All screening reactions were carried out on a 0.2 mmol scale at 0.1 M concentration; the reaction vial was purged with Ar or O_2 and sealed with PTFE cap. Yields are based on ^{1}H NMR analysis of the crude reaction mixture using 1,2-dichloroethane as an internal standard. [a]4 equiv of *n*PrI was used at 110 °C. [b]5 mol% of $Pd(OAc)_2$ at 110 °C (see conditions A in Scheme 2). [c]X = *p*-xylene. [d]PP = $(PhO)_2PO_2H$. [e]Isolated yield. [f]$PdCl_2$ was used as catalyst. [g]6 equiv of *i*PrI was used, 2 d.

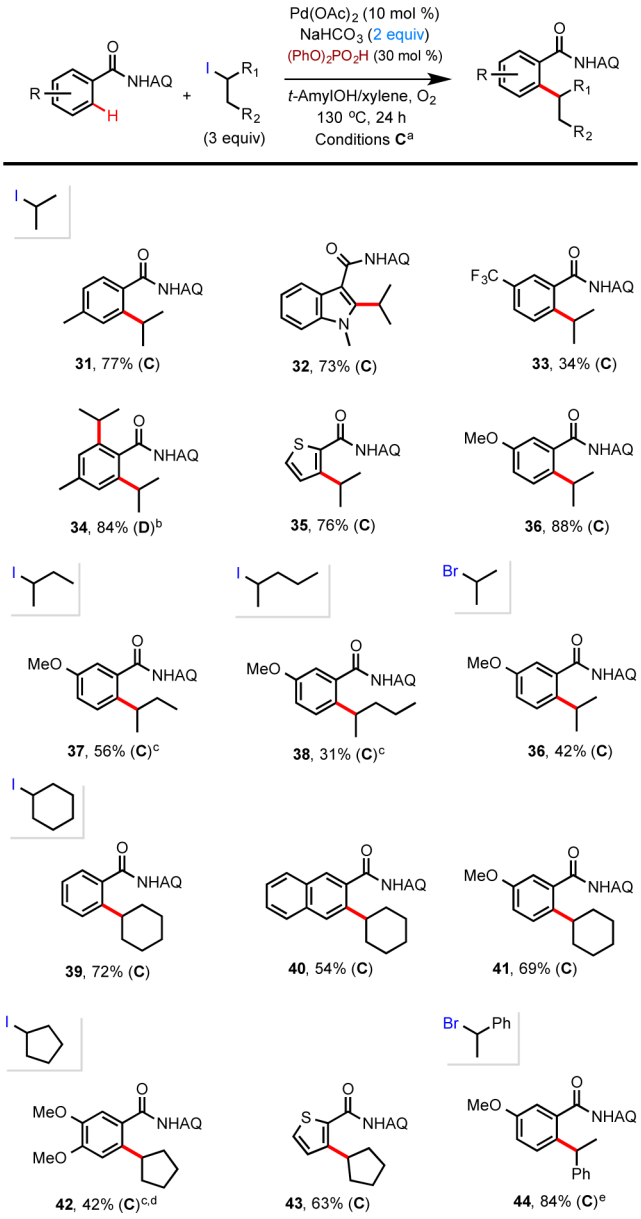
Removal of the AQ Auxiliary. The AQ group of the ortho dialkylated benzamide **25** can be removed via treatment with $BF_3{\cdot}Et_2O$ in MeOH at 100 °C to give ester **45** in good yield (eq 8).[14c] Naphthalene substrate **46** equipped with our recently



introduced 5-methoxy-8-aminoquinoline (MQ) auxiliary underwent *ortho* alkylation with ethyl α-iodoacetate under the standard conditions A (eq 9).[31] The MQ group of the alkylation product was readily removed with 3 equiv of cerium ammonium nitrate (CAN) in CH_3CN/H_2O at room temperature to give primary amide **47**.

Mechanistic Studies. The mechanism of this Pd-catalyzed *ortho*-C(sp^2)−H alkylation likely involves C−H palladation followed by functionalization of the palladacycle intermediate with alkyl halides through a high-valent Pd intermediate.[14b,32,33] Compared with the previous Pd-catalyzed AQ-directed C-(sp^3)−H alkylation system, which required Ag reagents, this Ag-free *ortho*-C(sp^2)−H alkylation system offers a less complex platform to examine the functional role of carboxylate, bicarbonate, and phosphate. Our current mechanistic understanding of this system is summarized below.

Scheme 5. Use of Secondary Alkyl Iodides



All reactions were carried out under the standard conditions on a 0.2 mmol scale; isolated yields are given. [a]Conditions C, see entry 8 of Table 2. [b]Conditions D: 6 equiv of alkyl iodides, 3.5 equiv of K_2CO_3, 2 d (see entry 15 of Table 2). [c]2 d. [d]3 equiv of $NaHCO_3$ was used. [e]1.3 equiv of $NaHCO_3$ was used.

1. C−H palladation is not the rate-limiting step for alkylation with secondary alkyl iodides. As shown in Scheme 6A, we observed small secondary KIE for the alkylation of D_5-substituted substrate **48** with *n*PrI and *i*PrI. The lack of a primary KIE suggests that *ortho*-C(sp^2)−H palladation is a relatively fast process compared with the subsequent functionalization step.

2. $NaHCO_3$ can be used as a ligand/base for C−H palladation. Carboxylates such as acetate and pivalate are well-

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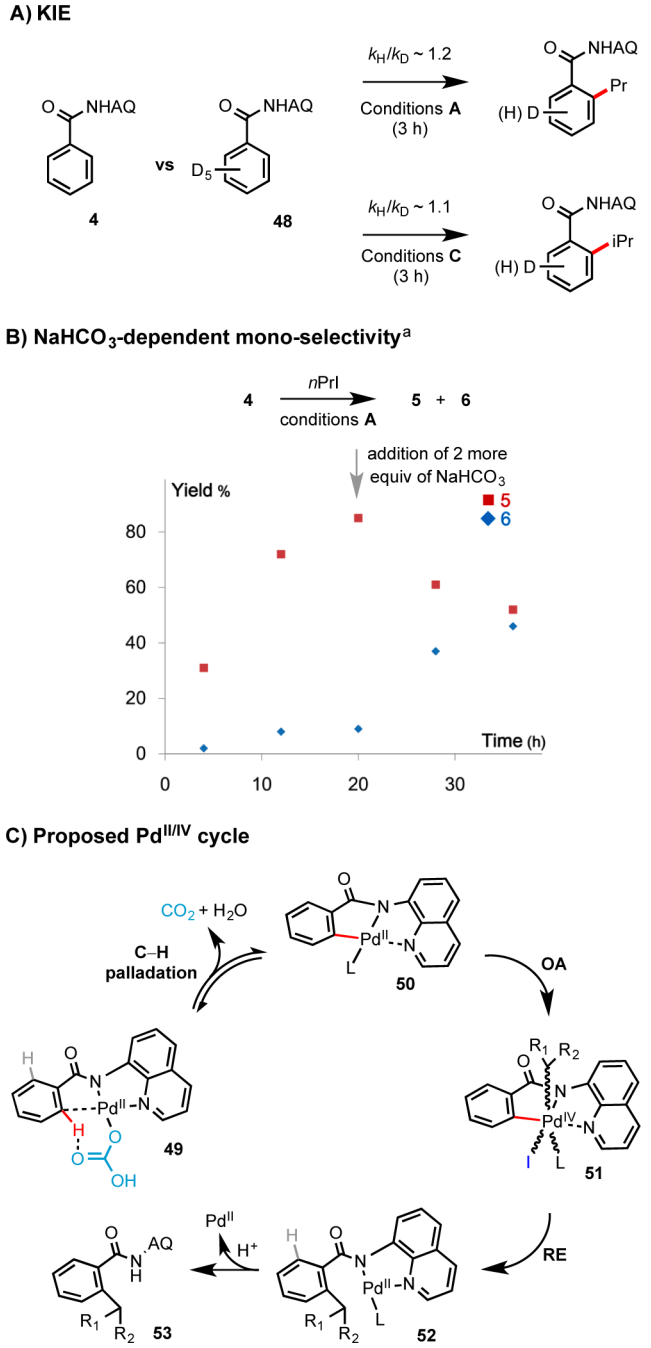
Scheme 6. KIE and Role of $NaHCO_3$[a]



[a]Time course analysis of the alkylation of **4** with *n*PrI under the general conditions A using 1.5 equiv of $NaHCO_3$. An additional 2 equiv of $NaHCO_3$ was added at 20 h. See Supporting Information for experimental details.

known ligands for Pd-catalyzed C–H functionalization.[34] Although $Pd(OAc)_2$ was used as the precatalyst, OAc ligand is not necessary for this reaction to proceed (see entry 18 of Table 1, and entry 14 of Table 2). Addition of carboxylate ligands actually leads to decreased monoselectivity (entry 19, Table 1). The majority of OAc from $Pd(OAc)_2$ is likely quickly consumed by reaction with primary alkyl iodides to form esters under our reaction conditions.[35] Like carboxylates, the bicarbonate ion can facilitate C–H palladation in this system through the concerted metalation–deprotonation (CMD)[34] mechanism (**50**, Scheme 6C).[36] Compared to carboxylates, HCO_3^- is a slightly less basic ligand for CMD. It is also less nucleophilic and does not react with primary alkyl halides, avoiding competing esterification side reactions. Furthermore, it quickly reacts with the H^+ produced to form CO_2 and H_2O. In comparison, phosphate is presumably an even less effective ligand for CMD due to its lower basicity (entry 15, Table 1).

3. Limiting $NaHCO_3$ is critical for achieving high selectivity for monoalkylation with primary alkyl halides. Accounting for 30 mol% of acidic $(BnO)_2PO_2H$, the 1.5 equiv of $NaHCO_3$ applied under the standard conditions A would be largely depleted when the reaction substrate has been monoalkylated. Time course analysis of alkylation of **4** with *n*PrI under the general conditions A (Scheme 6B) indicates that the alkylation of **4** is mostly completed in 20 h, forming predominately mono alkylated product **5** (entry 13, Table 1). Addition of a further 2 equiv of $NaHCO_3$ at 20 h effectively revived the reaction, forming dialkylated product **6** in ~45% yield after 30 h. Compared with carboxylates, $NaHCO_3$ is a slightly weaker promoter for palladation. Addition of carboxylates e.g. pivalate led to decreased monoselectivity (entry 19, Table 1). Together, the use of $NaHCO_3$ as a limiting reagent/base and its relatively weaker palladation-promoting ability is likely responsible for the observed high monoselectivity for primary alkyl halides. Compared with primary alkyl iodides, monoselective alkylation with secondary alkyl iodides is much easier to realize due to its more significant steric bulk.

4. There is evidence for a concerted oxidative addition pathway for secondary alkyl iodides. AQ-chelated palladacycle intermediates likely react with alkyl halides through an oxidative addition (OA) pathway (Scheme 6C). Depending on the nature of the alkyl halide, single-electron transfer, S_N2, and concerted OA mechanisms might be operative.[37] The absence of ring-opened side products in the alkylation of **4** with cyclopropylmethyl iodide (see **10m**, Scheme 2) and the absence of cyclized side products in the alkylation with 6-bromohexene (see **18**, Scheme 3A) make a radical mechanism unlikely for with primary alkyl halides. An S_N2 mechanism[38,39] for OA of primary alkyl halides onto metal centers has been invoked in a number of systems, especially for more reactive iodides e.g. MeI. While a S_N2 OA could be operative in this system, a concerted OA mechanism for primary alkyl iodides cannot be ruled out.[40]

Unlike primary alkyl halides, the OA mechanism of secondary alkyl halides will determine the stereochemical outcome of the reaction. To probe the OA mechanism of secondary alkyl halides, we performed the alkylation of palladacycle **55** with a pair of cyclohexyl iodides carrying a 4-Me group in either *cis* or *trans* configuration.[41] As shown in Scheme 7A, a stable 5-membered palladacycle intermediate **55** was obtained in high yield by reacting **54** with $Pd(OAc)_2$ in CH_3CN at 60 °C (see Supporting Information for X-ray structure of **55**). Both iodides **56** and **57** were prepared in high diastereomeric purity (>97% dr based on ^1H NMR) from the corresponding commercially available diastereomerically enriched alcohols via stereoselective inversion of the OH group. Reaction of **55** with *cis*-**56** in the absence of phosphate in *t*AmylOH/xylene (1:1) at 130 °C for 1 h (conditions E) gave the alkylated product **58** in 33% yield along with 59% of recovered **54** after acidic aqueous workup (Scheme 7B). Similarly, reaction of **55** with *trans*-**57** gave the alkylated product **59** in 35% yield alone with 52% of **54** under the same reaction conditions. To our surprise, both alkylation products

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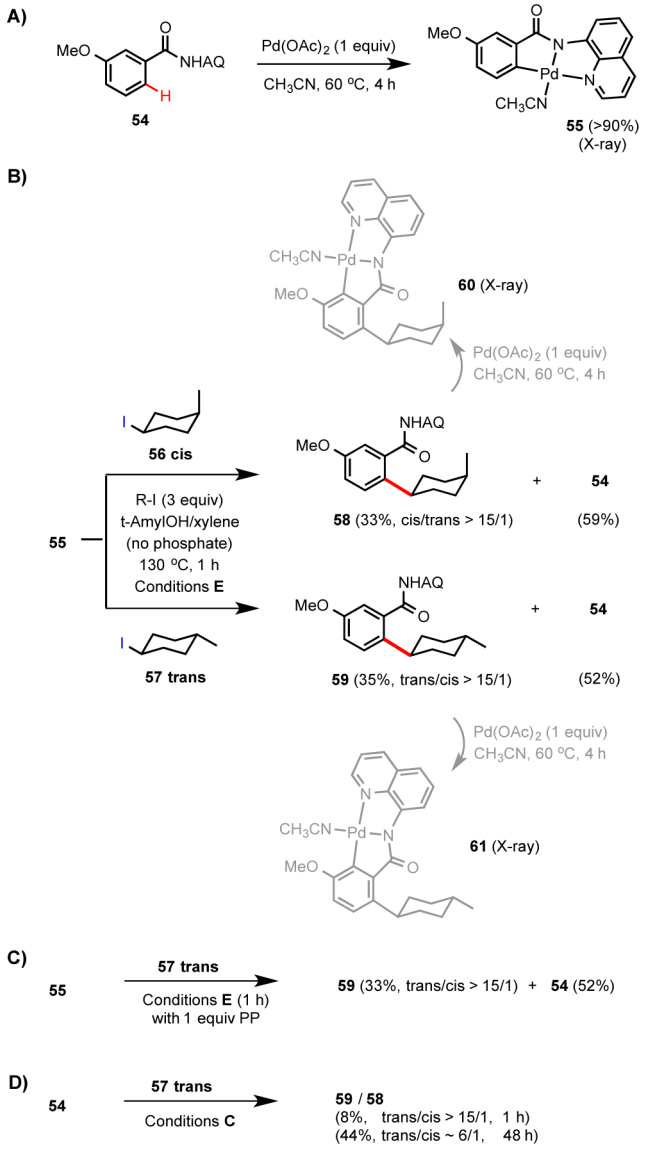
Scheme 7. Alkylation of Palladacycle 55 with 56 and 57[a]



[a]See Supporting Information for experimental details.

were obtained with excellent stereoretention (>15/1) based on ^{1}H NMR analysis of the isolated products (Isomers **58** and **59** have the same R_f value and cannot be separated by silica gel chromatography). The stereochemistry of **58** and **59** was further confirmed by X-ray analysis of their corresponding palladacycle derivatives (see Supporting Information). Similar results were obtained when the alkylation reaction of **55** with **56** and **57** was carried out in xylene solvent. As shown in Scheme 7C, the addition of phosphate had negligible effect on the alkylation of **55** with **57** under the same conditions.

These stereoretentive couplings of iodides **56** and **57** with **55** strongly suggest a rarely precedented concerted OA pathway for secondary alkyl iodides in this Pd-catalyzed system.[42−44] While several metal-catalyzed C−H couplings of secondary alkyl halides have been reported in the past few years, stereospecific coupling remains a unmet challenge. Although transformations proceeding via a S_N2 mechanism can selectively provide products with inverted stereochemistry, this has been rarely observed for the reaction of secondary alkyl halides.[37] Complementary to the S_N2 pathway, this AQ-directed C−H alkylation reaction potentially provides a valuable means for stereoretentive coupling of secondary alkyl halides. However, there are still issues associated with this Pd-catalyzed AQ-directed C−H alkylation concerning substrate scope: sterically more hindered secondary iodides show notably deceased reactivity (see **36**, **37** and **38** in Scheme 5). Consequently, epimerization of the stereochemically enriched secondary iodides during the course of reaction can cause an erosion of overall stereospecificity (Scheme 7D).

5. Phosphates are unlikely ligands for the palladacycle functionalization step. As shown in entry 14 of Table 1, and entry 9 of Table 2, alkylation of **4** with both *n*PrI and *i*PrI gave corresponding monoalkylation products in high selectivity but low yield (31% and 42%, respectively) using $NaHCO_3$ as limiting reagent alone. In comparison, addition of 30 mol% of BP or PP improved the monoalkylation yield to 82% (entry 13, Table 1) and 89% (entry 8, Table 2). Clearly, the addition of phosphate notably increases the reaction yield. However, as shown in Scheme 7c, the addition of BP had a very small effect on the alkylation of palladacycle **55** with *trans* iodide **57**, suggesting that phosphate is likely not involved in the critical palladacycle functionalization step. As phosphate is also unlikely involved in the C−H palladation step (vide supra), we speculate that phosphate may simply facilitate the dissociation of Pd(II) from Pd-bound alkylated product to accelerate catalyst turnover (see **52** to **53** in Scheme 6C) or may stabilize Pd(II) from decomposition to palladium black over extended reaction time.[45]

SUMMARY AND CONCLUSIONS

In summary, we have developed a readily applicable method for the monoselective alkylation of the *ortho*-C−H bonds of *N*-quinolyl benzamides with both primary and secondary alkyl halides under palladium catalysis. Monoselectively alkylating the *ortho*-C−H bonds of arenes offers a convenient strategy to desymmetrize easily accessible benzoic acid precursors and access products bearing complex substitution patterns via sequential C−H functionalization. These alkylation reactions feature the use of a combination of two promoters: $NaHCO_3$ and organic phosphate. The use of $NaHCO_3$ as a limiting reagent is critical for achieving the desired monoselectivity. The use of phosphate notably improves the alkylation yield, although it may not be directly involved in C−H palladation or the subsequent functionalization step.

KIE studies indicate that palladation is not the rate-limiting step in this C−H alkylation reaction. Examination of the reactions of an isolated palladacycle intermediate with both *cis*- and *trans*-4-methylcyclohexyl iodides revealed surprising stereoretentive couplings of these iodides. This evidence strongly suggests that functionalization of the Pd^{II} palladacycle with secondary alkyl halides proceeds through a rarely precedented concerted oxidative addition pathway. We hope that development of new ligands for this Pd-catalyzed AQ-directed C−H alkylation system will further improve reactivity and provide a high yielding and stereospecific coupling of sterically more hindered secondary alkyl iodides. Additional experimental and computational studies to further investigate the OA mechanism are underway.

ASSOCIATED CONTENT

Supporting Information

Additional experimental procedures, X-ray crystallographic analysis (CIF files for compounds **55**, **60**, and **61**), and

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spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(39) For reports of S_N2 OA of alkyl halides and tosylates to Pd^0, see: (a) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910. (b) Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340. For secondary homoallylic tosylate substrates, see: (c) Stokes, B. J.; Opra, S. M.; Sigman, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 11408.

(40) For discussion of S_N2-type OA of alkyl halides to other metal complexes, see: (a) de Waal, D. J. A.; Gerber, T. I. A.; Louw, W. J. *Inorg. Chem.* **1982**, *21*, 1259. (b) Labinger, J. A.; Braus, R. J.; Dolphin, D.; Osborn, J. A. *Chem. Commun.* **1970**, 612−613. (c) Ellis, P. R.; Pearson, J. M.; Haynes, A.; Adams, H.; Bailey, N. A.; Maitlis, P. M. *Organometallics* **1994**, *13*, 3215−3226. (d) Nabavizadeh, S. M.; Habibzadeh, S.; Rashidi, M.; Puddephatt, R. J. *Organometallics* **2010**, *29*, 6359.

(41) Although both *cis*-iodide **56** and *trans*-iodide **57** have been unambiguously characterized by ^1H NMR in the literature, neither compound has been prepared in high diastereoselectivity in those reports. For a preparation of **56** in 10:1 *cis*/*trans* selectivity, see: Cheung, C. W.; Ren, P.; Hu, X. *Org. Lett.* **2014**, *16*, 2566. Interestingly, diastereoselective synthesis of **57** was much more challenging and only vaguely described in the literature (possibly as a diastereomeric mixture): Seel, S.; Dagousset, G.; Thaler, T.; Frischmuth, A.; Karaghiosoff, K.; Zipse, H.; Knochel, P. *Chem.—Eur. J.* **2013**, *19*, 4614. See Supporting Information for our diastereoselective synthesis of **56** and **57** from the corresponding alcohols in excellent diastereoselectivity (>30/1). To the best of our knowledge, this is the first report that uses both isomers **56** and **57** as stereochemical probes to investigate metal-catalyzed coupling of secondary alkyl halides.

(42) For a mechanistic study of S_N2 OA of CH_3I to $[M(CO)_2I_2]^-$ (M = Rh, Ir), see: Griffin, T. R.; Cook, D. B.; Haynes, A.; Pearson, J. M.; Monti, D.; Morris, G. E. *J. Am. Chem. Soc.* **1996**, *118*, 3029. A "bent" transition state (TS) for S_N2 OA pathway, which could potentially give stereo-retentive coupling of CH_3I, was also evaluated computationally and found to be energetically much less favored than the classical "linear" TS for S_N2 OA. In principle, such a "bent" TS-mediated S_N2 pathway cannot be completely ruled out for our alkylation system.

(43) To the best of our knowledge, this is the first report that supports a concerted OA mechanism of secondary alkyl halides to Pd. For a related report that supported concerted OA of CH_3X and $CH_3CHBrCO_2CH_2CH_3$ to $Ir(CO)(SCN\ or\ Cl)(PR_3)_2$ complexes, see: Pearson, R. G.; Muir, W. R. *J. Am. Chem. Soc.* **1970**, *92*, 5519.

(44) OA of α-methylbenzyl bromide may proceed through a different pathway.

(45) As pointed out by a reviewer, the presence of an acetonitrile ligand on the isolated palladacycle **55** could change its reactivity compared to the putative palladacycle. Further investigations on the functional role of the phosphate are currently underway in our laboratory.

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