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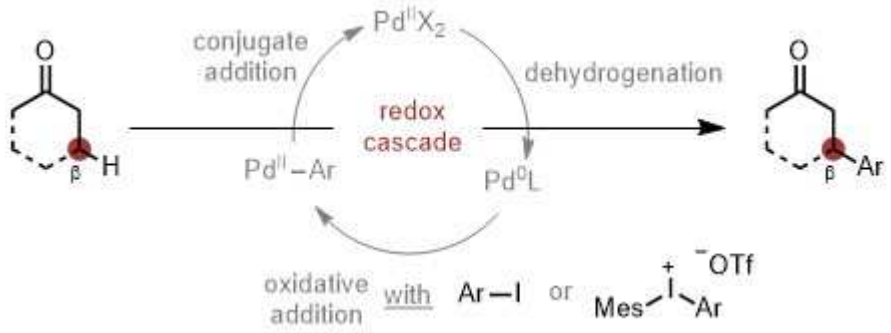


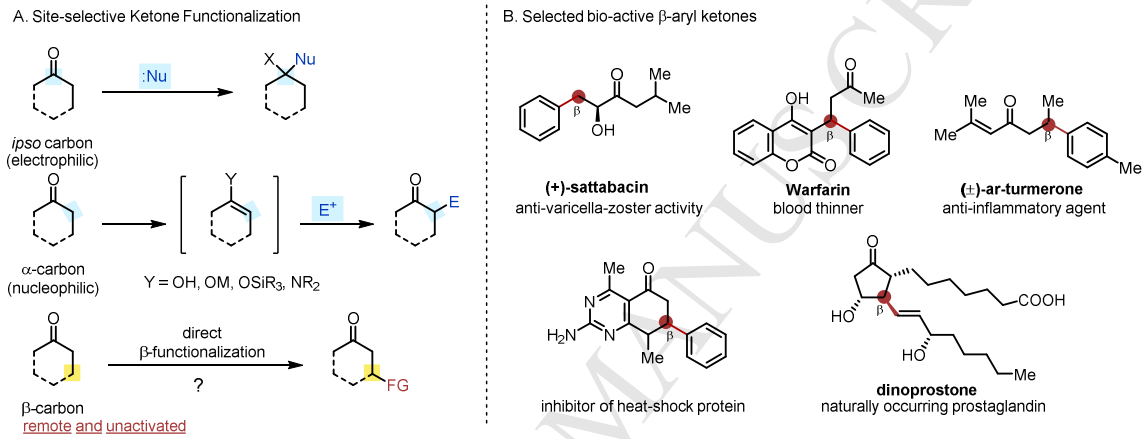
Palladium-Catalyzed Redox Cascade for Direct β-Arylation of Ketones

Zhongxing Huang and Guangbin Dong

Department of Chemistry, University of Chicago, Chicago, Illinois 60637, United States

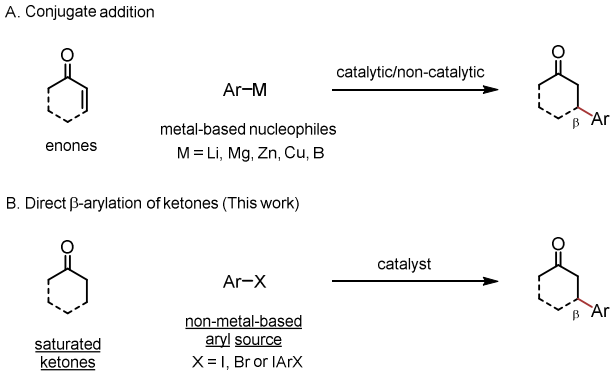
1 Introduction

Reactions of ketones have been cornerstones in organic chemistry.[1] Classic transformations of ketones hinge on the inherent acidity of the α-C−H bonds and the electrophilicity of the *ipso* carbon. Conventionally, the β-C−H bonds of ketones are considered inert due to their remote positions to the carbonyl group, and thus less likely to be directly functionalized (Scheme 1A).[2]



Scheme 1. Functionalization of Ketones

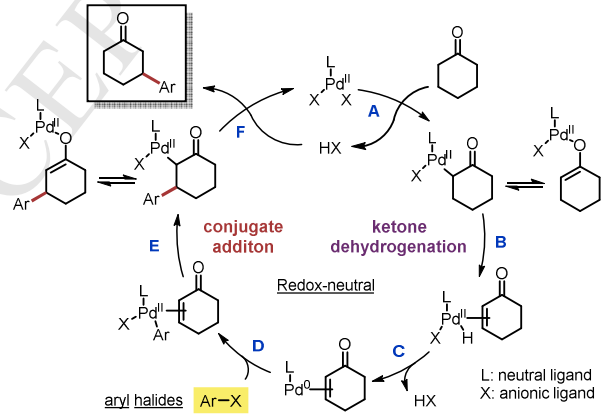
Nevertheless, β-substituted ketones are highly sought after as they are versatile synthetic intermediates and prevalent in bioactive compounds (Scheme 1B).[3] For more than a century, conjugate addition of metal-based nucleophiles (e.g. R-MgX, R-Li) to α,β-unsaturated ketones has been widely used to synthesize ketones with β-substituents (Scheme 2).[4] Continuous efforts from the synthetic community have led to a number of efficient catalytic and non-catalytic systems that enable the conjugate addition of a wide range of nucleophiles and enone acceptors. We envision that direct β-functionalization methods that employ saturated ketones as the substrate would offer an attractive alternative to the conjugate addition reactions considering the generally higher availability and lower cost of saturated ketones compared with the corresponding enones.[5] It is also desirable to avoid the use of basic and nucleophilic metal-based reagents for the β-functionalization reaction, as they often require stoichiometric reductant to synthesize and compromise the tolerance of certain functional groups, such as carbonyl groups and acidic protons. Herein, we present a detailed account of the design, development, and mechanistic understanding of a palladium-catalyzed redox cascade that enables the direct β-arylation of saturated ketones using readily available and non-metal based aryl sources.



Scheme 2. Direct β-Functionalization of Saturated Ketones with Non-Metal Aryl Sources

2 Design of a palladium-catalyzed redox cascade

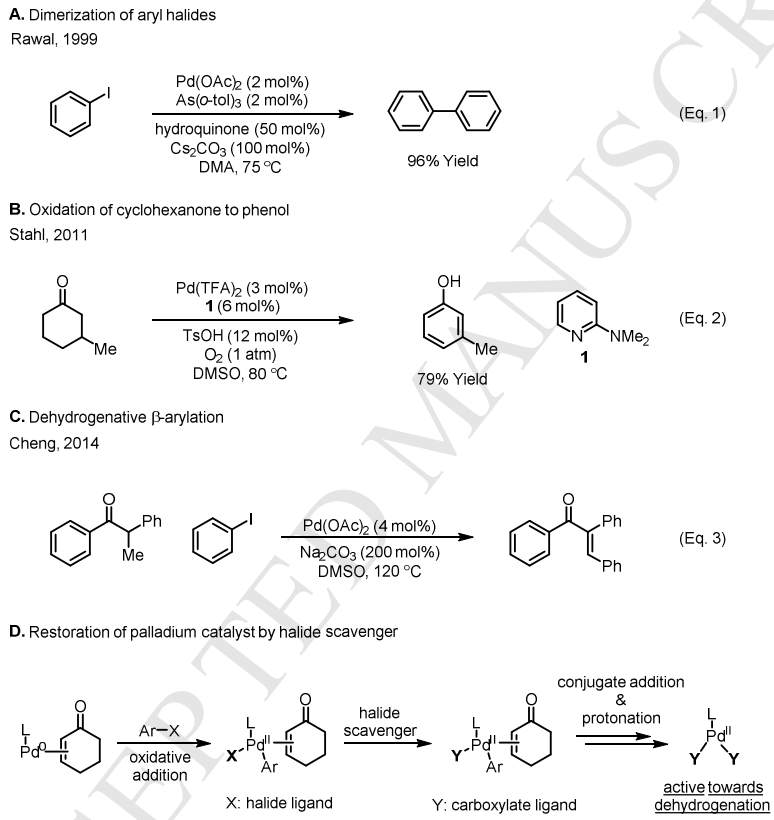
We conceived the idea of using saturated ketones and aryl halides as the substrates for the direct β-arylation reaction by merging palladium-catalyzed ketone dehydrogenation, C–X (X: halides) bond activation, and conjugate addition into a single catalytic cycle (Scheme 3). Since the seminal discovery by Theissen,[6] palladium-mediated dehydrogenation has been widely employed to prepare α,β-enones from saturated ketones.[7,8] The mechanism of this transformation has been studied and is proposed to proceed through a sequence of palladium enolate formation (Step A), β-hydride elimination (Step B), and reductive elimination to give the enone product and a Pd(0) species (Step C). A variety of catalytic dehydrogenation has been developed based on this mechanism by using different stoichiometric oxidants to regenerate the active Pd(II) catalyst from the Pd(0) intermediate. Here we hypothesize that aryl halides can serve as a stoichiometric oxidant for the catalyst regeneration as the oxidative addition of Pd(0) to aryl halides is well established (Step D).[9] It could also be envisaged the resulting Pd(II)-enone complex would undergo further migratory insertion to give Pd-enolate (Step E), which upon protonation, would yield the β-arylation product and release the Pd(II) catalyst (Step F). The migratory insertion and protonation steps have been established as key components of the mechanism of a large number of palladium-catalyzed conjugate addition reactions.[4b] A key feature of the designed catalytic cycle is the use of aryl halides as both the stoichiometric oxidant for the dehydrogenation step, and the aryl source for the conjugate addition step. Overall, saturated ketones and aryl halides serve as a redox pair for the β-arylation reaction, which in principle should be redox-neutral and requires no external oxidant or reductant.



Scheme 3. Proposed Palladium-Catalyzed Redox Cascade

While the constituent ketone dehydrogenation and conjugate addition are supported by a large number of precedents, we were aware of several challenges associated with the merged catalytic cycle. First, dehydrogenation of ketones often requires an electrophilic palladium catalyst to facilitate the ketone coordination

and subsequent palladium enolate formation.[7g] However, oxidative addition of C−X (X: halides) bonds prefers an electron-rich palladium complex.[9] Thus the choice of palladium catalysts for the merged redox cascade is non-trivial. Second, examples from prior literatures indicate several side reactions can take place, and thus need to be inhibited during the optimization of the β-arylation reaction. It is known that aryl halides can dimerize to biaryls in the presence of palladium catalysts and stoichiometric reductant (Scheme 4A).[10] Over-oxidation of the ketone substrates and/or the β-aryl ketone products should also be minimized, as palladium-catalyzed sequential dehydrogenation of ketones[11] (Scheme 4B) and dehydrogenative β-arylation of ketones[12] (Scheme 4C) have been reported. Third, carboxylate-type ligands have been proved important to maintain the reactivity of Pd(II) catalysts for the ketone dehydrogenation (Scheme 4D).[13] Nevertheless, during the oxidative addition step in our proposed catalytic cycle, a halide ligand is transferred to the palladium catalyst, which would presumably deactivate the catalyst for the next dehydrogenation. Therefore, efficient halide scavengers must be found to restore the palladium carboxylate catalyst by replacing the halide ligand.



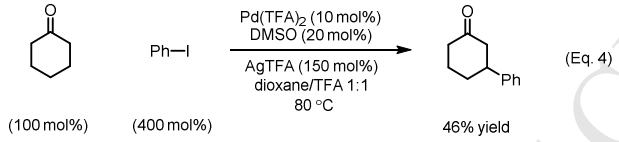
Scheme 4. Precedents of Possible Side-reactions and Requirement for Halide Scavenger

3 β-Arylation with aryl iodides

3.1 Optimization of conditions

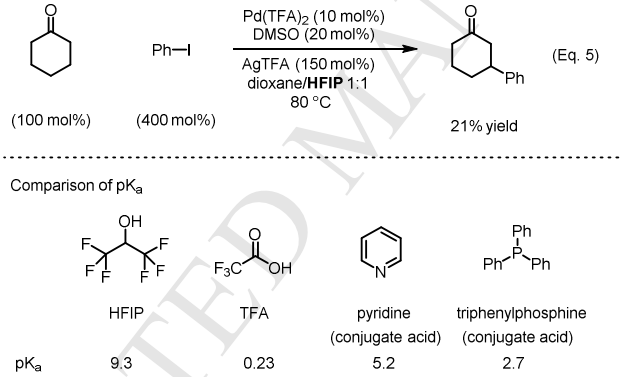
Guided by the proposed redox cascade, we were delighted to find the β-arylation product from the coupling between cyclohexanone and iodobenzene with $Pd(TFA)_2$/DMSO (palladium trifluoroacetate/dimethylsulfoxide) as the precatalyst (Scheme 5, Eq. 4). Our early screening of the reaction parameters, including precatalysts, additives and solvents, has revealed several preferences of the β-arylation reaction. First, silver salt can greatly promote the reaction. As designed in the catalytic cycle, the role of silver salt is to scavenge the iodide ligand and restore the active Pd(II) catalyst. Second, acetate or trifluoroacetate counter anion is indispensable for the

reaction. In the catalytic cycle, when the silver scavenges iodide from the palladium center, it also delivers its counter anion to the palladium. As the acetate-type ligand on palladium is crucial to maintain the palladium catalyst sufficiently electrophilic, silver trifluoroacetate is favored for the reaction. Second, acidic and coordinating solvents are both important for the reaction, as a mixed solvent consisting of equal volumes of dioxane and trifluoroacetic acid was found beneficial for the arylation reaction. It is anticipated that dioxane can stabilize the palladium intermediates as a weak ligand, and acidic reaction medium is proposedly critical for the last protonation step (*vide supra*, Scheme 3, Step F). Fourth, although different sorts of ligands (i.e. phosphine- and nitrogen-based ligands) are screened, they seemed to have undifferentiated effects on the reaction outcome. We hypothesize that due to the use of strongly acidic trifluoroacetic acid, a vast majority of phosphine, phosphite or nitrogen-based ligand can be protonated, and thus sluggish to coordinate to the palladium center. In addition, further optimization of other reaction parameters, including additives and solvents, did not turn out to be fruitful.



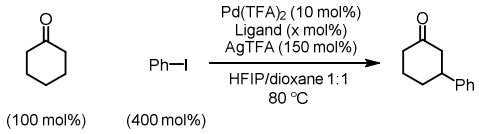
Scheme 5. Preliminary Conditions for β-Arylation with Aryl Iodides

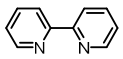
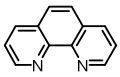
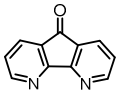
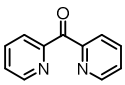
The protonation issue was largely alleviated when HFIP (hexafluoro-2-propanol) was used as the co-solvent instead of trifluoroacetic acid (Scheme 6, Eq. 5). Given that the pKa of HFIP is only 9.3, it is acidic enough to pronate enolates, but not acidic enough to protonate the majority of phosphine- and nitrogen-based ligands.



Scheme 6. Use of HFIP as Co-solvent

While HFIP initially didn't lead to a higher yield than trifluoroacetic acid, with HFIP as a co-solvent for the ligand screening, the differences among various types of ligands were revealed to be significant (Scheme 7). While simple pyridine was not an effective ligand (entry 1), bis-nitrogen-based ligands generally promoted the reaction (entries 2-5). Among these bidentate ligands, electron-deficient 4,5-diazafluoren-9-one[14] (entry 4) and 2,2'-dipyridyl ketone (entry 5) gave the highest yields, probably due to their π-acidity that facilitates the dehydrogenation. It is noteworthy that simple triphenylphosphine (entry 7) outperformed DMSO (entry 6) to deliver the β-arylation product in 42% yield. Further screening of phosphine ligands with a wide range of aryl or alkyl substitutions demonstrated electron-rich trialkylphosphine, especially PCy_3 (entry 14) and $P(i\text{-}Pr)_3$ (entry 15), are the best candidates for the reaction, while most bidentate phosphine ligands gave very low conversion (entries 18-21).

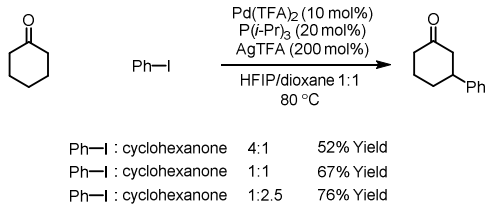


Entry	Ligand (mol%)		Yield (%)	Conversion (%)
1		(20)	trace	6
2		(10)	19	22
3		(10)	<5	6
4		(10)	27	55
5		(10)	31	32
6	DMSO	(20)	31	32
triaryl phosphine:				
7	PPh_3	(20)	42	51
8	$P(2\text{-furyl})_3$	(20)	12	17
9	$P(o\text{-tol})_3$	(20)	5	16
10	$P(2,6\text{-diOMeC}_6H_3)_3$	(20)	4	17
11	$P(p\text{-tol})_3$	(20)	27	43
12	$P(p\text{-OMeC}_6H_4)_3$	(20)	27	48
13	$P(C_6F_5)_3$	(20)	10	31
trialkyl phosphine:				
14	**PCy_3**	(20)	**48**	**50**
15	**$P(i\text{-Pr})_3$**	(20)	**51**	**52**
16	$P(n\text{-Bu})_3$	(20)	30	31
17	$P(t\text{-Bu})_3$	(20)	7	19
bidentate phosphine:				
18	dppm	(20)	26	50
19	dppe	(20)	trace	32
20	dppb	(20)	trace	<10
21	dppf	(20)	trace	<10

Scheme 7. Ligand Effect of β-Arylation with Aryl Iodides

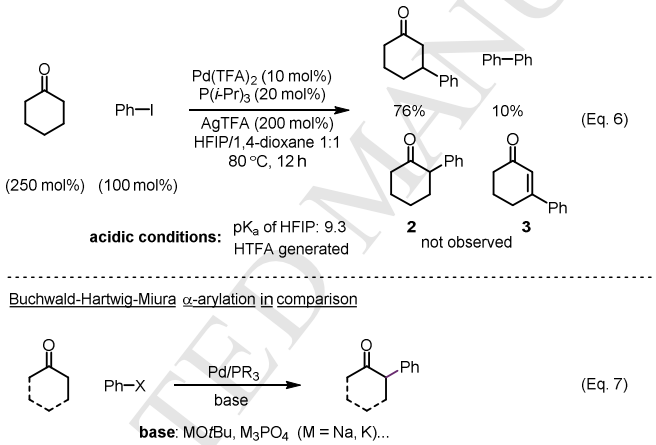
The ratio between two reactants also turned out to be crucial for the efficiency of the β-arylation reaction (Scheme 8). While reactions with excess iodobenzene led to yields around 50%, a reverse ratio of substrates resulted in a much improved yield (76%). We attributed the requirement for excess ketone substrates to the challenging dehydrogenation step, as the Lewis basicity of ketones is relatively low and thus they are sluggish to complex with palladium for dehydrogenation. These observations were also supported by Stahl's mechanistic

studies[7g] of the palladium-catalyzed aerobic dehydrogenation of ketones, where higher concentration of ketone substrates leads to higher initial rates.



Scheme 8. Effect of the Ratio of Substrates

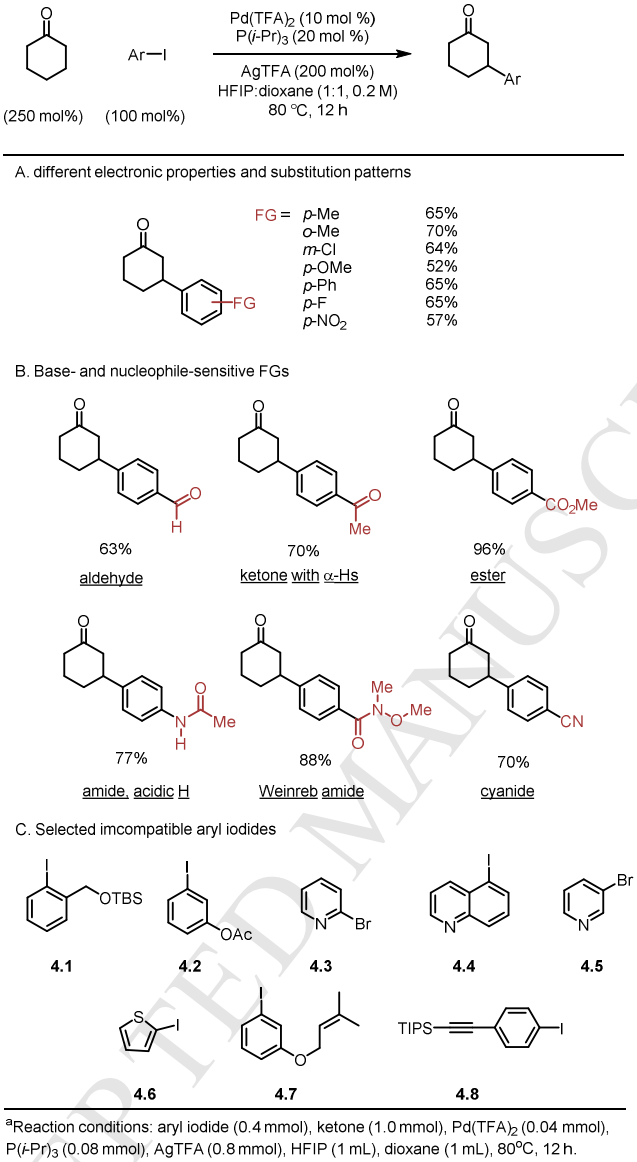
Upon reaching the optimal reaction conditions (Scheme 9, Eq. 6), detailed analysis of the reaction showed the major side-product of this transformation was the biphenyl resulted from the reductive homo-coupling of iodobenzene (*vide supra*, Scheme 4A). α-Arylation (**2**) and dehydrogenative β-arylation (**3**) products were not observed. It is worthy to mention that similar combinations of palladium catalysts and electron-rich phosphine ligands are frequently used in the Buchwald-Hartwig-Miura α-arylation of ketones (Eq. 7).[15] We proposed that the different pathway and site-selectivity observed here roots from different reaction medium employed: strong bases are used in the α-arylation reaction, whereas this β-arylation employs acid conditions (HFIP and trifluoroacetic acid[16]).



Scheme 9. Optimized Conditions for β-Arylation with Aryl Iodides

3.2 Substrate scope

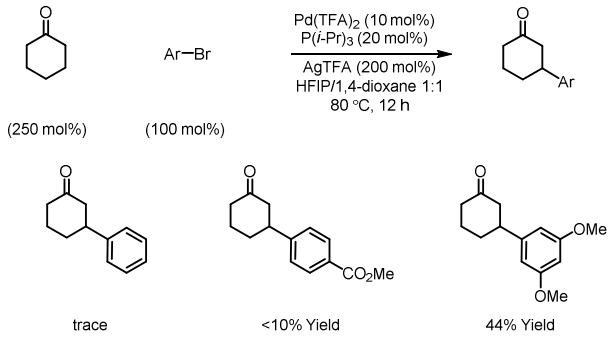
Several features regarding the substrate scope of the direct β-arylation reaction are noteworthy. The palladium-catalyzed redox cascade shows a broad scope of aryl iodides. Aryl iodides with different substitution patterns (*ortho*, *meta*, or *para* substitution) as well as different electronic properties (electron-neutral, -rich, and -poor) all reacted to give the desired β-aryl ketones under the reaction conditions (Scheme 10A). Besides, we were delighted to discover that many sensitive functional groups, such as ketones, aldehydes, and acidic protons, are compatible with the reaction conditions (Scheme 10B). These functional groups, on the other hand, are often not tolerated in conjugate addition reactions when using strongly basic and nucleophilic metal-based reagents (e.g. Grignard and organolithium reagents). The tolerance of these base- and nucleophile-sensitive functional groups is probably attributed to the acidic reaction medium in the absence of stoichiometric aryl-metal species. However, it should be pointed out that the acidic reaction medium and *in situ* generated trifluoroacetic acid during the course of the reaction has compromised the compatibility of some acid-labile functional groups, such as silyl-protected alcohol (**4.1**) and acetate (**4.2**) (Scheme 10C). In addition, with the electrophilic nature of the palladium catalyst, aryl halides with Lewis-basic (**4.3**-**4.5**) or electron-rich (**4.6**) heterocycles, as well as unsaturated C−C bonds (**4.7**-**4.8**) failed to give the β-arylation products, probably due to the catalyst poisoning and side-reactions of alkenes/alkynes.



[a]Reaction conditions: aryl iodide (0.4 mmol), ketone (1.0 mmol), $Pd(TFA)_2$ (0.04 mmol), $P(i\text{-}Pr)_3$ (0.08 mmol), AgTFA (0.8 mmol), HFIP (1 mL), dioxane (1 mL), 80°C, 12 h.

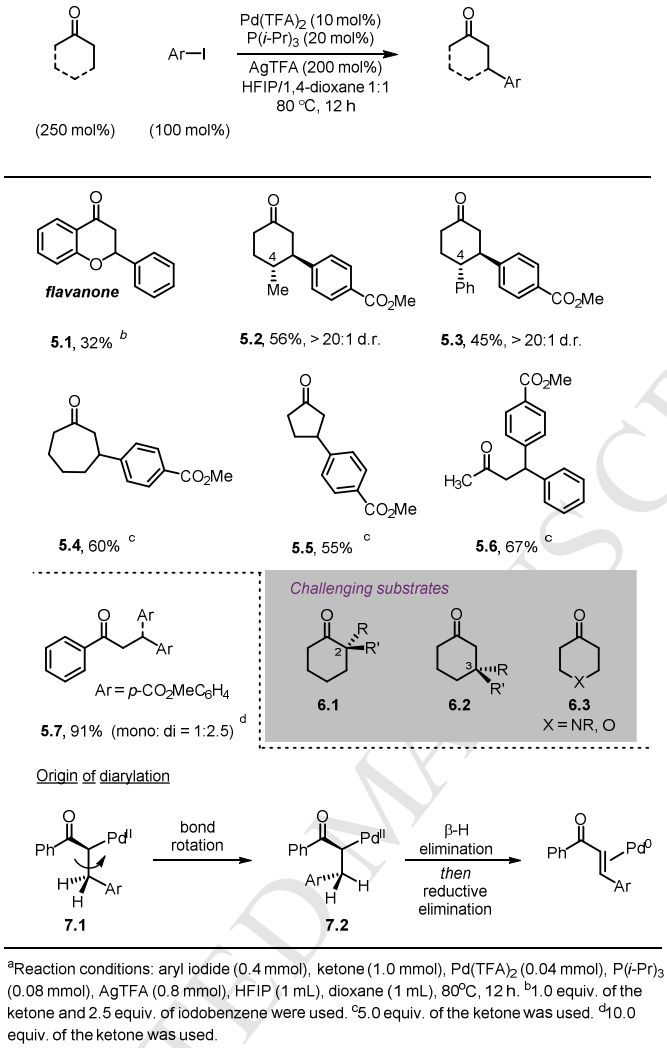
Scheme 10. Advantage and Limitation of the Scope of Aryl Iodides[a]

Aryl bromides exhibit much lower reactivity (Scheme 11). While methyl 4-bromobenzoate and simple bromobenzene gave low conversions, 3,5-dimethoxybromobenzene afforded the desired β-arylation product in a moderate yield. It is proposed that the major obstacle to achieving efficient β-arylation with aryl bromides is their slower oxidative addition compared with iodides. Without a rapid oxidative addition, the Pd(0) intermediate is prone to decomposition to palladium black through aggregation in the absence of excess ligands. It was found that addition of more phosphine ligands inhibited the ketone dehydrogenation step likely by blocking the coordination site for β-H elimination. The use of bidentate phosphine ligands may increase the rate of oxidative addition of Pd(0) and prevent decomposition. However, they are not effective for the ketone dehydrogenation step. Thus, the key to address the challenge of using ArBr as the coupling partner in the future is to find a suitable ligand that can stabilize the Pd(0) intermediate but meanwhile not interfere with the dehydrogenation step.



Scheme 11. β-Arylation with Aryl Bromides Using $Pd(TFA)_2/P(i\text{-}Pr)_3$

The scope of ketones was examined next (Scheme 12). The β-arylation reaction appears to be highly diastereoselective when cyclohexanones with substituents at the C4 position were submitted to the reaction, giving the *trans* products (**5.2**, **5.3**). Nevertheless, we were disappointed to find that substituents at the C2 or C3 position (**6.1**, **6.2**), as well as cyclohexanones with a heteroatom in the skeleton (**6.3**), are unsuitable substrates for the β-arylation reaction. Reactions with these ketones often resulted in a low conversion of ketones, indicating a difficult dehydrogenation step. On the other hand, simple cyclic ketones with ring-sized other than cyclohexanones (**5.4**, **5.5**) succeeded to give the β-arylation product. In addition, acyclic ketones are also able to participate in the β-arylation reaction (**5.5**-**5.7**). Intriguingly, propiophenone gave a large amount of diarylation product, which was not observed for the cyclic ketones. The diarylation product was proposed to be accessed from intermediate **7.1** after the first conjugate addition, instead of a separate β-arylation of the monoarylated product, as the β-arylation of β-phenyl propiophenone only gave a trace amount of diarylated product. We hypothesized that, due to the more flexible conformation and rotation of β C−C bond, the second β-hydrogen elimination of **7.2** is facile to take place, followed by conjugate addition and protonation to give the diarylation product.

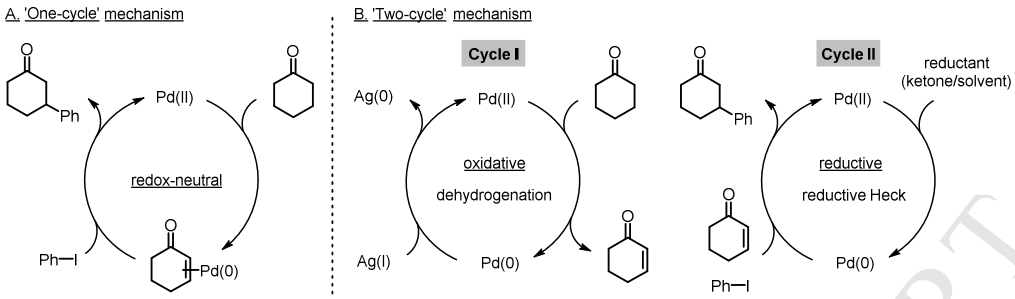


[a]Reaction conditions: aryl iodide (0.4 mmol), ketone (1.0 mmol), $Pd(TFA)_2$ (0.04 mmol), $P(i\text{-}Pr)_3$ (0.08 mmol), AgTFA (0.8 mmol), HFIP (1 mL), dioxane (1 mL), 80°C, 12 h. [b]1.0 equiv. of the ketone and 2.5 equiv. of iodobenzene were used. [c]5.0 equiv. of the ketone was used. [d]10.0 equiv. of the ketone was used.

Scheme 12. Scope and Limitation of Ketone Substrates[a]

3.3 Silver issue

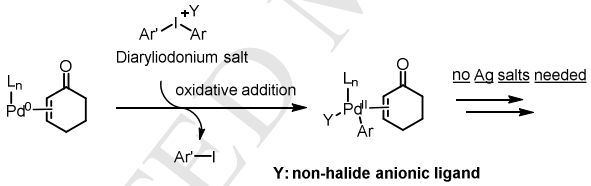
The use of stoichiometric AgTFA in our conditions was the key to avoid poisoning of halide and restore the active Pd(II) dicarboxylate catalyst. However, the disadvantages of using silver salts are, first, they are expensive and thus impractical on a process scale; second, they have cast some doubts on the reaction mechanism. In our proposed catalytic cycle, the saturated ketone and aryl halide serve as a redox-pair for the β-arylation reaction, rendering the catalysis redox-neutral (Scheme 13A). Nevertheless, it is known that Ag(I) salts are able to oxidize Pd(0) species. Thus, an alternative mechanism of the β-arylation reaction may involve two separate transformations, the palladium-catalyzed dehydrogenation and reductive Heck reaction (Scheme 13B). In this alternative mechanism, the Ag(I) additive serves as an stoichiometric oxidant for the palladium-catalyzed dehydrogenation (Cycle I), and the resulting enone enters the second catalytic cycle to undergo the palladium-catalyzed reductive Heck reaction (Cycle II), where excess ketones or solvents could serve as the reductant. Therefore, instead of being redox-neutral, the β-arylation with aryl halides requires both external oxidants and reductants if undergoing the 'two-cycle' mechanism. When stoichiometric silver salt is employed, the "two-cycle" mechanism cannot be excluded.



Scheme 13. Comparison between Redox-neutral cycle and 'Two-cycle' Mechanism

4 Arylation with diaryliodonium salts

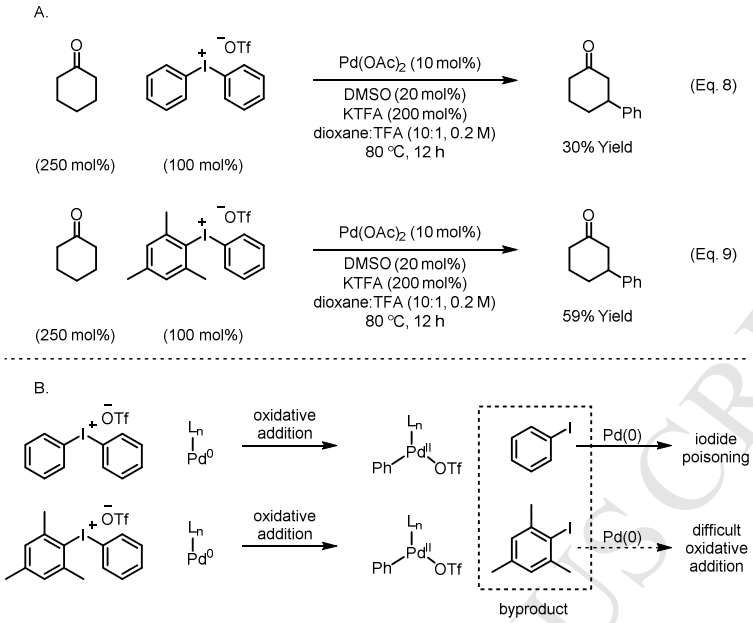
One indirect approach to solve the silver issue is to use aryl electrophiles that do not transfer a halide anion to palladium during the oxidative addition, thus avoiding the use of a halide scavenger at all. Towards this end, we found the diaryliodonium salt as a promising aryl source for the β-arylation without halide scavenger (Scheme 14).[17] Unlike aryl iodides, the oxidative addition of diaryliodonium salts to Pd(0) transfers an aryl and a non-halide anion to the metal, and release an molecule of aryl iodide at the same time.[18] As a result, silver salt is not necessary to extract the iodide ligand and regenerate the active palladium catalyst any more. Besides the silver issue, the use of diaryliodonium salts would also address the limitation of using air-sensitive P(*i*-Pr)$_3$ ligand under our previous β-arylation conditions, which necessitates air-free operations and highly purified reagents. As a more reactive aryl electrophile, oxidative addition of diaryliodonium salts generally does not need the assistance of electron-rich phosphine ligand. Thus, the new reaction conditions using diaryliodonium salts as the aryl source is expected to tolerate air.



Scheme 14. Oxidative Addition of Diaryliodonium Salts to a Pd(0)-Enone Complex

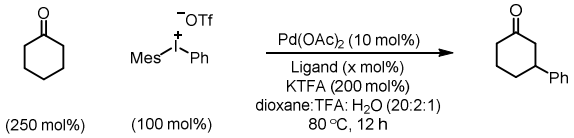
4.1 Optimization of conditions

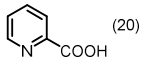
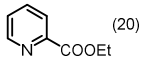
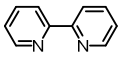
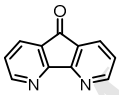
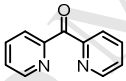
Indeed, the use of diphenyliodonium triflate as the aryl source led to a new set of β-arylation conditions that require no stoichiometric heavy metals as a halide scavenger, where Pd(OAc)$_2$ (palladium acetate)/DMSO serves as the precatalyst (Scheme 15A, Eq. 8). However, one concern about the use of diphenyliodonium salt in our preliminary conditions is that it can act as two equivalents of aryl source, as the oxidative addition of the salt to Pd(0) will produce one molecule of iodobenzene as a byproduct (Scheme 15B). Besides the complication of stoichiometry, the iodobenzene byproduct could potentially poison the palladium catalyst by undergoing oxidative addition with Pd(0) intermediate in the reaction. In order to avoid such an issue, we switched to mesitylphenyliodonium triflate as the aryl source. The rationale for the use of mesityl-based iodonium salts is two-fold. First, mesitylaryliodonium salts are known to transfer the less sterically hindered aryl group chemoselectively due to the bulk of mesityl group. Second, also due to the sterics, the byproduct from the aryl transfer, iodomesitylene, is hard to undergo oxidative addition to the Pd(0) intermediate, thus avoiding poisoning the palladium catalyst. As expected, replacement of diphenyliodonium salt with its mesityl counterpart resulted in improved efficiency of the β-arylation reaction under the same conditions (Eq. 9).



Scheme 15. Preliminary Conditions for the β-Arylation with Iodonium Salts

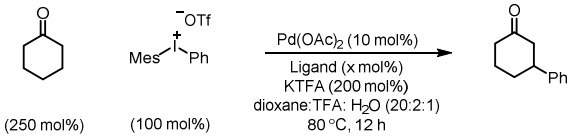
In terms of the choice of ligands, the new reaction conditions with iodonium salts are distinct from our previous $Pd(TFA)_2/P(i\text{-}Pr)_3$ system (Scheme 16). While phosphine and phosphite ligands still afforded the β-arylation product (entry 1-2), the yields were generally low, despite their outstanding performances for the previous conditions (*vide supra*, Scheme 7). Nitrogen-based ligands (either mono- or bidentate) were not suitable for the reaction with diaryliodonium salts (entry 4-9); the only exception being 4,5-diazafluoren-9-one that gave the product in 56% yield (entry 8). On the other hand, sulfur-based ligands are more favored for the new conditions, with simple DMSO outcompeting phosphine- and nitrogen-based ligands (entry 10).

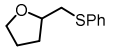
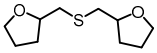
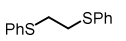
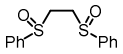
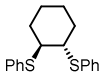
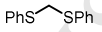
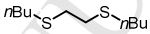
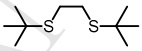


Entry	Ligand (x mol%)	Yield (%)
1	PPh_3 (20)	32
2	$P(OPh)_3$ (20)	22
3	dppe (20)	3
4	 (20)	0
5	 (20)	0
6	 (10)	0
7	dtbpy (20)	0
8	 (10)	56
9	 (10)	0
10	DMSO (20)	59

Scheme 16. Effects of Different Types of Ligands

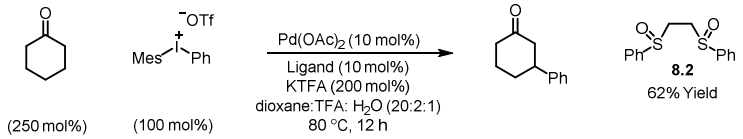
Subsequently, a large variety of sulfide- and sulfoxide-based ligands with different backbones was synthesized and examined (Scheme 17). While monodentate sulfide and sulfoxide ligands all gave the β-arylation product in good yields (entry 1-7), they are generally outperformed by their bidentate derivatives. Especially, 1,2-bis(phenylthio)ethane (**8.1**), as well as its sulfoxide counterpart (**8.2**),[19] originally employed by White and coworkers for the allylic C−H activation, proved to be a superior ligand for the reaction. Increasing the bite angle of the bis-sulfide ligand (entry 10) or using a conformationally fixed derivative (entry 11) decreases the efficiency of the reaction; eliminating one carbon on the backbone of the ligand (entry 12) totally shut down the reaction. Replacing the phenyl groups on the ligand with alkyl groups resulted in lower yields (entry 13), and the use of an electron-donating *tert*-butyl-substituted bis-sulfide ligand (entry 14) gave no β-arylation product, probably by inhibiting the dehydrogenation step.

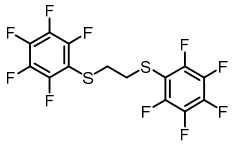
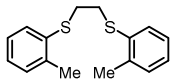
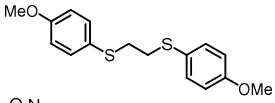
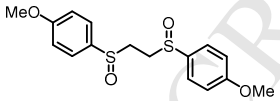
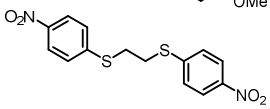
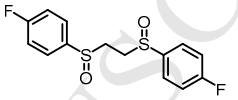
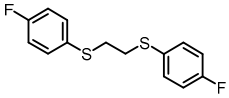
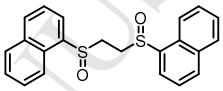
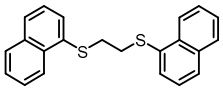
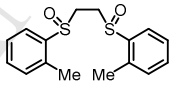


Entry	Ligand (x mol%)		Yield (%)
1		(20)	56
2		(20)	48
3		(20)	44
4		(20)	47
5		(20)	45
6		(20)	48
7		(20)	21
8	 **8.1**	(10)	59
9	 **8.2**	(10) (20)	62 61
10		(10)	53
11		(10)	48
12		(10)	0
13		(10)	55
14		(10)	0

Scheme 17. Effects of Different Sulfide and Sulfoxide Ligands

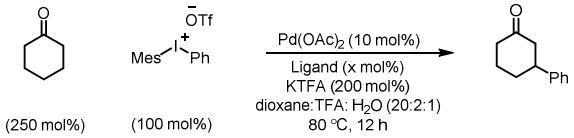
Based on the backbone of **8.1** and **8.2**, we modified the aryl substituents to examine their effects on the reaction efficiency (Scheme 18). However, alternating the electronic properties of the arenes seemed to have little effects on the reaction; ligands with either electron-donating or -withdrawing substituents gave comparable or lower yields than **8.2**. Increasing the steric hindrance of the sulfur ligands (entry 6 and 10), however, only afforded the product in a lower or similar yield.

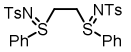
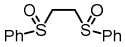
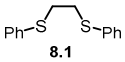
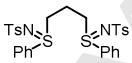


Entry	Ligand (x mol%)	Yield (%)	Entry	Ligand (x mol%)	Yield (%)
1		42	6		42
2		59	7		59
3		62	8		62
4		61	9		61
5		63	10		63

Scheme 18. Ligand Optimization Based on **8.1** and **8.2**

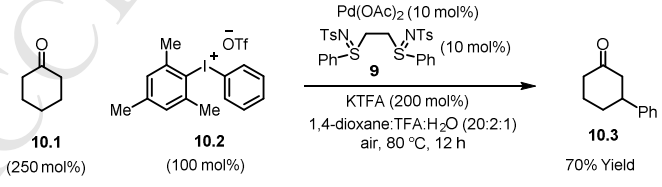
Finally, several sulfilimine ligands were synthesized, examined, and compared with sulfide and sulfoxide ligands for the β-arylation reaction (Scheme 19). To our delight, bis-*N*-tosylsulfilimine ligand **9** turned out to be superior, giving a higher yield than its sulfide and sulfoxide counterparts (entry 2 and 3). This ligand was easily prepared in one step from 1,2-bis(phenylthio)ethane and Chloramine-T, and the *meso* and *racemic* ligand demonstrated nearly identical reactivity. Although sulfides and sulfoxides are frequently employed as ligands, to the best of our knowledge, the class of bis-sulfilimines has not been previously used as ligands for transition metals. Monodentate sulfilimine ligands (entry 4-6) and the bis-sulfilimine ligand with an elongated backbone (entry 7) were all found inferior.



Entry	Ligand (x mol%)		Yield (%)
1	 **9**	(10)	70%
2	 **8.2**	(10)	60%
3	 **8.1**	(10)	59%
4		(20)	29%
5		(20)	22%
6		(20)	41%
7		(10)	47%

Scheme 19. Effects of Sulfilimine Ligands

Besides the ligand effect, several other features of this new generation of β-arylation are noteworthy. First, a combination of KTFA (potassium trifluoroacetate) and TFA (trifluoroacetic acid) was employed (Scheme 20A). While acidic medium is generally required for the final protonation of the palladium enolate to release the product, the role of KTFA here is proposed to prevent the acidity of the reaction from going too high by neutralizing strong acids generated (i.e. triflic acid and its equivalent). This hypothesis was also supported by the detrimental effect of added strong acids (i.e. triflic acid). Third, partly due to the absence of electron-rich phosphine ligands, the new reaction conditions tolerate air/moisture and can be set up without a glovebox or any Schlenk techniques (Scheme 20B). Furthermore, the reactivity of the new conditions can be sustained under lower temperatures with an elongated reaction time (Scheme 20C).



A. KTFA/TFA as 'buffer pair'

Control reactions	Yield (%)
w/o KTFA and TFA	13
w/o TFA	36
w/o KTFA	34
100 mol% HOTf instead of TFA	2

B. Air/Moisture compatible

Control reactions	Yield (%)
w/o H_2O	47
N_2 instead of air	73

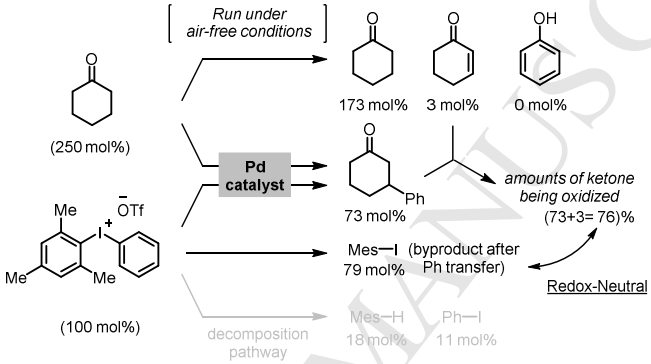
C. Milder conditions

55 °C, 3 days: 70% Yield
45 °C, 5 days: 65% Yield

Scheme 20. Optimized Conditions for the β-Arylation with Mesitylphenyliodonium Salts

4.2 Redox count

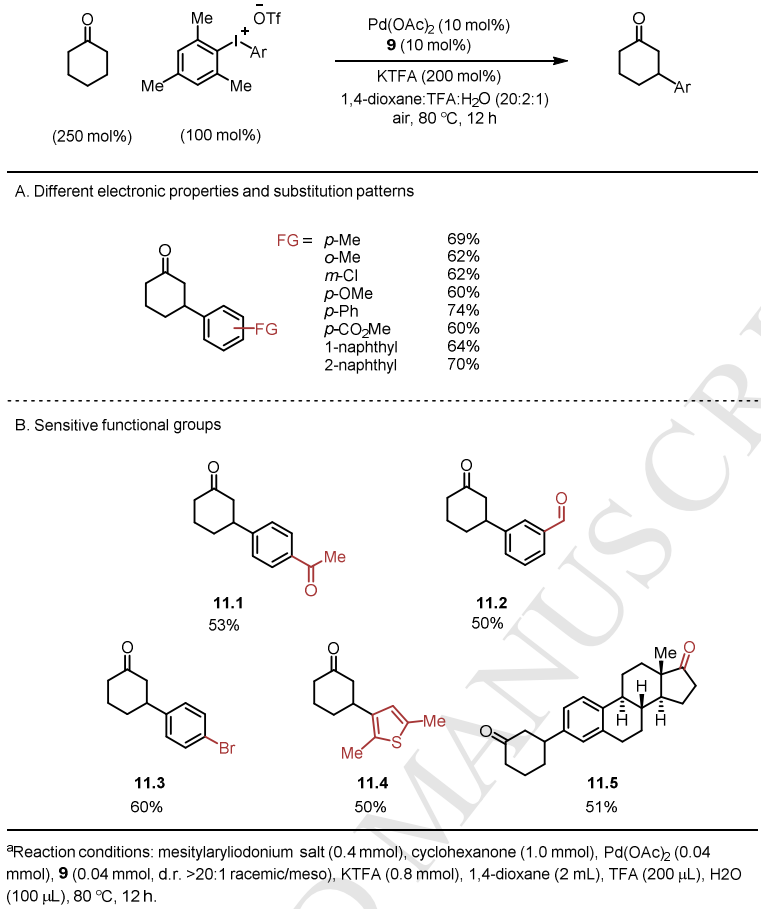
More importantly, as no redox-active additives were used under the new conditions, a clear analysis of the redox property of the β-arylation can be executed (Scheme 21). A detailed identification and quantification of products and byproducts of the new β-arylation reaction was carried out. For the cyclohexanone part, while excess ketone was necessary for a fast reaction initiation, a high recovery of the unreacted ketone was obtained. Only a trace amount of cyclohexen-1-one was formed, and no phenol from the over-oxidation was observed. For the mesitylphenyliodonium salt part, there are two major reaction pathways. About three quarters of the iodonium salts participated in the β-arylation pathways to give the desired β-arylated ketone with iodomesitylene as the byproduct. Most of the remaining iodonium salt proceeded through a decomposition pathway to mesitylene and iodobenzene. Altogether, the substrates being oxidized and reduced under the palladium catalysis are nearly of the equal amount, thus supporting that the reaction between cyclohexanone and mesitylphenyliodonium salt is indeed redox-neutral.



Scheme 21. Redox Property of the β-Arylation with Mesitylphenyliodonium Salts

4.2 Substrate scope

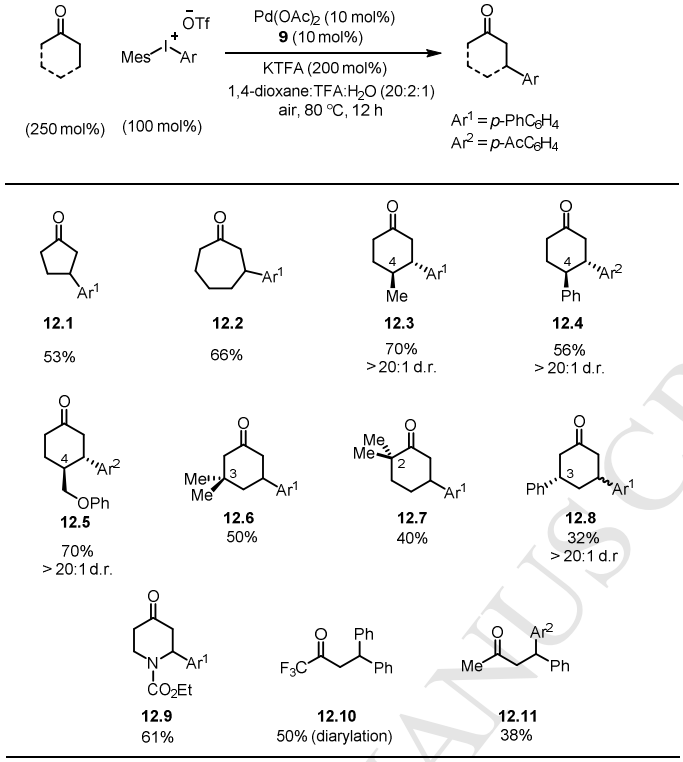
When a wide range of mesitylaryliodonium salts were subjected to the optimized conditions, a similar scope of aryl groups was found compared with the $Pd(TFA)_2/P(i\text{-}Pr)_3$ system. Besides aryl groups with different electronic properties and substitution patterns (Scheme 22A), the tolerance of functional groups that are hard to survive under conjugate addition conditions, e.g. aldehyde and a second ketone, was also observed (**11.1** and **11.2**). Moreover, it is interesting to note that aryl bromide (**11.3**), a functional group that was not compatible with β-arylation using $P(i\text{-}Pr)_3$, can be tolerated under the new conditions, probably due to the less electron-rich palladium catalyst used. The iodonium salt with an electron-rich thiophenes moiety also reacted to give the corresponding arylation product (**11.4**), while the previous method did not show tolerance of heterocycle substrates. The high chemoselectivity was also demonstrated in the reaction with an estrone-derived iodonium salt, where the cyclohexanone was selectively arylated in the presence of the cyclopentanone moiety in estrone (**11.5**).



[a]Reaction conditions: mesitylaryliodonium salt (0.4 mmol), cyclohexanone (1.0 mmol), $Pd(OAc)_2$ (0.04 mmol), **9** (0.04 mmol, d.r. >20:1 racemic/meso), KTFA (0.8 mmol), 1,4-dioxane (2 mL), TFA (200 μL), H2O (100 μL), 80 °C, 12 h.

Scheme 22. Scope of Aryl Groups

Both linear (**12.10** and **12.11**) and cyclic ketones with different ring sizes (**12.1** and **12.2**) participated in the β-arylation with iodonium salts (Scheme 23). A significant improvement in terms of the ketone scope was that cyclohexanones with C2-, C3-, or C4-substituents, including sterically demanding 2,2-dimethylcyclohexanone, all reacted to give the corresponding arylated ketones (**12.3**-**12.8**), whereas the previous method only accommodates C4-substituted cyclohexanones. Additionally, the previously incompatible 4-piperidinone derivatives are suitable substrates using the new method (**12.9**). We hypothesized that the extended ketone scope is attributed to a more cationic palladium catalyst generated during the reaction. While trifluoroacetate stayed as the counter anion for the palladium catalyst throughout the reaction in the $Pd(TFA)_2/P(i\text{-}Pr)_3$ system, oxidative addition of the iodonium salts in the new reaction would transfer less-coordinating anions (*i.e.* OTf) to the palladium center, which in turn, would facilitate the ketone dehydrogenation step.

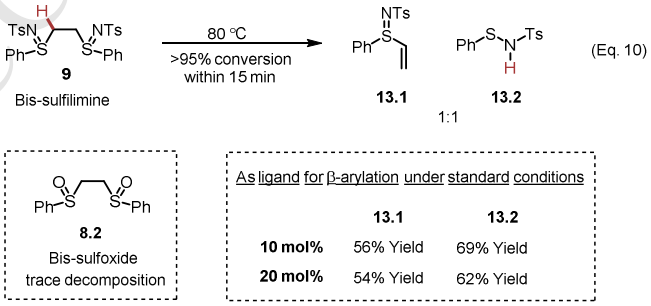


[a]Reaction conditions: mesitylaryliodonium salt (0.4 mmol), ketone (1.0 mmol), $Pd(OAc)_2$ (0.04 mmol), **9** (0.04 mmol, d.r. >20:1 racemic/meso), KTFA (0.8 mmol), 1,4-dioxane (2 mL), TFA (200 μL), H2O (100 μL), 80 °C, 12 h.

Scheme 23. Improved Scope of Ketones[a]

4.3 Mechanistic studies

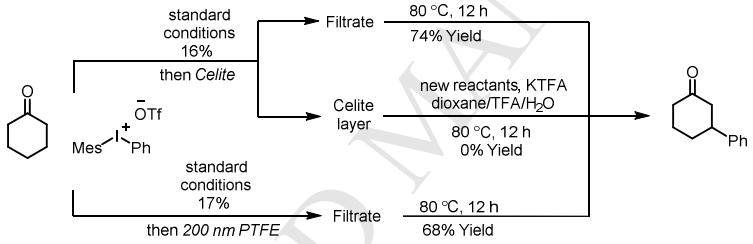
Monitoring of the reaction progress by gas chromatography revealed an induction period for the β-arylation reaction, during which an opaque and dark red solution was formed. Careful analysis of the reaction mixture during the induction period also indicated the full conversion of bis-sulfilimine ligand **9** to give a pair of elimination products **13.1** and **13.2** (Scheme 24, Eq. 10). Literature precedents[20] and our control reactions further demonstrated the elimination of sulfilimine could take place under heated conditions without any other additives (e.g. palladium and potassium salts, trifluoroacetic acid, or water). It is also interesting to note that compared with the sulfilimine ligand, bis-sulfoxide ligand **8.2** only afforded a trace amount of elimination products under the reaction conditions. Further control experiments show that both of the elimination products (**13.1** and **13.2**) are suitable ligands for the β-arylation reaction, giving comparable yields as using bis-sulfilimine ligand **9**.



Scheme 24. Elimination of Sulfilimine Ligand

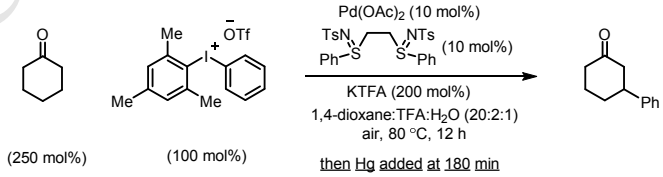
Based on these above features, which are distinct from typically homogeneous palladium catalysis, we hypothesized this new β-arylation reaction might be promoted by palladium nanoparticles or heterogeneous palladium catalysts formed *in situ*. A large number of prior reports have demonstrated the facilitating effects of sulfur-based ligands, acid, and salts for the formation and stabilization of palladium nanoparticle species.[21] Especially, Stahl and coworkers have executed a detailed study and elucidated the role of palladium nanoparticles in the aerobic dehydrogenation reaction of ketones.[22a] In addition, a recent report has also demonstrated that the reductive Heck reaction could also be catalyzed by palladium nanoparticles.[22b] Thus, a series of experiments were devised to probe the involvement of palladium nanoparticles for the new β-arylation conditions.

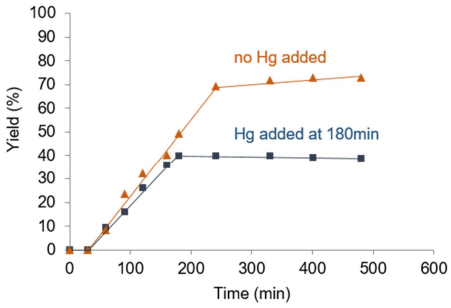
As the precipitation of palladium black was noted during and after the reaction, hot filtration test was first employed to distinguish between a soluble nanoparticle and a heterogeneous catalyst.[23] Parallel reactions were set up under the reaction conditions and the conversion was monitored by gas chromatography (Scheme 25). When the reactions initiated and reached around 20% yield, the reaction mixtures were passed through either a short plug of Celite or a 200 nm PTFE filter to remove over-sized particles. Both reactions afforded dark red filtrates. Subsequently, heat was restored to theses filtrates. Regarding the Celite layer, the heterogeneous filtrand was added to a reaction vessel with newly mixed substrates, additives and solvents, and the reaction was then run at 80 °C for 12 h. We observed that the filtrates from both the Celite and PTFE filtration showed comparable catalytic activity as the standard conditions. However, the filtrand from the Celite layer failed to catalyze the β-arylation reactions with the new mixture of reactants. This hot filtration test suggested that the active palladium catalyst generated during the induction period sustained the solubility, and those heterogeneous species were not responsible for the transformation.



Scheme 25. Hot Filtration Tests

Dynamic lighting scattering (DLS) experiments[24] were also employed to confirm the presence of small particles. When the β-arylation product started to form after the induction period, a sample of the reaction solution was submitted for the scan and indicated to have particles with an average size of 0.9 and 204 nm. In addition, mercury poisoning test has also been carried out. A complete loss of reactivity was observed when excess mercury was added to the reaction during the growth of yield (Scheme 26). Such an observation is consistent with the involvement of palladium nanoparticles, as molecular mercury has been known to amalgamate metal nanoparticles and thus inhibit the catalysis,[25] though the possibility of homogeneous Pd(0)-involved catalysis cannot be completely excluded.[26] Overall, these above experiments, as well as precedents of palladium nanoparticle-catalyzed dehydrogenation and reductive Heck reaction, are consistent with the involvement of nanoparticle catalysts in the proposed pathway of the redox cascade.





Scheme 26. Mercury Test

5 Conclusion

In summary, a palladium-catalyzed redox cascade strategy for direct β-arylation of ketones has been devised through merging ketone dehydrogenation, aryl-halide bond activation, and conjugate addition. Two catalytic systems have been developed. The $Pd(TFA)_2$/P(*i*-Pr)$_3$ system allows use of simple aryl halides as the aryl source. The $Pd(OAc)_2$/bis-sulfinimine system employs diaryliodonium salts as the aryl source, which avoids use of stoichiometric silver salts and tolerates air and moisture. Both conditions show satisfactory substrate scopes and functional group compatibility. These β-arylation methods represent an attractive alternative to the conjugate addition for the synthesis of β-aryl ketones, as they employ readily available saturated ketones as the substrate and avoid the use of strongly basic and/or nucleophilic metal reagents. Future work will be focused on developing more efficient catalytic systems with a broader substrate scope and enabling enantioselective transformations.

6 Experimental

6.1 General procedure for the β-arylation with aryl iodides

An 8 mL vial was charged with $Pd(TFA)_2$ (13.3 mg, 0.1 equiv.), AgTFA (176 mg, 2.0 equiv.), Hexafluoro-2-propanol (1 mL), ketone (1.0 mmol, 2.5 equiv.) and aryl iodide (0.4 mmol). The vial was sealed with a PTFE lined cap and transferred to a glove box. The vial was opened and 1,4-dioxane (1 mL) and P(*i*-Pr)$_3$ (16 μL, 0.2 equiv.) were added under N_2 purging. The vial was then sealed again, taken out of the glove box, and heated in a pie-block at 80^{o}C for 12 hours under stirring. Then, the vial was allowed to cool to room temperature and the mixture was filtered through a small plug of silica gel, eluted with diethyl ether. The solvent of the filtrate was then removed *in vacuo* and flash column chromatography (hexane/ethyl acetate or DCM/methanol) of the residue gave the arylation product.

6.2 General procedure for the β-arylation with diaryliodonium salts

An 8 mL vial was charged with $Pd(OAc)_2$ (9.0 mg, 0.1 equiv.), KTFA (122 mg, 2.0 equiv.), Mesitylaryliodonium salt (0.4 mmol), bis-sulfilimine ligand **9** (24 mg, 0.1 equiv.), TFA (200 μL), ketone (1.0 mmol, 2.5 equiv.), H_2O (100 μL) and 1,4-dioxane (2 mL). The vial was sealed with a PTFE lined cap (no inert atmosphere is required) and heated in a pie-block at 80 °C for 12 hours under stirring. Then, the vial was allowed to cool to room temperature and the mixture was filtered through a small plug of silica gel, eluted with diethyl ether. The solvent was then removed *in vacuo* and flash column chromatography (hexane/ethyl acetate or DCM/methanol) of the residue gave the arylation product.

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