

C–H Activation

An Efficient Palladium-Catalyzed C–H Alkoxylation of Unactivated Methylene and Methyl Groups with Cyclic Hypervalent Iodine (I³⁺) Oxidants**

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Over the last two decades, transition-metal-catalyzed direct functionalization of C–H bonds has emerged as a valuable tool for organic synthesis.^[1] Compared to C(sp²)–H bond activation, however, the catalytic functionalization of C(sp³)–H bonds,^[2,3] especially unactivated methylene C(sp³)–H bonds, remains an important fundamental challenge. Because of steric hindrance and intrinsic inertness, methylene C–H bonds are significantly more difficult to cleave than primary C–H bonds. In addition, the potential competing β-hydride elimination from cyclometallates also complicates the process. Therefore, only a few examples of C(sp³)–H bond activations of unactivated methylenes have been reported thus far.^[4] Among these successful discoveries of methylene C(sp³)–H bond activation, the majority of studies were focused on C–H arylation, acetoxylation, or amidation. In a recent C(sp³)–H amidation study,^[4b] NFSI served as both an intriguing oxidant and nitrogen source, and further theoretical studies revealed a low-energy barrier for reductive C–N bond formation from a high-oxidation-state palladium catalyst. More recently, an elegant example of ligand-enabled C–H arylation of methylene C(sp³)–H bonds was reported by Yu and co-workers (Scheme 1).^[5] However, to the best of our

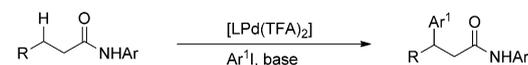
knowledge, C(sp³)–H alkoxylation^[6,7] of unactivated methylene positions has not yet been achieved.

Alkyl ethers serve as important structural motifs found in a diversity of pharmaceuticals and natural products.^[8] The classic approaches^[9] to alkyl ethers, such as Williamson and Mitsunobu reactions, suffer from shortcomings which have limited their applications in the synthesis of complex alkyl ethers. Although a number of new protocols^[10] have been developed in recent years, new methods for alkyl ether synthesis are still in great demand. Direct transformation of readily available alkanes into valuable complex alkyl ethers by transition-metal-catalyzed C(sp³)–H functionalization of unactivated methylenes is arguably a highly efficient and atom-economic method toward these compounds.

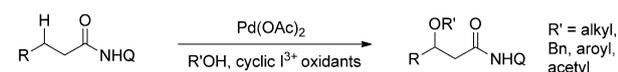
Herein, we report the first example of a palladium(II)-catalyzed C(sp³)–H alkoxylation of an unactivated methylene with cyclic hypervalent iodine (I³⁺) oxidants. Our preliminary mechanistic study revealed that either DMP^[11] (I⁵⁺) or 1-acetoxy-1,2-benziodoxole-3(1*H*)-one serve as intriguing precursors to the oxidant I³⁺ for the C(sp³)–H alkoxylation.

In our continuous studies of C–O bond formation through palladium catalysis,^[12] we envisioned that certain oxidative conditions^[13] could promote palladium(II)-catalyzed C(sp³)–H bond activation through an orthometalation process by coordination with specific directing groups. In a subsequent step C(sp³)–O bond formation by the reductive elimination could afford the corresponding alkyl ether derivatives with suitable oxidants and alcohol partners (Scheme 1). To test our hypothesis, a model study was initiated with the butyramide derivative **1**, which contains an 8-aminoquinoline-derived auxiliary (Q; Table 1). This specific auxiliary^[14] (Q) was first reported by the group of Daugulis and has been developed as an effective directing group for the activation of C(sp³)–H bonds. At the beginning of our investigations, a variety of oxidants, such as PhI(OAc)₂, PhI(TFA)₂, K₂S₂O₈, NaIO₄, NaIO₃, and selectfluor, were examined in the presence of Pd(OAc)₂ in a MeOH/xylene cosolvent system. Among them, a small amount of the desired product **2a** (12–15%) was observed with PhI(OAc)₂ and NaIO₄ (entries 1 and 8). However, further attempts failed to improve the yields, with methoxylation of the 8-aminoquinoline auxiliary (**2b**) leading to the major product. We then turned our attention to other hypervalent iodine reagents. Delightfully the methoxylation product **2a** was observed in 31% yield in the presence of IBX (entry 9). Further investigations revealed that DMP was superior to IBX with a notably higher level of efficiency (entry 10). A control reaction showed that omission of the Pd(OAc)₂ catalyst resulted in complete inactivity of this

Ligand-enabled methylene C(SP³)-H arylation (Yu's work)



Cyclic I³⁺-promoted methylene C(SP³)-H alkoxylation (this work)



Scheme 1. A new approach for unactivated methylene C(sp³)–H bond alkoxylation. TFA = trifluoroacetate, Q = 8-aminoquinoline-derived auxiliary.

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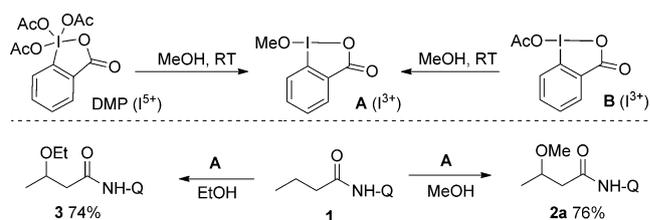
Table 1: Optimization of the reaction conditions.

Entry	Oxidant ^[a]	Solvent	T [°C]	t [h]	2a Yield [%] ^[b]	2b Yield [%] ^[b]
1	PhI(OAc) ₂	MeOH/ <i>p</i> -xylene(1:4)	100	12	12	25
2	PhI(OAc) ₂	MeOH	100	12	0	35
3	PhI(TFA) ₂	MeOH/ <i>p</i> -xylene(1:4)	100	12	0	30
4	PhITs(OH)	MeOH/ <i>p</i> -xylene(1:4)	100	12	0	0
5	K ₂ S ₂ O ₈	MeOH/ <i>p</i> -xylene(1:4)	100	12	0	0
6	(NH ₄) ₂ S ₂ O ₈	MeOH/ <i>p</i> -xylene(1:4)	100	12	0	0
7	NaIO ₃	MeOH/ <i>p</i> -xylene(1:4)	100	12	trace	0
8	NaIO ₄	MeOH/ <i>p</i> -xylene(1:4)	100	12	15	0
9	IBX	MeOH/ <i>p</i> -xylene(1:4)	100	12	31	0
10	DMP	MeOH/ <i>p</i> -xylene(1:4)	100	12	47	0
11	DMP	MeOH/ <i>p</i> -xylene(1:1)	100	12	57	0
12	DMP	MeOH/ <i>p</i> -xylene(4:1)	100	12	70	0
13	DMP	MeOH	RT	12	trace	0
14	DMP	MeOH	50	12	15	0
15	DMP	MeOH	80	12	50	0
16	DMP	MeOH	100	12	76	0
17	DMP	MeOH	110	10	72	0
18	DMP	MeOH	120	10	71	0
19 ^[c]	DMP	MeOH	100	12	0	0
20	A	MeOH	100	7.5	75	0
21	B	MeOH	100	7.5	73	0

[a] Used 2 equiv. [b] Yield of isolated product. [c] No Pd(OAc)₂, **A**: 1-methoxy-1,2-benziodoxole-3(1*H*)-one, **B**: 1-acetoxy-1,2-benziodoxole-3(1*H*)-one. DMP = Dess-Martin periodinane, IBX = *o*-iodoxybenzoic acid, Ts = 4-toluenesulfonyl-

catalytic system. Encouraged by this preliminary result, we started to optimize the reaction conditions. It was found that the MeOH/xylene cosolvent system is not essential and methanol can be employed as the sole solvent for this reaction. Pleasingly, the side product **2b** was not found and only the desired **2a** was obtained in good yields under the new reaction conditions. Interestingly, we found the reaction can be promoted by DMP in methanol at much lower temperatures, such as 50 °C, albeit in low yield (entry 14). In general, 0.1 equivalents of Pd(OAc)₂ was enough to effectively catalyze the reaction. Typically the reaction proceeds to completion in methanol within 11 hours^[15] in a clean manner with 1.1 equivalents of DMP at 110 °C. Besides DMP, we found that cyclic hypervalent iodine (I³⁺) reagents can promote this reaction effectively as well (entries 20 and 21). It's noteworthy that this protocol was conducted without the need for air- or moisture-proof conditions.

Preliminary investigations were performed to gain some insight into how DMP promotes the alkoxylation in this reaction (Scheme 2). Since DMP (I⁵⁺) can react with alcohols to generate the cyclic hypervalent iodine (I³⁺)^[16] reagent, which could be the true oxidant for C–H alkoxylation, we prepared the oxidant **A** by simply mixing DMP with methanol. 1-Acetoxy-1,2-benziodoxole-3(1*H*)-one (**B**) was also smoothly transformed into **A** in the same way. As illustrated in Scheme 2, directly using **A** in the reaction with different solvents gave very interesting results. If alcohols are

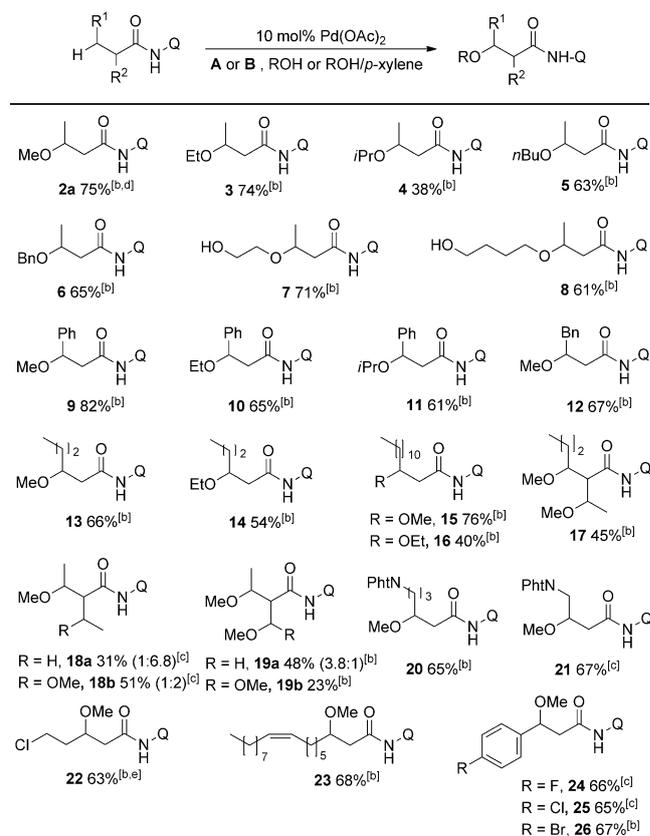


Scheme 2. A preliminary mechanistic study. Yields are unoptimized. Reaction conditions: 10 mol % Pd(OAc)₂, **A** (2.0 equiv), solvent, 110 °C.

employed as solvents, the corresponding alkyl ether products were obtained as major products (**2a**, **3**). Impressively, when *t*BuOH, acetic acid, and DCE were used as the solvent, the corresponding *tert*-butyl ether, acetoxylation, and benzyloxylation products were observed in significant amounts (for details, see the Supporting Information). The above experiments suggested that **A** serves as the true terminal oxidant for efficiently promoting this reaction.

Having identified these optimal reaction conditions, we set out to explore the scope for this new reaction with either **A** or **B** as the oxidant for this reaction. As displayed in Table 2, the scope of this new C–H alkoxylation reaction was found to be very broad. A variety of linear and branched carboxylic acid derivatives were efficiently transformed into the corre-

Table 2: Linear methylene C(sp³)–H alkoxylation.^[a]

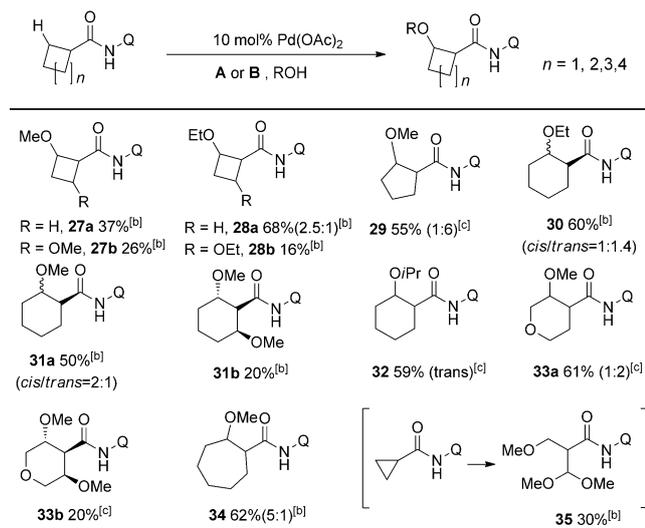


[a] Yield of isolated product. [b] Using **A** as the oxidant. [c] Using **B** as the oxidant. [d] Using microwave. Conversion ratio about 53 % within 40 mins. [e] Yield based on recovered starting material.

sponding β -alkoxylated products in moderate to good yields. Not only simple linear alcohols like methanol, ethanol, and *n*-butanol, but also sterically hindered isopropyl alcohol can be employed to smoothly provide corresponding ether products (**4**, **11**). Pleasingly, we found that BnOH gave the corresponding benzyl ether **6** in good yield as well. It is notable that benzyl group can be readily removed by hydrogenation to provide a free hydroxy group. We found dihydroxy alcohols can be used to furnish interesting ethers (**7**, **8**) and the free hydroxy groups can be further elaborated to provide useful bifunctional molecules. Delightfully, long linear carboxylic acid derivatives (**13–16**) were efficiently alkoxylated as well. For substrates containing two methylene groups, both C–H bonds can be alkoxylated effectively (**17**, **18b**) with more than two equivalents of oxidant. For substrates containing one methylene and one methyl groups, the methyl C–H bond was preferentially alkoxylated over that of the methylene (**19a,b**). Moreover, the reaction exhibits a good functional-group tolerance. For instance, substrates containing different halides, amines, and olefins (**20–26**), could be readily converted into desired products in good yields.

Gratifyingly, this new method was successfully applied in activating cyclic methylene C–H bonds as well (**27–34**; Table 3). For cyclopentyl, cyclohexyl, and cycloheptyl sub-

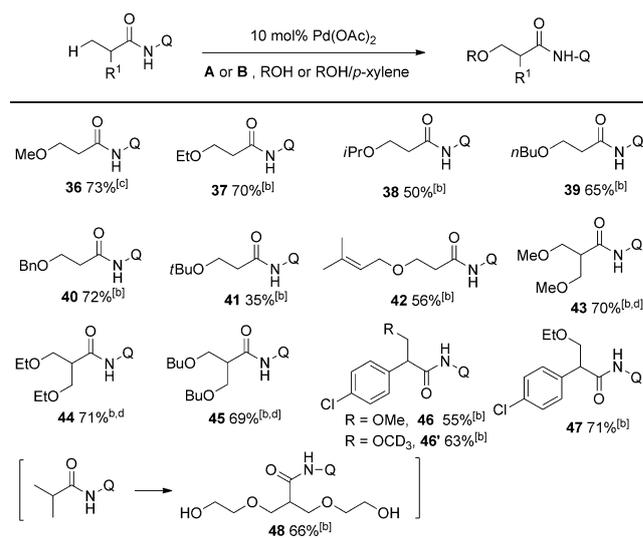
Table 3: Cyclic methylene C(sp³)-H Alkoxylation.^[a]



[a] Yield of isolated product. [b] Using **A** as the oxidant. [c] Using **B** as the oxidant.

strates, the corresponding monoalkoxylation products were formed as the major products (**29**, **30**, **32**, **34**). In contrast, methoxylation of cyclobutyl and tetrahydro-2*H*-pyranyl substrates gave a significant amount of the di-methoxylation products (**27b**, **33b**). Remarkably, it was found that not only methanol and ethanol, but also isopropyl alcohol can be employed to provide a complex alkyl ether (**32**) in a 59% yield. It was observed that the amount of the *trans*-alkoxylation products increased with increasing steric bulk of the alcohol (**30–32**). Interestingly, methoxylation of the cyclopropyl substrate resulted the ring-opening tri-methoxylation

Table 4: Methyl C(sp³)-H alkoxylation.^[a]



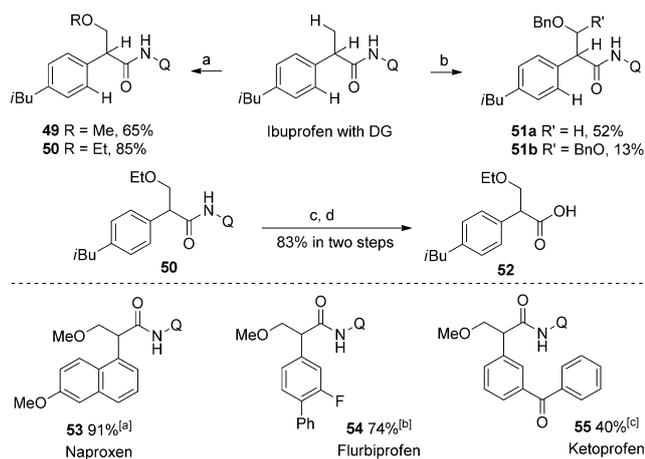
[a] Yield of isolated product. [b] Using **A** as the oxidant. [c] Using **B** as the oxidant. [d] 2.2 equiv oxidants used.

product **35**, which might be due to the ring strain in cyclopropane.

To further expand the scope of this new reaction, we examined the efficiency of our protocol in alkoxylation of unactivated methyl C(sp³)-H bonds. As demonstrated in Table 4, the optimized reaction conditions were found to be effective in the alkoxylation of methyl groups with a variety of alcohols. Besides monoalkoxylation products (**36–40**), a small amount of an acetal product from double alkoxylation can be obtained as well. Pleasingly, we found that these acetals can be the major products with a higher oxidant loading. It is noteworthy that additional hydrolysis of this type of acetal can furnish special aldehydes (3-oxopropanoic acid derivatives). Notably, the corresponding alkyl ethers were smoothly obtained in good yields with isopropyl alcohol (**38**), benzyl alcohol (**40**), and isoprenol (**42**). With 2.2–2.5 equivalents of the oxidant, both methyl groups from isobutyric acid derivatives can undergo an efficient C–H alkoxylation to give the compounds **43–45**. To our delight, sterically demanding *t*BuOH also provided the *tert*-butyl ether **41** in 35% yield and an interesting di-alkoxylation product (**48**) was readily prepared with ethane-1,2-diol in a satisfactory yield.

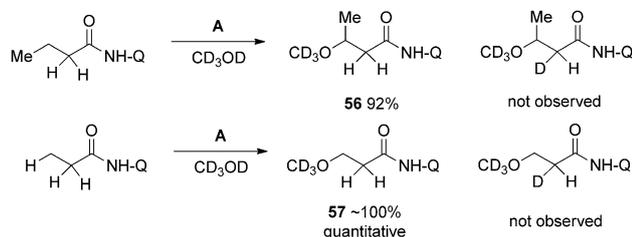
Additionally, the synthetic utility of this new reaction was exemplified by late-stage modification of anti-inflammatory drugs (Scheme 3). We were pleased to find that the reactions demonstrated excellent regio- and chemoselectivity, as well as reactivity with different alcohols to afford novel alkoxylated analogues of Ibuprofen (**49–51**). A sequential two-step deprotection procedure can easily remove the 8-aminoquinoline-derived auxiliary (Q) to furnish the product **52**, which contains a free carboxylic acid. By using the same protocol, three other anti-inflammatory drugs were smoothly modified to give methoxylated analogues (**53–55**) in modest to excellent yields.

Additional investigations were performed to gain insights into the reaction mechanism. One possible reaction pathway



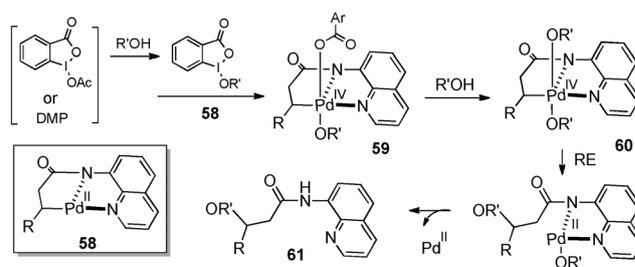
Scheme 3. Direct modification of anti-inflammatory drugs. Reaction conditions: a) 10 mol % Pd(OAc)₂, 1.1 equiv **A**, ROH, 60°C, 2–7 h; b) 10 mol % Pd(OAc)₂, 2 equiv **A**, BnOH, 100°C, 12 h; c) Boc₂O, DMAP, MeCN, 70°C, 20 min; d) LiOH, H₂O₂, THF/H₂O (1:1), RT, 3 h. [a] 10 mol % Pd(OAc)₂, 1.5 equiv **A**, MeOH/*p*-xylene (1:1), 80°C, 5.5 h. [b] 10 mol % Pd(OAc)₂, 2 equiv **B**, MeOH, 80°C, 3 h. [c] 20 mol % Pd(OAc)₂, 3 equiv **A**, MeOH, 120°C, 24 h. Boc = *tert*-butoxycarbonyl, DG = directing group, DMAP = *N,N*-(dimethylamino)pyridine, THF = tetrahydrofuran.

could involve a β-hydride elimination with subsequent alkoxylation through an oxa-michael reaction to provide the desired products. To test this possibility, deuterated methanol was employed as the reaction solvent (Scheme 4). The compounds **56** and **57** were formed in almost quantitative yields, and no corresponding α-deuterated products were



Scheme 4. Study using deuterated solvent. Reaction conditions: 10 mol % Pd(OAc)₂, **A** (1.0–2.0 equiv), solvent, 70–110°C.

observed, thus excluding the above proposed probability. Although details about the mechanism remain to be ascertained, a plausible mechanism, based on these observations, for this reaction is depicted in Scheme 5. The first step involves a chelate-directed C(sp³)–H activation of the substrate to afford the five-membered cyclopalladium(II) intermediate **58**. In the second step, Pd^{II} is oxidized into a Pd^{IV} intermediate^[17] (**59**) by an in situ generated cyclic hypervalent iodine oxidant from 1-acetoxy-1,2-benziodoxole-3(1*H*)-one or DMP. In the presence of alcohols, the ArCO₂ ligands of **59** could be displaced to form the Pd^{IV} intermediate **60**. The final step involves C–O bond-forming reductive elimination to the afford alkoxyated products **61** and converted Pd^{IV} back into Pd^{II}.



Scheme 5. Plausible mechanism.

In conclusion, we have developed a novel palladium(II)-catalyzed alkoxylation of unactivated methylene and methyl C(sp³)–H bonds with a cyclic hypervalent iodine (I³⁺) oxidant. This new method represents the first example of using cyclic hypervalent iodine oxidants in C(sp³)–H bond functionalization. The reaction demonstrates excellent reactivity, good functional-group tolerance, and high yields. Preliminary mechanistic studies reveal that the in situ generated cyclic hypervalent iodine (I³⁺) reagents [with either Dess–Martin periodinane or 1-acetoxy-1,2-benziodoxole-3(1*H*)-one] serve as the true oxidants for C–H alkoxylation. Our studies show an interesting difference of reactivity and selectivity between cyclic and acyclic hypervalent iodine (I³⁺) oxidants. Further investigations into the applications and mechanism of this new reaction are in progress in our laboratory.

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