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Iridium(III)-Catalyzed Direct Arylation of C-H Bonds with Diaryliodonium Salts

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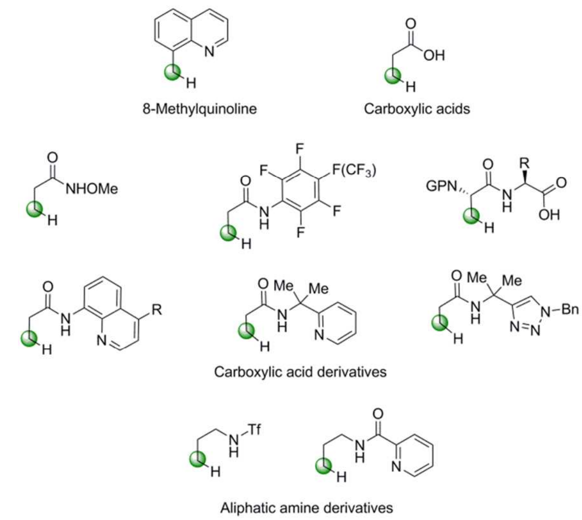
ABSTRACT: By developing a new Ir(III)-catalyzed C-C cross-coupling, a versatile method for direct arylation of sp^2 and sp^3 C-H bonds in ketoximes, nitrogen-containing heterocycles, various arenes and olefins has been established. The key to this arylation depends on the appropriate choice of catalyst and the use of diaryliodonium triflate salts as the coupling partners. This transformation has good functional group compatibility and can serve as a powerful synthetic tool for late-stage C-H arylation of complex compounds. Mechanistic studies by DFT calculations suggested that the sp^3 C-H activation were realized by a triflate-involved CMD process, and the following oxidation of Ir(III) to Ir(V) is the most favorable when a bistriflimide is contained in the diaryliodonium salt. Calculations indicated both steps are enabled by initial anion-exchange between the reactant complexes.

INTRODUCTION

Transition-metal-catalyzed C-H activation reactions have emerged as one of the most useful and powerful tools in organic synthesis.[1] The aliphatic C-H bonds, which are ubiquitous in organic molecules are most challenging targets for effective and selective functionalization to construct a variety of C-C and C-heteroatom bonds. Direct C-H arylation has advantages over traditional coupling protocols especially when the regioselective introduction of halides in a particular synthetic intermediate is problematic or requires multistep operation.[2] Notable advances have been made in sp^3 C-H arylation reactions in different compounds chelating with directing groups (Scheme 1).[3] Early studies were initiated by Pd(II)-catalyzed direct arylation of 8-methylquinoline which was a good substrate because of its chelating ability.[4] In order to functionalize alkyl C-H bonds in more synthetically useful substrates, many strategies have been developed. Yu et al. demonstrated Pd(II)-catalyzed direct arylation of aliphatic acids, amides, amino acid derivatives and peptides by using external ligands such as amino acids, pyridines, quinolines and so on to control the reactivity and selectivity of the catalyst.[5] Another powerful strategy exploited chelation assistance is the utilization of a bidentate directing group such as picolinamide or 8-aminoquinolinyl moiety in palladium-catalyzed C-H arylation reactions.[6] Remarkably, Nakamura[7], Chatani[8] and Ackermann[9] et al. recently discovered that the Fe and Ni catalysts were also applicable in aliphatic C-H arylation in conjunction with the bidentate directing groups.

Despite the great progress made in this field, these well-established C-H activation reactions still have several limitations. First, the cyclometalation intermediates are formed in presence of different ligands, oxidants, bases and solvents, thereby making discovery of a versatile catalytic system applicable to various substrates difficult. Second, the substrates are typically limited to 8-methylquinoline, carboxylic acids, aliphatic amines and their related derivatives and expanding the scope to include other types of substrates remains a critical challenge. Third, arylation of methyl groups adjacent to quaternary centers is described in most cases especially in Fe and Ni catalytic systems.[7-9] Ketoxime is an ideal directing group, which can be easily introduced and removed from the substrates.[10] The β-arylated ketoxime is a

Scheme 1. The Development of Transition-metal-catalyzed sp^3 C-H Arylation Reactions.



prominent structural motif which can convert to many bioactive natural products and pharmaceutically important compounds such as 15-keto Latanoprost acid,[11a] 6-Ginerol,[11b] Symphyoketone[11c] and Loxoprofen[11d] (Scheme 2). To the best of our knowledge, there is no general method available for the introduction of a phenyl group in the β-position of ketoximes via aliphatic C-H activation. Herein, we demonstrate $[(Cp^*IrCl_2)_2]$-catalyzed intermolecular direct arylation of sp^3 C-H bonds in ketoximes with diaryliodonium triflate salts. Moreover, heterocycle-directed

Scheme 2. β-Arylketone Motifs in Natural Products and Pharmaceutical Compounds.

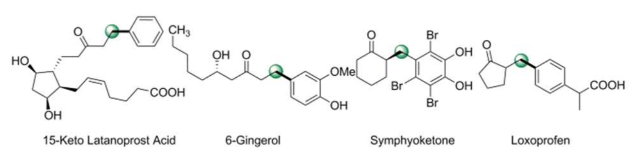


Table 1. Optimization the Reaction Conditions.[a]

1a + 2a → 3aa + 4aa

entry	catalyst (mol%)	additives (equiv)	solvent	T(°C)	Yield of **3aa**(%)[b]
1	$[(Cp^*IrCl_2)_2]$ (5) + $AgNTf_2$ (20)	-	cyclohexane	100	28 (95 : 5)
2	$[(Cp^*IrCl_2)_2]$ (5) + $AgNTf_2$ (20)	CsOPiv (3.0)	cyclohexane	100	6 (99 : 1)
3	$[(Cp^*IrCl_2)_2]$ (5) + $AgNTf_2$ (20)	AgOAc (3.0)	cyclohexane	100	30 (97 : 3)
4	$[(Cp^*IrCl_2)_2]$ (5) + $AgNTf_2$ (20)	PivOH (3.0)	cyclohexane	100	43 (95 : 5)
5	$[(Cp^*IrCl_2)_2]$ (5) + $AgNTf_2$ (20)	PivOH (3.0) + 4Å MS	cyclohexane	100	86 (96 : 4)
6	$[(Cp^*IrCl_2)_2]$ (2.5) + $AgNTf_2$ (10)	PivOH (3.0) + 4Å MS	cyclohexane	100	65 (98 : 2)
7	**$[(Cp^*IrCl_2)_2]$ (2.5) + $AgNTf_2$ (15)**	**PivOH (3.0) + 4Å MS**	**cyclohexane**	**100**	**89 (98 : 2), (86%)**[c]
8	$[(Cp^*IrCl_2)_2]$ (1) + $AgNTf_2$ (6)	PivOH (3.0) + 4Å MS	cyclohexane	100	71 (97 : 3)
9	$[(Cp^*IrCl_2)_2]$ (2.5) + $AgNTf_2$ (15)	PivOH (3.0) + 4Å MS	cyclohexane	70	81 (97 : 3)
10	$[(Cp^*IrCl_2)_2]$ (2.5) + $AgNTf_2$ (15)	AcOH (3.0) + 4Å MS	cyclohexane	100	67 (98 : 2)
11	$[(Cp^*IrCl_2)_2]$ (2.5) + $AgNTf_2$ (15)	PivOH (3.0) + 4Å MS	DCE	100	17 (98 : 2)
12	$[(Cp^*IrCl_2)_2]$ (2.5) + $AgNTf_2$ (15)	PivOH (3.0) + 4Å MS	acetone	100	19 (99 : 1)
13[d]	$[(Cp^*IrCl_2)_2]$ (2.5) + $AgNTf_2$ (15)	PivOH (3.0) + 4Å MS	cyclohexane	100	67 (75 : 25)
14	$[(Cp^*RhCl_2)_2]$ (5) + $AgSbF_6$ (20)	PivOH (3.0) + 4Å MS	cyclohexane	100	0
15	$[\{RuCl_2(p\text{-cymene})\}_2]$ (5) + $AgPF_6$ (20)	PivOH (3.0) + 4Å MS	cyclohexane	100	0
16	$[(Cp^*Co(CO)_2I_2)_2]$ (5) + $AgSbF_6$ (20)	PivOH (3.0) + 4Å MS	cyclohexane	100	0

[a] Reaction Conditions: **1a** (0.60 mmol), **2a** (0.20 mmol), catalyst, additives, and in solvent (1.0 mL) at 100 °C, 12 h, under Ar. [b]Yield was determined by GC analysis of mixture and values in parentheses indicated the *mono*/*di* ratio of products. [c]Isolate yield. [d]using 0.4 mmol **1a**.

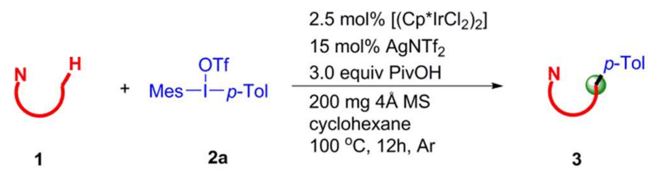
sp^3 C-H bonds, various aryl and vinylic C-H bonds are also compatible in this versatile catalytic system. The synthetic application and plausible mechanism of the current reaction were also studied.

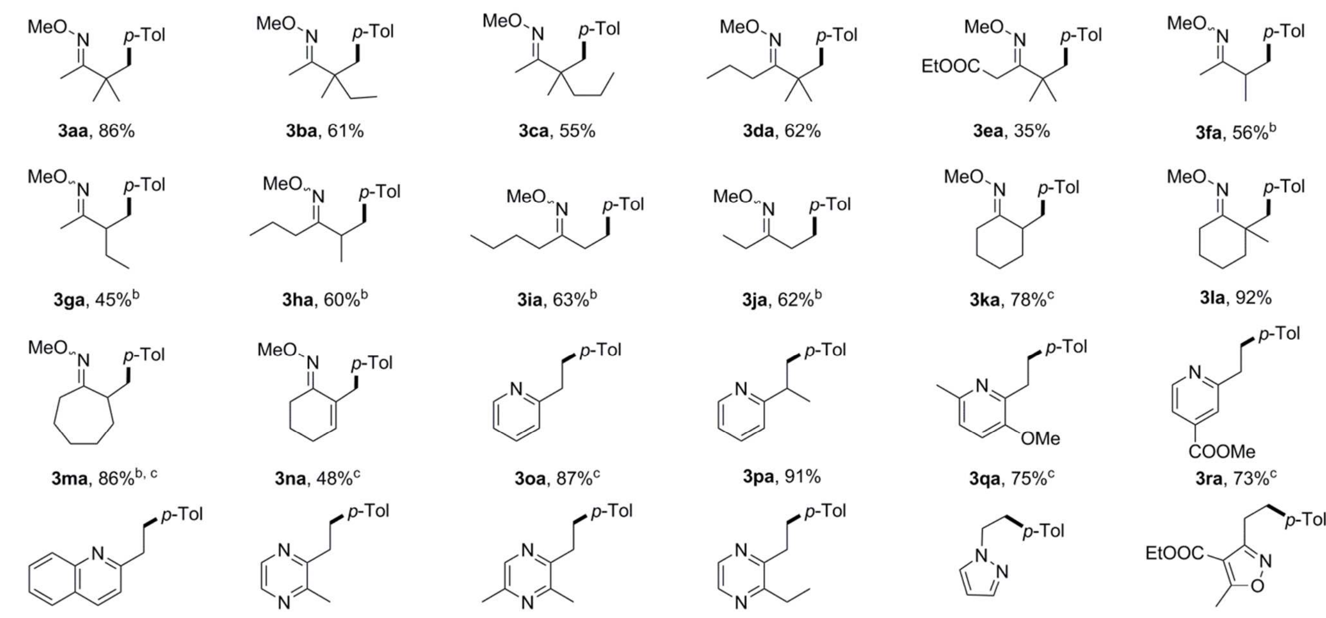
RESULTS AND DISCUSSION

Direct arylation of aliphatic C-H bonds with Diaryliodonium Salts. Half-sandwich Ir(III) complexes have received recent research interest in C-H activation because of their catalytic activity toward various chemical transformations.[12, 13] However, most of these reactions proceed through cleavage of aryl C-H bonds, and aliphatic C-H activation reactions are still rare.[10d-e, 14] In 2014, Li et al. developed Ir(III)-catalyzed C-H alkynylation of (hetero)arenes using hypervalent iodine-alkyne reagents.[15] Inspired by this chemistry, we reasoned that diaryliodonium triflate salts[16] could be desirable arylating reagents making the challenging aliphatic C-H activation feasible *via* concerted metalation-deprotonation (CMD) mechanism.[17] To evaluate the potential of the high valent iridium catalyst for aliphatic C-H activation, we first investigated the reactions of pinacolone oxime (**1a**) with *p*-tolyl (mesityl)iodonium triflate (**2a**). By employing 20 mol% $AgNTf_2$ as the halide abstractor and 5 mol% $[(Cp^*IrCl_2)_2]$ as the precatalyst to generate cationic Cp*Ir(III) in situ in cyclohexane at 100 °C, we indeed observed the desired product **3aa** by GC-MS analysis, with a very small amount of disubstituted byproduct **4aa** (entry 1). However, the addition of base such as CsOPiv was proved to be disadvantageous to the reaction, as the yield was markedly decreased (entry 2). Switching the additive to AgOAc increased the yield to 30% (entry 3), and the use of PivOH as an alternative to AgOAc resulted in a significantly improved yield (entry 4). During our research, we found the fresh distilled cyclohexane was much better than old one. Consequently, addition of 4Å MS indeed improves the efficiency of the reaction, affording **3aa** in 86% yield (entry 5). The application of lower catalyst loadings to 2.5 mol% $[(Cp^*IrCl_2)_2]$ and 10 mol% $AgNTf_2$ resulted in a reduced yield (entry 6). However, the addition of a slight excess of $AgNTf_2$ (15 mol%) maintained the high reactivity, affording the product **3aa** in 89% yield (entry 7). Notably, when 1 mol% catalyst loading (entry 8) or lower reaction temperature (70 °C) was used (entry 9), the conversions are still high. Further examination of other cheaper acids such as AcOH provides worse results (entry 10). The solvent strongly affected the reactivity of this reaction. When the reaction was performed in polar solvents such as DCE and acetone, the yield was remarkably decreased (entries 11-12). The using of three equivalent of oxime **1a** resulted in the predominant formation of *mono*-arylated product **3aa** and changing the substrate ratio led to an increase in amount of byproduct **4aa** (entry 13). Note that other common catalytic systems, including $[(Cp^*RhCl_2)_2]$, $[Ru(p\text{-cyeme})Cl_2]$ and $[Cp^*Co(CO)_2I_2]$ could not form any arylation products (entries 14-16).

With the optimized conditions in hand, we first investigated the substrate scope of ketoximes with *p*-tolyl(mesityl)iodonium triflate (**2a**). In the case of substrates **1a**-**1c**, with the increasing of steric bulk from methyl to *n*-propyl adjacent to the quaternary centers, the yield of the corresponding products **3aa**-**3ca** gradually decreased. Ketoxime **1d** occurred exclusively at the methyl group adjacent to the quaternary center. Interestingly, a functionalized ketoxime **1e** derived from ethyl acetoacetate was also employed successfully in this reaction. Most importantly, ketoximes **1f**-**1j** with α-hydrogens were compatible for this process and afforded *mono*-arylation products **3fa**-**3ja** in moderate yields. Reactions of **1g**, which contains multiple possible sites for the direct arylation, showed extremely high selectivity for activation of primary β-C-H bonds in lieu of those at secondary carbon centers. The six and seven-membered ring ketoximes **1k**-**1m** were efficiently arylated to afford the desired products **3ka**-**3ma** in good yield, probably because of the less flexible nature of these cyclic conformers.

Table 2. Scope of the sp^3 C-H Arylation of Ketoximes and Nitrogen-containing Heterocycles.[a]





3aa, 86%; **3ba**, 61%; **3ca**, 55%; **3da**, 62%; **3ea**, 35%; **3fa**, 56%[b]

3ga, 45%[b]; **3ha**, 60%[b]; **3ia**, 63%[b]; **3ja**, 62%[b]; **3ka**, 78%[c]; **3la**, 92%

3ma, 86%[b, c]; **3na**, 48%[c]; **3oa**, 87%[c]; **3pa**, 91%; **3qa**, 75%[c]; **3ra**, 73%[c]

3sa, 77%[c]; **3ta**, 95%[c]; **3ua**, 88%[c]; **3va**, 74%; **3wa**, 52%[c]; **3xa**, 45%[c]

[a] Reaction Conditions: **1** (0.60 mmol), **2a** (0.20 mmol), 2.5 mol% $[(Cp^*IrCl_2)_2]$, 15 mol% $AgNTf_2$, 3.0 equiv PivOH and 200 mg 4Å MS in cyclohexane (1.0 mL) at 100 °C, 12 h, under Ar; isolated yield. [b]Isolate as a mixture of oxime E/Z isomers. [c]Using 0.30 mmol **1**.

Ketoxime **1n** with olefinic double bond was compatible though in reduced yield and the alkene arylation product was not observed.[16e] Since the heterocycles including pyridine, pyrazine, quinoline, pyrazole, isoxazole and so on are commonly occurring structural motifs found in numerous pharmaceuticals and biologically active compounds,[18] we envisioned that a reliable method for direct arylation of these heterocycle-directed sp^3 C-H bonds would be very meaningful. To our delight, we found a variety of heterocycles were effective directing groups, and functionalization of methyl groups containing *α*-hydrogens were well tolerated under this optimized procedure. Both pyridine and quinoline substrates with unactivated sp^3 C-H bonds underwent arylation to afford *mono*-substituted products **3oa**-**3sa** in good yields. Additionally, reactions of pyrazine derivatives **1t**-**1v** bearing two N atoms chelating with catalyst still proceeded very well. It was interesting to find that the reaction of five-membered-ring heterocycles such as pyrazole **1w** and isoxazole **1x** were also proved facile and occurred exclusively at the methyl group.

Next, we sought to expand this transformation to the transfer of diverse aryl groups and we were pleased to find that a range of substituted diaryliodonium triflates worked well with pinacolone oxime (**1a**). (Table 3). Aromatic groups displaying electron-neutral and electron-rich substituents at the meta- and para-position (**3ab**-**3ac** & **3ae**-**3ah**) were transferred in particularly good yields from the corresponding diaryliodonium triflates. *Orth*-methyl substituted aryl derivative led to a reduced yield (**3ad**), presumably as a result of increased steric congestion around the iridicycle intermediate, preventing oxidation or reductive elimination steps. Useful halogenated arenes were accommodated (**3ai**-**3al**), thereby providing possibilities for subsequent chemical transformations. Electron-withdrawing substituted group such as ethyl ester could be tolerated in this protocol although reduced yield was observed (**3am**). We were pleased that the coupling of the polycyclic and heterocyclic aromatic motif were possible and proceeded in moderate to excellent yields (**3an**-**3ap**), thus further enhancing the scope of our reaction.

Late-stage sp^3 C-H arylation of complex molecules. The Lanostane-type triterpenoids have been demonstrated to exert diverse bioactivities, particularly cytotoxic, antitumor and anti-inflammatory activities. Encouraged by this successful Ir(III)-catalyzed sp^3 C-H arylation reactions, we turned our attention to utilize this method as a key step for regioselective C-H arylation of Lanostane. As shown in Scheme 3, our synthesis commenced with the preparation of oxime **4b** using commercial available substrate Lanosterol **4a**. Under the catalytic system, substrate **4c**

Scheme 3. Potential Route from Lanosterol to C(*β*)-Arylated Lanostane 4d.

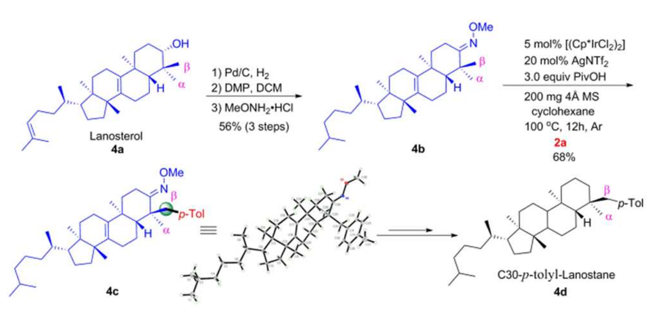
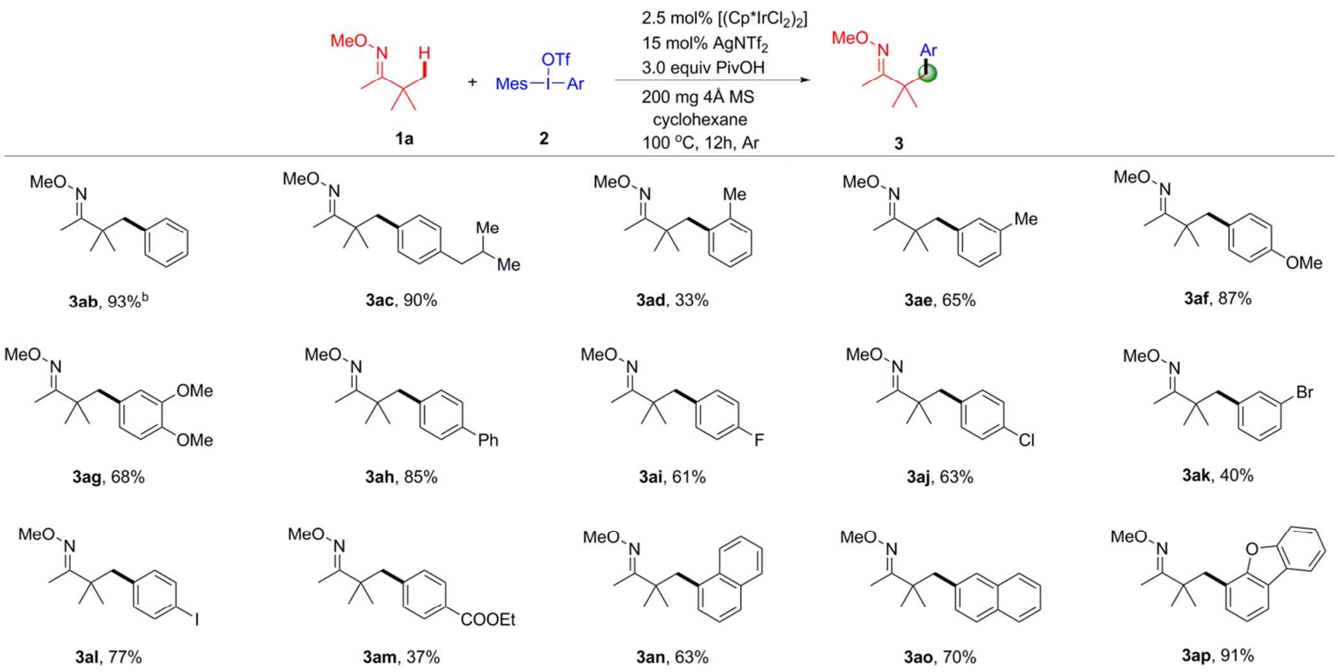


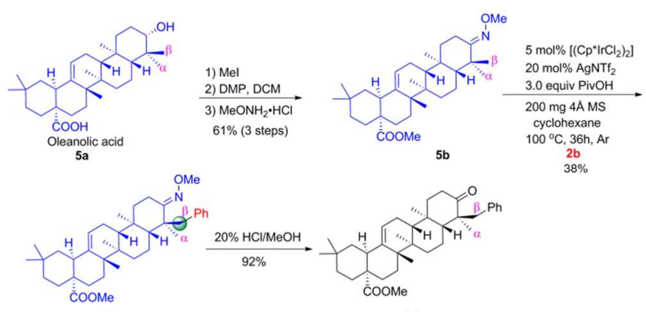
Table 3. Aryl Transfer in Aliphatic C-H arylation of Pinacolone Oxime 1a.[a]



[a] Reaction Conditions: **1** (0.60 mmol), **2** (0.20 mmol), 2.5 mol% [$(Cp^*IrCl_2)_2$], 15 mol% $AgNTf_2$, 3.0 equiv PivOH and 200 mg 4Å MS in cyclohexane (1.0 mL) at 100 °C, 12 h, under Ar; isolated yield. [b]Using Ph_2IOTf instead of PhMesIOTf.

could be employed in selective direct arylation of the C(*β*) methyl group affording product **6** in 68% yield with completely regioselective as confirmed by X-ray diffraction. The further deprotection[19] and reduction of **4c** could form the C(*β*)-arylated Lanostane **4d**.[20]

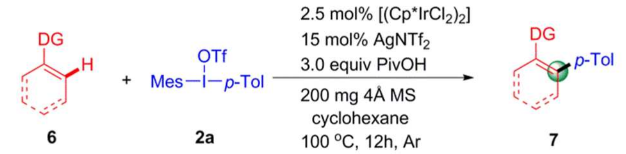
Scheme 4. Late-stage sp^3 C-H Arylation of Oleanolic Acid and Removal of the Auxiliary Group.

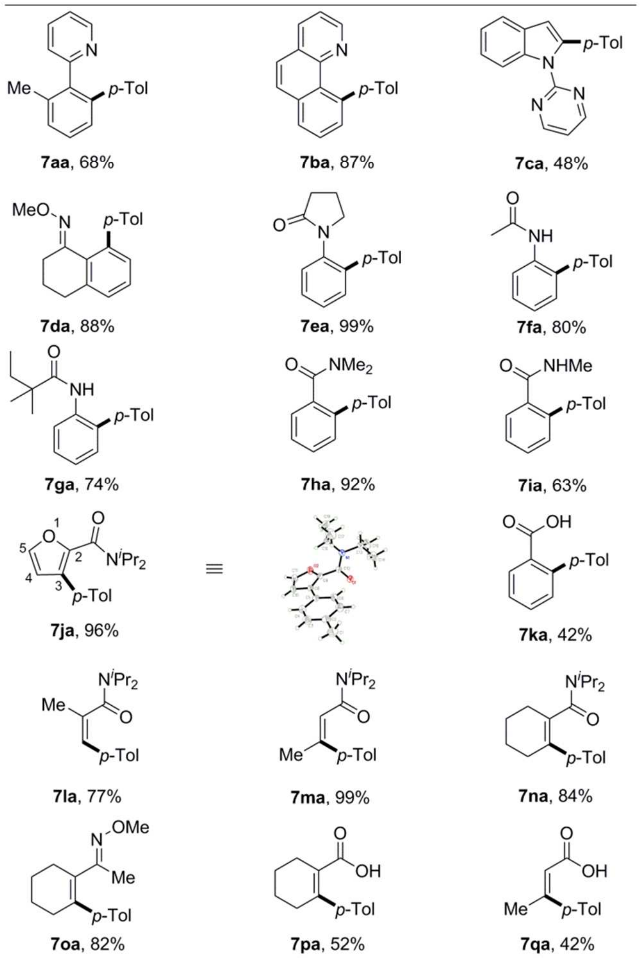


Oleanolic acid is a non-toxic, hepatoprotective triterpenoid found in Phytolacca Americana which exerts antitumor and antiviral properties. It was also found to exhibit weak anti-HIV and weak anti-HCV activities, and more potent synthetic analogs are being investigated as potential drugs.[21] To further illustrate the functional-group tolerance and synthetic versatility of this developed method, we next surveyed it in selective arylation of this complex natural compound (Scheme 4). We began our synthesis with Oleanolic acid **5a**, which was converted to the corresponding ketoxime **5b** in three steps. Similarly, the arylation of the **5b** with Ph_2IOTf (**2b**) provided arylated product **5c** in 38% yield with complete selective arylation of the *β*-C position confirmed by 2D NMR. The auxiliary group of **5c** was then removed in HCl (aq)/MeOH solution to give a free ketone intermediate **5d** in nearly quantitative yield, which can recover to C(*β*)-arylated Oleanolic acid via further reduction and hydrolysis.

Broad C-H Arylation of Arenes and Alkenes with Diaryliodonium Salts. Although the direct sp^2 C-H arylation reactions have been well developed in the presence of different transition metals including Pd, Ni, Cu, Ru, Rh and so on,[22] Ir(III)-catalyzed C-H arylation of arenes still remains relatively rare.[23] With the developed catalytic system in hand, we next aimed to extend it to sp^2 C-H bonds. Heterocycle-directed arylation was evaluated firstly. Phenylpyridine **6a**, benzo[*h*]quinoline (**6b**) and 1-(pyrimidin-2-yl)-1H-indole (**6c**) underwent smooth couplings affording the corresponding products with yields between 48-87%. The arylation reactions also worked well for other arenes including *O*-methyloxime **6d**, *N*-phenyl amides **6e**-**6g**, benzamides **6h**-**6i**, heterocycle **6j** and benzoic acid (**6k**) Among these substrates, while *N*-phenyl amide **6g** contains several aliphatic and aryl C-H bonds that are available for C-H arylation, only sp^2 C-H activation product **7ga** was detected in 74% yield. This suggests that the sp^3 C-H activation is more difficult as compared with the sp^2 C-H activation. Interestingly, Glorius et al. recently found that Rh(III)-catalyzed halogenation of electron-rich heterocyclic compounds such as **6j** at the 3-position of furan and the inherent 5-position was suppressed by the Rh(III) catalyst.[24] In our catalytic system, we also observed **7ja** as the sole arylation product in excellent yield with complete regiochemistry.[25] The palladium-catalyzed coupling of olefins with aryl or vinyl halides, known as the Heck reaction, is one of the most powerful methods to form a new carbon-carbon bond in modern synthetic chemistry.[26] However, this reaction occurred with *E* selectivity and multi-substituted vinylic substrates have low reactivites. To further explore our catalytic system, the compatibility of this cross-coupling reaction with vinylic substrates was examined. In case of the enamide **6l** with both vinylic and allylic C-H bonds, the sp^2 C-H arylation product **7la** can be selectively obtained, indicating the functionalization of a vinylic C-H bond is also much more favorable. Reaction of differently substituted enamides **6m**-**6n**, *O*-methyloxime **6o** and even vinyl carboxylic acids **7p**-**7q** can yield the desired products **7ma**-**7qa** in 42-99% yields. Remarkably, these coupling reactions

Table 4. *Ortho* C-H Arylation of Various Arenes and Olefins.[a]



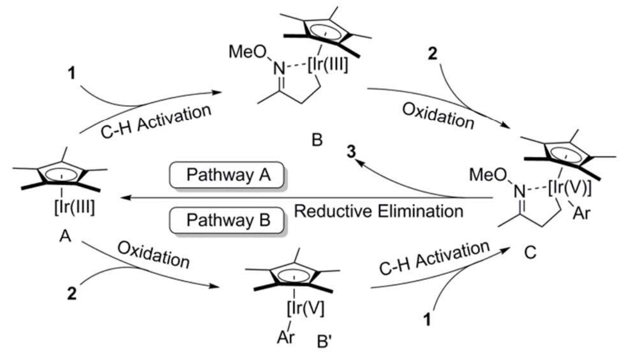


[a] Reaction Conditions: **1a** (0.22 mmol), **2** (0.20 mmol), 2.5 mol% $[(Cp^*IrCl_2)_2]$, 15 mol% $AgNTf_2$, 3.0 equiv PivOH and 200 mg 4Å MS in cyclohexane (1.0 mL) at 100 °C, 12 h, under Ar; isolated yield.

occurred with complete *Z* selectivity. This stereoselectivity is highly valuable because of its potential synthetic applications.

Mechanistic Investigations. As the Ir(III)-catalyzed aliphatic C-H arylation by diaryliodonium salt has not been studied previously, we next sought to gain a more detailed mechanistic understanding of the transformation. The mechanistic studies of Pd(II)-catalyzed aryl C-H arylation reactions with diaryliodonium salts via a Pd^{II}/Pd^{IV} redox cycle were elaborated in Sanford's group.[27] In light of their work, we depict a plausible catalytic cycle in Scheme 5. First, an iridium species A induces C-H cleavage of oxime **1** to generate an iridicycle complex B. Oxidation of the intermediate B with diaryliodonium salt **2** forms an Ir(V) species C,[28] which then undergoes reductive elimination leading to the desired product **3** (Pathway A). Since more traditional nucleophiles like $PhB(OH)_2$ and $PhSiMe_3$ were ineffective phenylating reagents in our catalytic and stoichiometric reaction conditions, an alternative process involving oxidation of the iridium species A to an Ir(V) species B' ahead of C-H activation is also possible (Pathway B).

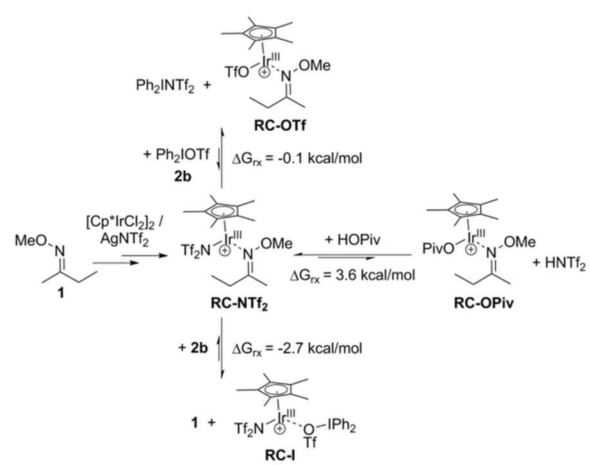
Scheme 5. Plausible Catalytic Cycle for Ir(III)-catalyzed sp³ C-H Arylation of Ketoximes.



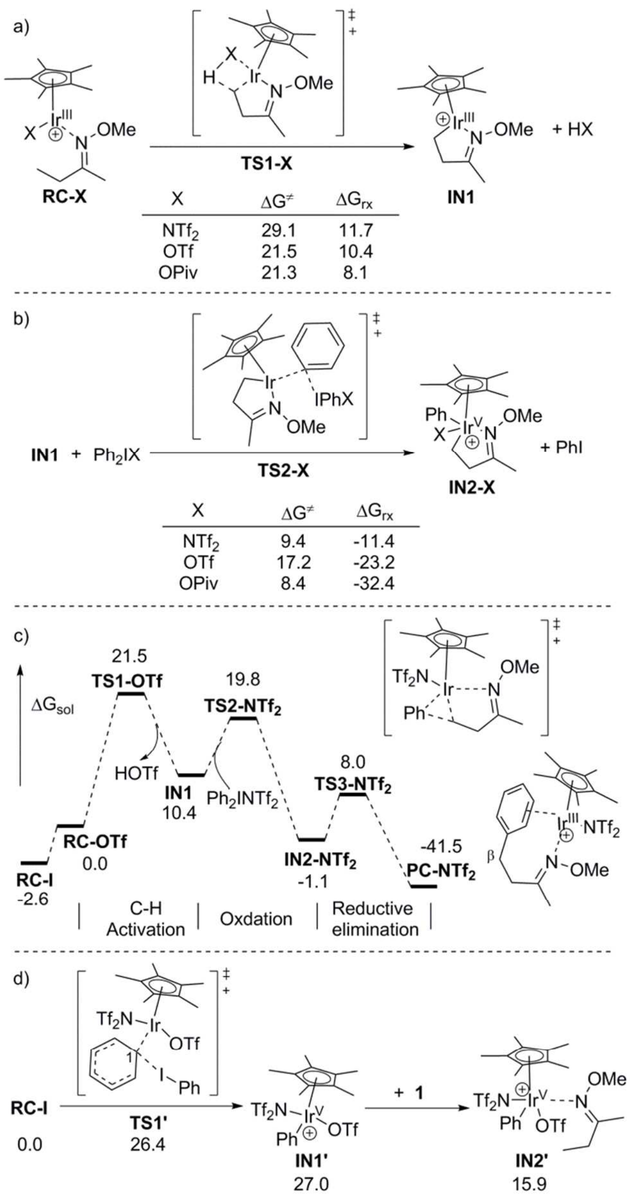
To uncover which pathway is more favorable for the current sp3 C-H arylation, DFT calculations[29] at the M06 level were first performed to simulate the reaction between butan-2-one O-methyl oxime (**1**) and Ph_2IOTf (**2b**). First of all, the generation of possible reactant complexes was studied (Scheme 6). According to the reaction condition, cationic complex $[Cp^*IrNTf_2]^+$ could possibly act as a catalytically active species in the system, and reactant complex RC-NTf_2 may be generated first. To evaluate the possibility for the formation of complexes containing other counterions, the equilibrium of RC-NTf2 to RC-OTf and RC-OPiv, respectively, by anion exchange with **2b** and HOPiv additive were calculated. The relative free energies in Scheme 6 show that such anion exchange reactions should be facile as the formation of RC-OTf and Ph_2INTf_2 is almost an energetically neutral process while RC-OPiv is unfavorable thermodynamically by 3.6 kcal/mol. Alternatively, the exchange of the neutral ligand between RC-NTf_2 and RC-I was also calculated, showing the reactant complex of **2b** (RC-I) is more stable by 2.7 kcal/mol.

As the energy gaps among the possible reactant complexes are relatively small (Scheme 6), the energies for subsequent transformations from these complexes are compared in Scheme 7. For complexes containing the oxime substrate, the *β*-C-H activation could be realized via a concerted metallation-deprotonation (CMD)

Scheme 6. Energetics for the Generation of Possible Cationic Reactant Complexes.[29]



Scheme 7. Computational Results (Energies in kcal/mol).[29]

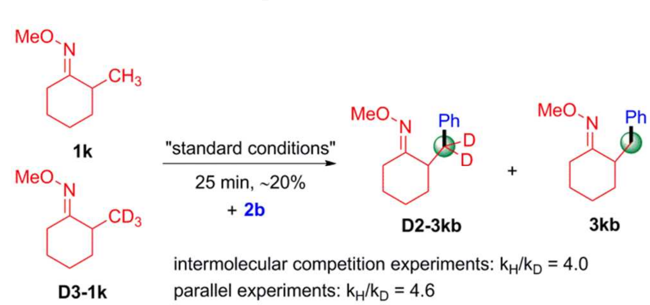


process via **TS1-X** (Scheme 7a), in which the anionic ligand (X) is a base for deprotonation of the C(β)-H bond (Calculations found that from **RC-X** the direct insertion of Ir(III) into the C(β)-H bond to form an Ir(V)-H species is higher in energy, details are given in the Supporting Information). Accordingly, the C-H activation is the least favorable when the NTf_2 anion is contained, which requires an activation barrier of 29.1 kcal/mol to generate iridicycle **IN1**. A remarkably reduced activation barrier of 21.5 kcal/mol was calculated from **RC-OTf**,[30] suggesting the triflate-involved CMD process is much more favorable (The geometry of **TS1-OTf** indicates the C-H bond is cleaved via a 6-membered ring TS, see the Supporting Information for details). Although a comparable activation barrier of 21.3 kcal/mol was predicted from **RC-OPiv**, an overall barrier of 25.0 kcal/mol should be required if considering the fact that **RC-OPiv** is 3.7 kcal/mol higher in energy than **RC-OTf**. Upon the generation of iridicycle **IN1**, the oxidation of Ir(III) to Ir(V) with diaryliodonium salt was next studied (Scheme 7b),[31] which occurs via **TS2-X** and releases one molecule of PhI into the reaction media. Theoretically, different counterions could be possibly contained in the diaryliodonium salt due to the low energy anion exchange reactions. Indeed, when using **Ph_2INTf_2** as an oxidant, which could be formed exergonically from reaction of **RC-NTf_2** with Ph_2IOTf (Scheme 6), an activation barrier of 9.4 kcal/mol was calculated (X = NTf_2), which is 7.8 kcal/mol lower than the oxidation by the originally added oxidant Ph_2IOTf (X = OTf), showing the dramatic difference in calculated energies with different counterions (In **TS2-X** the counterion is associated with the iodide moiety and no interaction with the Ir atom is found, geometries are given in the Supporting Information). The larger exergonicity associated with the formation of **IN2-OTf** than **IN2-NTf_2** could be attributed to steric reason because the latter intermediate is more crowded with a bulkier NTf_2 ligand. The involvement of a pivalate anion in the oxidation step was also studied and found to have a lowest barrier of 8.4 kcal/mol, however, such a possibility was considered to be less likely because the high energy associated with the formation of **Ph_2IOPiv**.[32] Thus, the **IN2-NTf_2** is suggested as a possible Ir(V) species formed in the reaction. Finally, the C(sp^3)- C(sp^2) coupling could be realized by reductive elimination from **IN2-NTf_2**, which occurs facilely via **TS3-NTf_2** with a barrier of 9.1 kcal/mol and generates product complex **PC-NTf_2** highly exergonically (Scheme 7c).

Based on the above results, the whole potential energy surface depicted in Scheme 7c suggests the triflate-involved C-H activation requires a highest activation barrier of 24.1 kcal/mol from **RC-I**, and the C(β)-arylation product will be formed irreversibly with facile oxidation and reductive elimination steps. Further support of the calculated energy profile could be obtained by the result of isotopically labeled substrate **D3-1k**, which led to a considerable kinetic isotope effect for both parallel experiments ($k_H/k_D \approx 4.0$) and competition experiments ($k_H/k_D \approx 4.6$) in Scheme 8.[33] It should be noted that the KIE results are also consistent with the involvement of Ph_2INTf_2 as an oxidant (Scheme 7c), because if the Ph_2IOTf is a reaction partner in this step, the relative energy of **TS2-OTf** will be 6.1 kcal/mol higher than **TS1-OTf** on the potential energy surface, making the C-H activation step reversible.

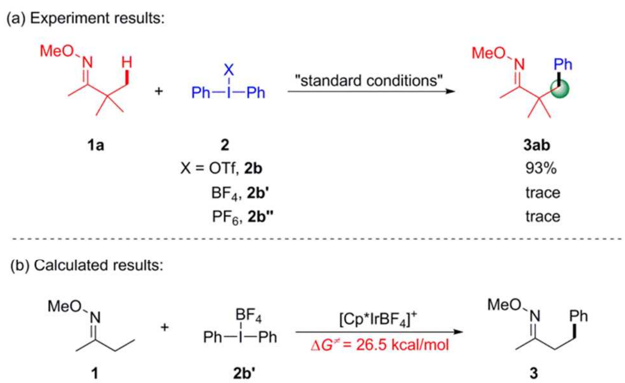
To make clear if the arylation could be achieved by the alternative mechanism of sequential oxidation/C-H activation (Pathway B, Scheme 5), the reaction from the most stable reactant complex **RC-I** was studied theoretically (Scheme 7d). The oxidation of Ir(III) to Ir(V) via **TS1'** requires a barrier of 26.4 kcal/mol. This is less favorable by 2.3 kcal/mol compared with the C-H activation via **TS1-OTf** (the energy difference of 2.6 kcal/mol between **RC-OTf** and **RC-I** was taken into consideration). The generated Ir(V) species **IN1'** is calculated to be even slightly higher in energy than **TS1'**. Incorporation of oxime **1** forms a more stable complex **IN2'**, however, the following C-H activation are impossible with activation barriers over 60 kcal/mol. This should be attributed to the fact that the Ir center is coordination saturated in **IN2'**, and dissociation of one of the ligands was observed during optimizations of the CMD transition states. Thus, Pathway B could be discarded according to the calculated energies.

Scheme 8. Kinetic Isotope Effect Studies.



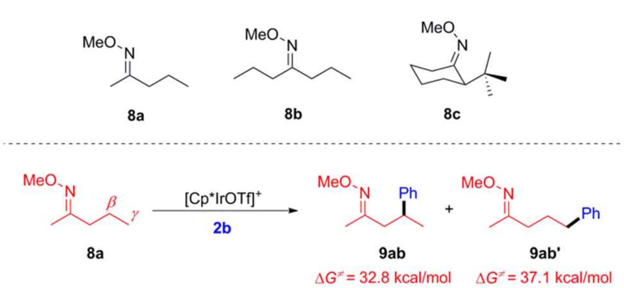
In previous reports, the diaryliodonium tetrafluoroborate (**2b'**) was utilized as the arylating reagent for Pd-catalyzed sp^2 C-H arylation reactions.[27d, 34] However, in our conditions, the diaryliodonium triflate (**2b**) was a superior coupling partner as diaryliodonium salts with other counterions (**2b'** and **2b''**) were totally unreactive (Scheme 7a). To understand this divergence, the reaction between **1** and **2b'** was studied theoretically by similar procedure described above. It was found that the pivalate anion may be involved in the C(β)-H deprotonation process for generation of iridicycle **IN1**. However, higher energy is required for the following oxidation by Ph_2INTf_2. The predicted activation energy for the whole reaction between **1** and **2b'** is 26.5 kcal/mol (Scheme 9b, detailed potential energy surfaces and discussion are given in the Supporting Information), being in qualitative agreement with the experiments that only trace of product was obtained.

Scheme 9. Different Counterions in Diaryliodonium salts Investigation.



In addition, it's also noticed that a primary β-carbon is necessary for this C-H arylation and γ-carbon has much lower reactivity compared with β-carbon, since ketoximes **8a**-**8c** failed to this reaction. The unique β-selectivity of this current methodology could also be understood by the calculated mechanism. The reaction between pentan-2-one *O*-methyl oxime (**8a**) and **2b** was simulated to see whether β- or γ-arylation product could be formed. Calculated results found increased activation energies are required for both the C-H activation and oxidation steps, and the latter step becomes the rate-determining step. Higher activation energies are required for both the β- and γ-arylations of **8a** (32.8 and 37.1 kcal/mol, respectively, Scheme 10) as results of the increased energies for the oxidation processes (activation energies in Scheme 10 are determined by the energy gap between the most stable reactant complex and the oxidation TS, details are given in the Supporting Information).

Scheme 10. Failed Substrates Analysis.



CONCLUSIONS

In summary, we have developed a versatile Ir(III)-catalyzed C-H arylation system. Under these developed conditions, we not only presented the first examples on β-arylation of aliphatic C-H bonds in ketoximes, heterocycles such as pyrazine, pyrazole and isoxazole but also applied this C-C coupling in various aryl and vinylic C-H bonds. This protocol can also serve as an efficient tool for late-stage C-H arylation of complex molecules in synthetic and medicinal chemistry. Therefore, this transformation has significant potential application, particularly as a result of the high selectivities. Further investigation of the mechanism of this transformation was carried out by DFT calculations, which suggested the reaction is initiated by anion-exchange between cationic reactant complex and diaryliodonium triflate. Such a process enables the triflate-involved CMD for C-H activation and the following oxidation of Ir(III) to Ir(V) by Ph_2INTf_2, which are the most favorable among other possibilities. These findings should be useful for future development of new sp^3 C-H activations.

ASSOCIATED CONTENT

Supporting Information. A brief statement in nonsentence format listing the contents of material supplied as Supporting Information should be included, ending with "This material is available free of charge via the Internet at http://pubs.acs.org." For instructions on what should be included in the Supporting Information as well as how to prepare this material for publication, refer to the journal's Instructions for Authors.

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(29) All calculations were done at the (PCM)M06/6-31G(d)-LANL2DZ level by running Gaussian 09. Relative solvation free energies were used for discussion. Computational details and citation of the software are given in the Supporting Information.

(30) If the arylation of sp^2 C-H bond follows a similar mechanism, the calculated energy for triflate-invovled C(sp^2)-H activation step of acetophenone *O*-methyl oxime is only 15.6 kcal/mol, being consistent with the more facile cleavage of the sp^2 C-H bonds.

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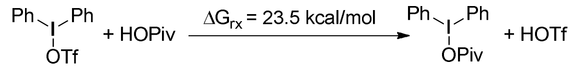
(32) The generation of Ph_2IOPiv by anion excahnge between **2b** and HOPiv is unfavorable:



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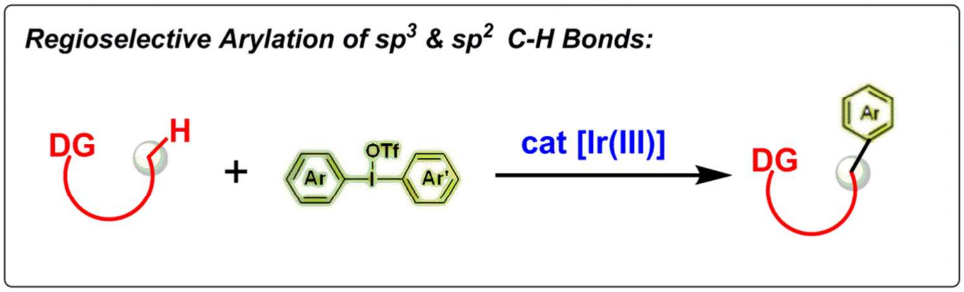
Regioselective Arylation of sp3 & sp2 C-H Bonds:
DG
H
OTf
Ar
I
Ar'
cat [Ir(III)]
DG
Ar