JOC The Journal of Organic Chemistry

Article

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C−C Activation by Retro-Aldol Reaction of Two β-Hydroxy Carbonyl Compounds: Synergy with Pd-Catalyzed Cross-Coupling To Access Mono-α-arylated Ketones and Esters

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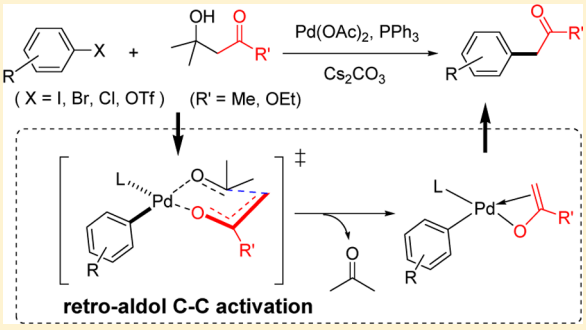
Supporting Information

ABSTRACT: A retro-aldol reaction of two β-hydroxy compounds in synergy with Pd-catalyzed cross-coupling of aryl halides is reported herein, which produces selectively mono-α-arylated ketones and esters in good yields. This reaction is compatible with a broad range of aryl iodides, bromides, chlorides, and triflates and can tolerate an array of functional groups on the aromatic ring. Ready scale-up of this reaction to gram level is applicable without an appreciable decrease in the reaction yield. Furthermore, concise syntheses of biologically active isocoumarin and indole derivatives have been achieved to greatly demonstrate the synthetic value of this retro-aldol reaction. Finally, the reaction mechanism has been discussed on the basis of experimental observations and DFT computational results. A regulated six-membered-ring transition structure has been located for the key retro-aldol C−C cleavage, which constitutes the rate-determining step of a full catalytic cycle. The concept of C−C activation by retro-aldol reaction may also find applications in other fundamental reactions.



1. INTRODUCTION

The integral connection of C−C bonds constitutes the backbone of a diversity of compounds ranging from simple hydrocarbons and basic functionalized organic molecules to more complicated natural products and biologically active compounds and further to tremendous supramolecular assemblies and polymeric materials. Therefore, the formation and activation of C−C bonds are two kinds of transformations that are of fundamental significance to organic chemistry. However, compared with C−C bond formation reactions, which have witnessed great progress and form the foundation of organic chemistry,[1] the reverse process of C−C bond activation has received far less attention. This is largely due to the inertness of C−C bonds and the ensuing difficulty in achieving efficient and practical C−C activation reactions. However, in recent years C−C activation reactions, particularly those promoted by transition metal complexes, have begun to attract increasingly more attention of chemists from across the world.[2] Significant progress has been achieved through the wise implementation of effective promoting strategies, including the release of ring strain,[3] chelation assistance,[4] β-C elimination, etc.[5]

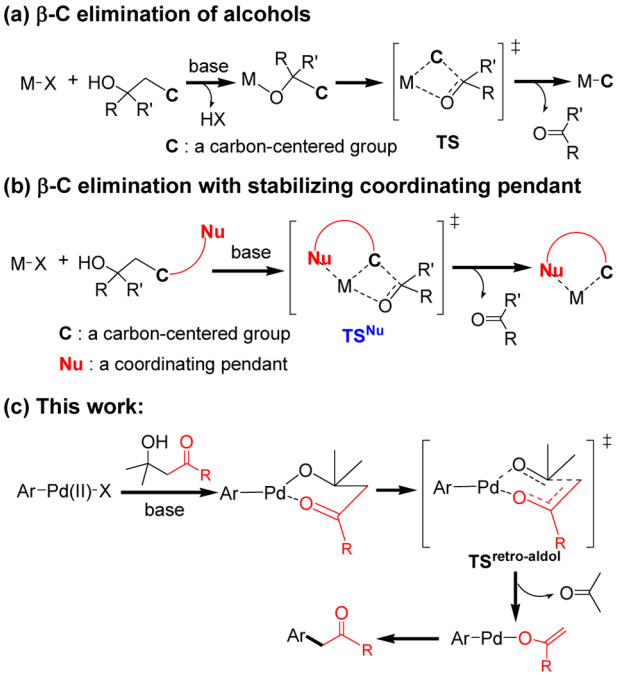
Alcohols are a preferred and versatile class of substrates that are greatly utilized in transition-metal-mediated C−C activation reactions.[6,7] A mechanism of β-C elimination has often been invoked for the key C−C bond cleavage of alcohols, which involves a typical four-membered-ring transition state (Scheme 1a).[8] Organometallic M−C intermediates are thus generated with the release of a ketone byproduct and undergo further reactions. To stabilize the M−C intermediates and avoid possible decomposition pathways resulting from β-H elimination, typically aryl, heteroaryl, and allyl groups have been reported for the carbon-centered group in the literature. However, harsh reaction conditions such as high temperatures and long reaction times are still required for many of the reactions reported. We hypothesized that in the key transition state **TS**, the presence of an additional pendant group in the alcohol that can coordinate to the metal center should effectively assist in stabilizing the key transition state ($\mathbf{TS}^{\mathbf{Nu}}$ in Scheme 1b) and therefore may promote C−C activation in the alcohol.

To explore the feasibility of this hypothesis, a carbonyl pendant group was initially considered. Thus, a β-hydroxy ketone substrate was studied for the activation of the C_α−C_β bond, which is the microscopic reverse process of the classic aldol reaction. Because of the keto−enol tautomerization of the carbonyl group, a potential conformationally regulated six-membered-ring transition state $\mathbf{TS}^{\mathbf{retro\text{-}aldol}}$, reminiscent of the chairlike conformation of cyclohexanes, can be favorably generated in principle (Scheme 1c). Thus, by synergy of this retro-aldol strategy with classic Pd-catalyzed cross-coupling of aryl halides, key aryl-Pd(II) enolate intermediates could be

Received: September 7, 2015

DOI: 10.1021/acs.joc.5b02098
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 1. Transition-Metal-Promoted C−C Activation of Alcohols



obtained, which are known to undergo reductive elimination to deliver α-arylated ketones (Scheme 1c).[9]

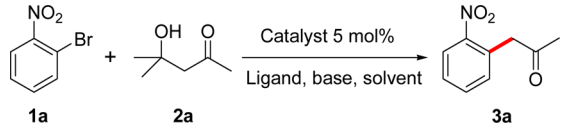
α-Arylated ketones are important synthetic intermediates for biologically active compounds. Therefore, α-arylation of carbonyl compounds has been intensively studied in the past decades by Pd-catalyzed cross-coupling of aryl halides with carbonyl compounds in the presence of a base.[10] Notably in this area, Buchwald, Hartwig, and Miura independently reported elegant pioneering work on the α-arylation of ketones with aryl halides.[11] Following these seminal reports, numerous studies concerning the development and application of α-arylation of ketones,[12,13] aldehydes,[14] esters,[15] amides,[16] nitriles,[17] etc. have been described. However, these reactions are often troubled by over-α-arylation due to the presence of excess α-hydrogens and the higher reactivity of monoarylated carbonyl compounds compared with their parent counterparts. Selective mono-α-arylation of ketones in the presence of additional active hydrogen atoms represents a challenging task. Additionally, the quest for other novel ways to generate metal enolates in a mild and controllable manner would clearly be valuable to the development of new α-arylation chemistry.

In this report, we describe in detail the novel retro-aldol strategy to generate the key Pd enolate intermediate, which in synergy with Pd-catalyzed cross-coupling[18] provides an alternative and efficient method for selective access to mono-α-arylated ketones and esters (Scheme 1c). Because of the stronger acidity of the alcohol than the monoarylated ketone product,[19] overarylation of the monoarylation product can be effectively avoided, and thus, the mono-α-arylation product is selectively obtained with high efficiency. Furthermore, a broad range of aryl electrophiles with diverse electronic properties are compatible with the reaction conditions. The reaction development, substrate scope, and mechanism are elucidated along with applications to the synthesis of biologically active compounds that show the great promise of this reaction for practical applications in organic synthesis.

2. RESULTS AND DISCUSSION

2.1. Reaction Development. Our study commenced with reaction of **1a** with **2a** to produce **3a** via C−C bond cleavage in **2a** to transfer the acetonyl group to the aryl ring (Table 1).

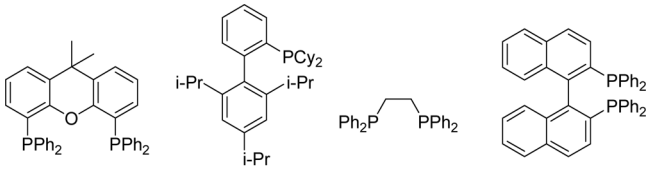
Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3a**

entry	catalyst	ligand	base	solvent	yield (%)[b]
1	$Pd(OAc)_2$	P(*p*-tolyl)$_3$	Cs_2CO_3	toluene	45
2	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	toluene	56
3	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	toluene	30
4	$Pd(OAc)_2$	XantPhos	Cs_2CO_3	toluene	37
5	$Pd(OAc)_2$	XPhos	Cs_2CO_3	toluene	32
6	$Pd(OAc)_2$	BINAP	Cs_2CO_3	toluene	0
7	$Pd(OAc)_2$	DPPE	Cs_2CO_3	toluene	0
8	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	toluene	45[c]
9	$Pd(OAc)_2$	XantPhos	Cs_2CO_3	toluene	20[c]
10	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMSO	<10
11	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	0
12	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	NMP	0
13	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMA	0
14	$Pd(OAc)_2$	PPh_3	K_3PO_4	toluene	17
15	$Pd(OAc)_2$	PPh_3	NaO*t*Bu	toluene	0
16	$Pd(OAc)_2$	PPh_3	Na_2CO_3	toluene	0
17	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	toluene	60[d]
18	**$Pd(OAc)_2$**	**PPh_3**	**Cs_2CO_3**	**toluene**	**80**[e]
19	$Pd(dba)_2$	PPh_3	Cs_2CO_3	toluene	82[e]
20	–	PPh_3	Cs_2CO_3	toluene	0[e]
21	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	toluene	76[e,f]

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), catalyst (0.025 mmol), ligand (0.1 mmol), base (0.75 mmol), and solvent (3 mL) were stirred at 120 °C (oil bath) for 5 h under N_2. [b]Isolated yields after silica gel column chromatography. [c]Ligand (0.05 mmol). [d]**2a** (2.0 mmol). [e]**2a** (3.0 mmol). [f]At 90 °C.



Initial intensive screening of the ancillary ligand (entries 1−7) indicated that P(*p*-tolyl)$_3$ and PPh_3 are efficient for this task with 5 mol % $Pd(OAc)_2$ as the catalyst in toluene, giving the desired **3a** in isolated yields of 45% and 56% (entries 1 and 2). Notably, the use of 20 mol % phosphine ligand (4 equiv relative to the $Pd(OAc)_2$ catalyst) is preferred. When 10 mol % phosphine ligand was used, the reaction yield decreased significantly (entries 8 and 9). It is possible that excess phosphine is needed for reduction of the $Pd(OAc)_2$ precursor to the Pd(0) active catalyst, which reacts with aryl halides to initiate the reaction.

Next, the solvent effect was studied by examining a series of common organic solvents other than toluene, such as DMSO, DMF, NMP, and DMA. These solvents gave the desired product **3a** in less than 10% yield or led to no reaction at all (entries 10−13). Furthermore, a number of bases other than

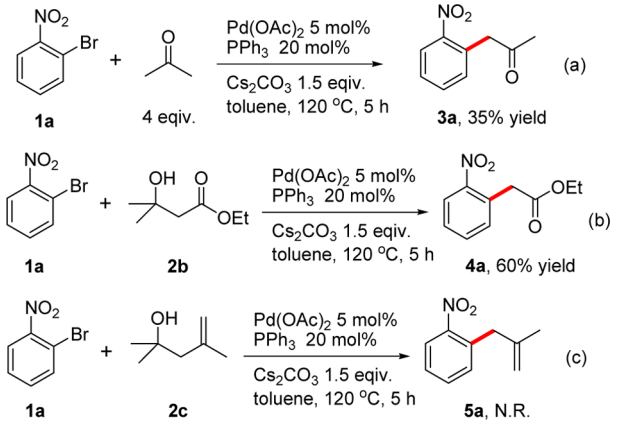
DOI: 10.1021/acs.joc.5b02098
J. Org. Chem. XXXX, XXX, XXX−XXX

Cs_2CO_3 were also examined, including K_3PO_4, NaO*t*Bu, and Na_2CO_3, but gave considerably lower yields compared with Cs_2CO_3 (entries 2 and 14−16). Notably, the amount of **2a** has a great impact on the reaction yield. The reaction of 4 equiv of **2a** with **1a** produced **3a** in a little higher yield of 60% (entry 17). When 6 equiv of **2a** was used, the reaction yield increased greatly to 80% (entry 18). These results suggest that reversible deprotonation of **2a** may be involved before or in the rate-determining step of the catalytic cycle.

No reaction occurred in the absence of Pd catalyst (entry 20). This confirmed the crucial role of the Pd salt in this reaction and makes the S_NAr mechanism of direct attack of the enolate on the aromatic ring unlikely. Additionally, a Pd(0) catalyst gave similar results as $Pd(OAc)_2$ (entry 19), which also supports the hypothesis that the reaction proceeds via initial oxidative addition of the aryl halide to a Pd(0) active catalyst. Finally, the reaction temperature has a substantial effect on the reaction yield. When the reaction was conducted at 90 °C, a yield of 76% was obtained, which was a little lower than the yield at 120 °C (entry 21).

Because of the equilibrium of **2a** with acetone under basic conditions, the reaction may proceed by the direct reaction of acetone with the aryl halide to deliver the α-arylated product **3a**.[13] To clarify this issue, additional experiments were done as shown in Scheme 2. If the reaction of **1a** and **2a** proceeds via

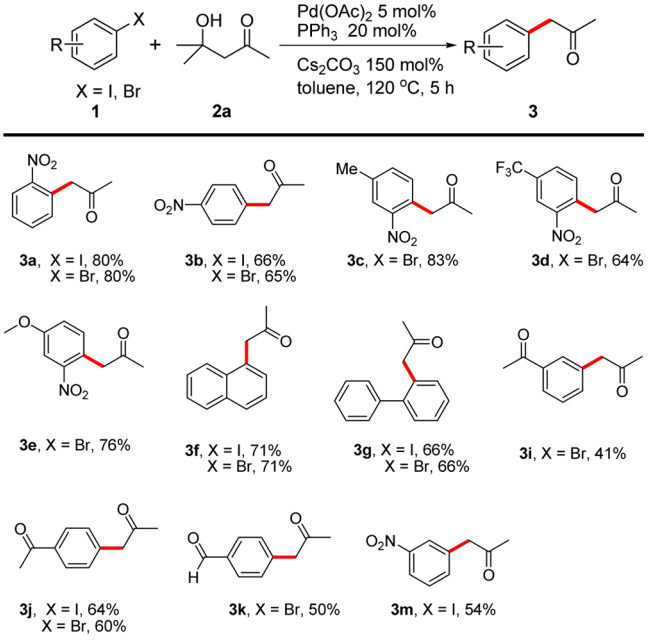
Scheme 2. Reactions of Other β-Hydroxy Carbonyl Compounds and Acetone with 1a



acetone α-arylation, then the direct reaction of **1a** with excess acetone under otherwise identical conditions should produce **3a** in a higher yield or at least a similar yield. However, the fact is against this deduction, as the reaction of **1a** with 4 equiv of acetone under the optimized conditions gave **3a** in a much lower yield of 35% (Scheme 2a). Therefore, **2a** should be more reactive than acetone and represent the major reactant for the formation of **3a**. The observation of the ineffectiveness of Xantphos and BINAP (Table 1, entries 4 and 6) also implies that acetone should not be the major active coupling substrate because previous studies showed that Xantphos and BINAP are very good ligands for promoting the coupling of acetone with aryl halides and sulfonates under similar conditions.[13b] Furthermore, the analogous β-hydroxy ester **2b** reacted in a similar way with **1a** to give mono-α-arylated acetic ester **4a** in 60% yield (Scheme 2b). The yield could further be improved to 71% by using the $Pd(TFA)_2/PCy_3$ catalyst system in xylene. The byproduct arising from acetone α-arylation was not observed in an appreciable amount (<7%). It is known that the α-H atoms of esters are much less acidic than those of ketones (e.g., the pK_a values for the α-H atoms of ethyl acetate and acetone are 29.5 and 26.5, respectively[19]). This means that the reaction should occur directly via retro-aldol reaction of the β-hydroxy ester to generate the Pd enolate of the ester. Furthermore, this also indicates that the generation of the Pd enolate by retro-aldol C−C cleavage is kinetically much faster than the potential generation of acetone enolate by deprotonation of acetone. Otherwise, the acetone α-arylation product should be formed significantly. All of these results strongly indicate that it is the β-hydroxy carbonyl compound that directly participates in the coupling reaction with the aryl halide through $C_\alpha-C_\beta$ bond cleavage and the attachment of the α-carbon of the β-hydroxy carbonyl compound to the aromatic ring. Finally, the reaction of **2c** with **1a** under the optimized conditions led to no reaction at all (Scheme 2c), which underscores the indispensable presence of coordinating carbonyl group to effectively promote this reaction via the concerted six-membered-ring transition structure $\mathbf{TS}^{\text{retro-aldol}}$ (Scheme 1c).

2.2. Substrate Scope. With the optimized reaction conditions in hand, we next studied the substrate scope for this retro-aldol reaction to evaluate its synthetic capability (Table 2). Various substituted aryl bromides were compatible

Table 2. Pd-Catalyzed Retro-Aldol Reaction of β-Hydroxy Ketone 2a with Various Aryl Bromides and Iodides[a,b]



[a]Reaction conditions: **1** (0.5 mmol), **2a** (3.0 mmol), $Pd(OAc)_2$ (0.025 mmol), Cs_2CO_3 (0.75 mmol), PPh_3 (0.1 mmol), and toluene (3 mL) were stirred at 120 °C (oil bath) for 5 h under N_2. [b]Isolated yields using silica gel column chromatography are shown.

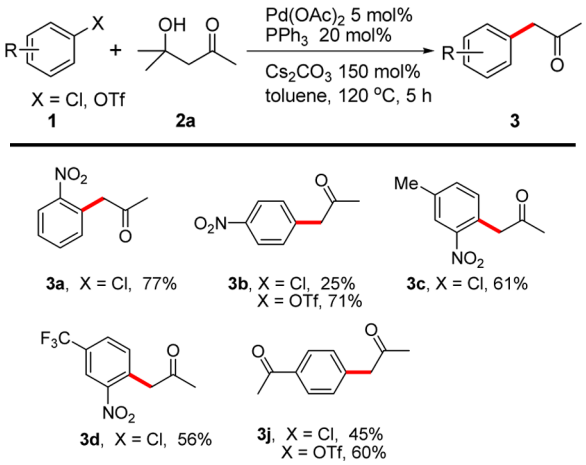
with the optimized reaction conditions. Aryl bromides with alkyl, methoxy, nitro, phenyl, acetyl, aldehyde, and trifluoromethyl groups at the *ortho*, *meta*, and *para* positions were able to give the desired mono-α-arylated ketones in good yields. Notably, the reaction of 4-bromobenzaldehyde bearing a highly reactive aldehyde with **2a** gave the desired product **3k** in 50% yield with the aldehyde group intact. Some multiply substituted aryl bromides were also good substrates for this reaction (**3c**−**e**). Additionally, naphthyl and biphenyl bromide also gave the desired products in good yields (**3f** and **3g**).

DOI: 10.1021/acs.joc.5b02098
J. Org. Chem. XXXX, XXX, XXX−XXX

Aryl iodides reacted with reactivity similar to that of aryl bromides (Table 2). All of the *o*-, *m*-, and *p*-nitro aryl iodides reacted with **2a** to produce the desired α-arylated products in good to satisfying yields (**3a**, **3b**, and **3m**). 1-Naphthyl, 2-biphenyl, and *p*-acetylphenyl iodide reacted with **2a** to give good yields comparable to those for the corresponding bromides (**3f**, **3g**, and **3j**). Heteroaryl iodides such as 2-pyridyl iodide and 2-thiophenyl iodide were also examined but did not give the desired α-arylated products.

In addition, aryl chlorides, which have been shown to be more challenging in ketone α-arylation reactions and other types of cross-coupling reactions, are also compatible with the optimized reaction conditions (Table 3). Good yields were

Table 3. Pd-Catalyzed Retro-Aldol Reaction of β-Hydroxy Ketone 2a with Various Aryl Chlorides and Triflates[a,b]



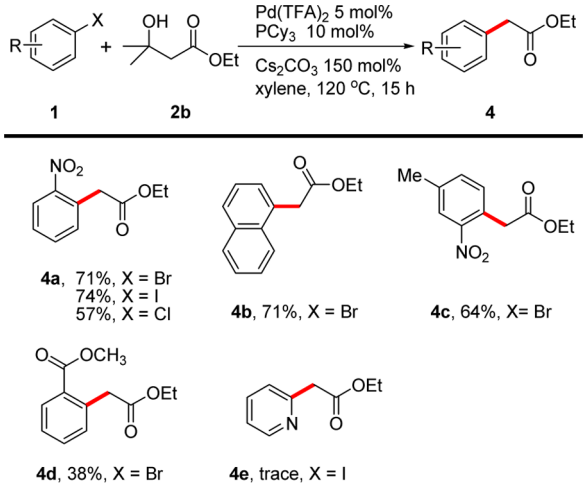
[a]Reaction conditions: **1** (0.5 mmol), **2a** (3.0 mmol), $Pd(OAc)_2$ (0.025 mmol), Cs_2CO_3 (0.75 mmol), PPh_3 (0.1 mmol), and toluene (3 mL) were stirred at 120 °C (oil bath) for 5 h under N_2. [b]Isolated yields using silica gel column chromatography are shown.

generally obtained for the production of **3** from various chlorides. It is noteworthy that *o*-nitrophenyl chloride reacted with **2a** to give a reaction yield similar to those for the corresponding bromide and iodide (please compare the results for **3a** in Tables 2 and 3). Other chlorides gave a little lower yields than the corresponding bromides and iodides. To further expand the substrate scope, aryl triflates were also subjected to the optimized reaction conditions and found to exhibit good reactivity, comparable to those of aryl bromides and iodides. *p*-Nitro- and *p*-acetylphenyl triflates gave the desired products **3b** and **3j** in 71% and 60% yield, respectively, which are comparable to or even higher than the yields for the aryl halide counterparts.

To summarize, the reactivity of various aryl electrophiles with **2a** generally follows the trend of ArI ~ ArBr ~ ArOTf, all of which are a little more reactive than ArCl. This suggests that aryl halide activation is unlikely to be the rate-limiting step of the catalytic cycle. Additionally, it seems that both electronic and steric effects of the substituents play a role in this reaction. It is possible that the steric effect of the substituents influences the approaching and subsequent coordination of the β-hydroxy carbonyl to the Ar−Pd(II)−X intermediate generated from oxidative addition of the aryl halide to Pd(0). Electronic effects could be explained as influencing both the oxidative addition and retro-aldol C−C cleavage steps where aryl group is involved.

In addition to **2a**, **2b** was also studied to react with aryl halides to give α-aryl acetic esters in good yields (Table 4). The

Table 4. Pd-Catalyzed Retro-Aldol Reaction of β-Hydroxy Ester 2b with Aryl Halides[a,b]



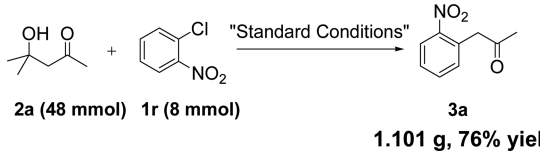
[a]Reaction conditions: **1** (0.5 mmol), **2b** (1.5 mmol), $Pd(TFA)_2$ (0.025 mmol), Cs_2CO_3 (0.75 mmol), PCy_3 (0.05 mmol), and xylene (3 mL) were stirred at 120 °C (oil bath) for 15 h under N_2. [b]Isolated yields using silica gel column chromatography are shown.

reactions were found to perform better using the $Pd(TFA)_2$/PCy_3 catalyst system compared with the $Pd(OAc)_2$/PPh_3 system. These mono-α-arylated esters are also important synthetic intermediates for biologically active compounds. No appreciable amounts of overarylation products were observed, as evidenced by TLC analyses of the crude product mixtures. Additionally, the byproducts arising from acetone α-arylation were also negligible in all cases, which strongly supports the retro-aldol mechanism proposed in this study.

2.3. Applications. The general compatibility of this reaction with various aryl iodides, bromides, chlorides, and triflates and the tolerance of a range of functional groups make this reaction very attractive for organic synthesis. The robust nature of the reaction conditions (which are not sensitive to adventitious moisture or air) further enhances the synthetic value of this retro-aldol reaction. Here we will show the usefulness of this reaction by three additional examples (Schemes 3−5).

As shown in Scheme 3, this reaction could be easily scaled up to gram level. The reaction of 8 mmol of chloro derivative **1r**

Scheme 3. Scale-Up of This Reaction to Gram Level

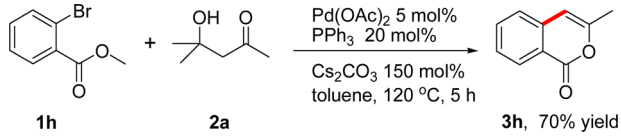


with an excess amount of **2a** delivered the desired product **3a** in 76% yield (1.101 g). It is worth pointing out that the scale-up of this reaction did not reduce the reaction yield appreciably (76% in this case vs 77% in Table 3). This feature is particularly important for practical large-scale applications given the fact that many academic reactions have performed poorly when scaled up.

DOI: 10.1021/acs.joc.5b02098
J. Org. Chem. XXXX, XXX, XXX−XXX

As an interesting special case of this retro-aldol reaction, **1h** with an *o*-ester group directly gave 3-methylisocoumarin (**3h**) in 70% yield (Scheme 4). It is possible that the initially formed

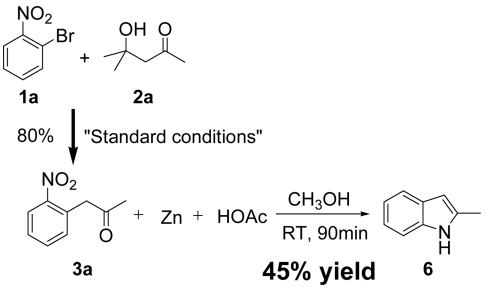
Scheme 4. One-Step Synthesis of a Biologically Active Isocoumarin



α-arylated ketone undergoes subsequent intramolecular nucleophilic substitution at the ester carbonyl group to deliver the annulated product. Coumarin derivatives are important biologically active compounds that are widely used as drug intermediates, luminescent fluorophores, and agrochemicals.

To further showcase the significance of this reaction, it was applied to the concise synthesis of indole derivatives (Scheme 5), which represent a key structural motif in many naturally

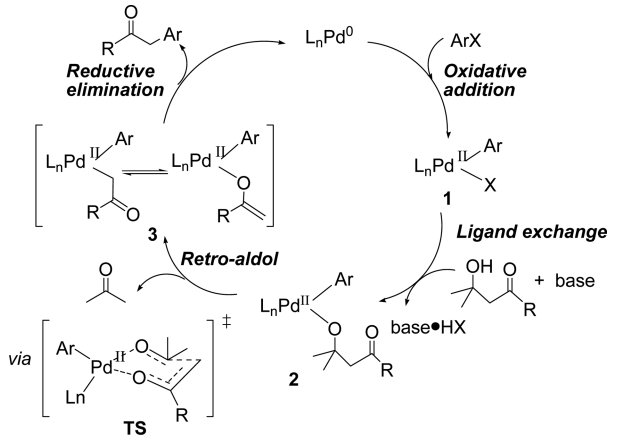
Scheme 5. Concise Two-Step Synthesis of 2-Methylindole



occurring compounds, pharmaceuticals, and biologically active molecules.[20] Typical methods for the synthesis of indole derivatives are the intramolecular hydroamination of *o*-alkynylanilines[21] and transition-metal-catalyzed multistep tandem reactions starting from *o*-haloanilines or *o*-haloarylalkynes.[22] These methods are limited by either the expensive and uncommon reagents or the multistep complex procedures. Here, by means of the retro-aldol reaction developed in this study, the synthesis of 2-methylindole (**6**) was readily achieved in only two steps from readily available and cheap aryl bromide **1a** and alcohol **2a** (Scheme 5). The reaction of **1a** with **2a** to give **3a** in 80% yield was followed by a one-pot tandem reduction of the *o*-nitro group by Zn/HOAc and intramolecular condensation at room temperature for 90 min.[23] This resulted in the formation of **6** in a total yield of 36% in only two steps, which is a streamlined and operationally convenient route from cheap and readily available starting materials. Notably, introducing a simple *methyl* group into biologically active compounds imparts significant changes in the properties such as conformation and bioavailibility of the resulting methylated targets and represents an important and challenging task for drug development.[24]

2.4. DFT Insights into the Reaction Mechanism. On the basis of the observations in section 2.1 and mechanistic proposals for related α-arylation reactions and alcohol C−C activation,[2,8,10] a plausible mechanism for this reaction is suggested as shown in Scheme 6. Oxidative addition of the aryl halide to the Pd(0) active catalyst leads to the formation of intermediate **1**. Subsequent ligand exchange and deprotonation

Scheme 6. Plausible Mechanism for This Retro-Aldol Reaction



of the alcohol are achieved in the presence of base, resulting in the formation of the key aryl-Pd(II) alkoxide intermediate **2**. This ligand exchange step may possibly be reversible and is therefore promoted in the presence of excess alcohol substrate. The key retro-aldol step occurs from **2** to generate aryl-Pd(II) enolate intermediate **3** with the release of acetone byproduct, which was confirmed by GC analysis of the crude reaction mixture.[25] A concerted transition structure **TS** is proposed for this step featuring concurrent C−C bond cleavage and Pd−O bond formation. This retro-aldol C−C cleavage step should be the rate-determining step of the catalytic cycle. Finally, reductive elimination of **3** delivers the desired α-arylated carbonyl product and regenerates the active Pd(0) catalyst.

To provide further evidence supporting this mechanistic proposal, DFT computational studies were conducted in order to locate the key intermediates proposed and to construct a full catalytic cycle of this reaction.[26] As summarized in Figure 1, the catalytic cycle is proposed to comprise three key stages: oxidative addition, retro-aldol C−C cleavage, and reductive elimination. Oxidative addition of the aryl halide to the Pd(0) catalyst is relatively facile, with an activation barrier of 19.2 kcal/mol (**TS1** in Figure 1), leading to the formation of *trans* intermediate **CP1-trans**. Subsequent deprotonation of the alcohol by **CP1-trans** in the presence of base is reversible and forms **CP2**, which is endergonic by 11.9 kcal/mol. This is consistent with the experimental observations that excess alcohol benefits the reaction outcome and our hypothesis. For the retro-aldol reaction to occur, a free coordination site in **CP2** is required, and therefore, a PPh_3 ligand dissociates. This leads to the generation of **CP3** with the stabilizing coordination of carbonyl group. From **CP3**, the key retro-aldol reaction occurs to cleave the C_α−C_β bond, producing the critical (Ar)Pd^{II}(enolate) intermediate **CP5** with concurrent release of acetone. The key transition structure for this step, **TS2**, is shown in Figure 1. It features a six-membered ring, and the geometric parameters are consistent with the electronic structure assigned. In **CP5**, there is stabilizing π coordination of the double bond of the enolate to the Pd(II) center, forming a Pd(II)−oxyallyl-type structure. This retro-aldol C−C cleavage step has an overall activation barrier of 26.2 kcal/mol as calculated from the free energies of low-lying **CP1-trans** and high-lying **TS2**. Finally, reductive elimination from **CP5** delivers the desired product and regenerates the active Pd(0) catalyst. This step is quite facile, with an activation free energy

DOI: 10.1021/acs.joc.5b02098
J. Org. Chem. XXXX, XXX, XXX−XXX

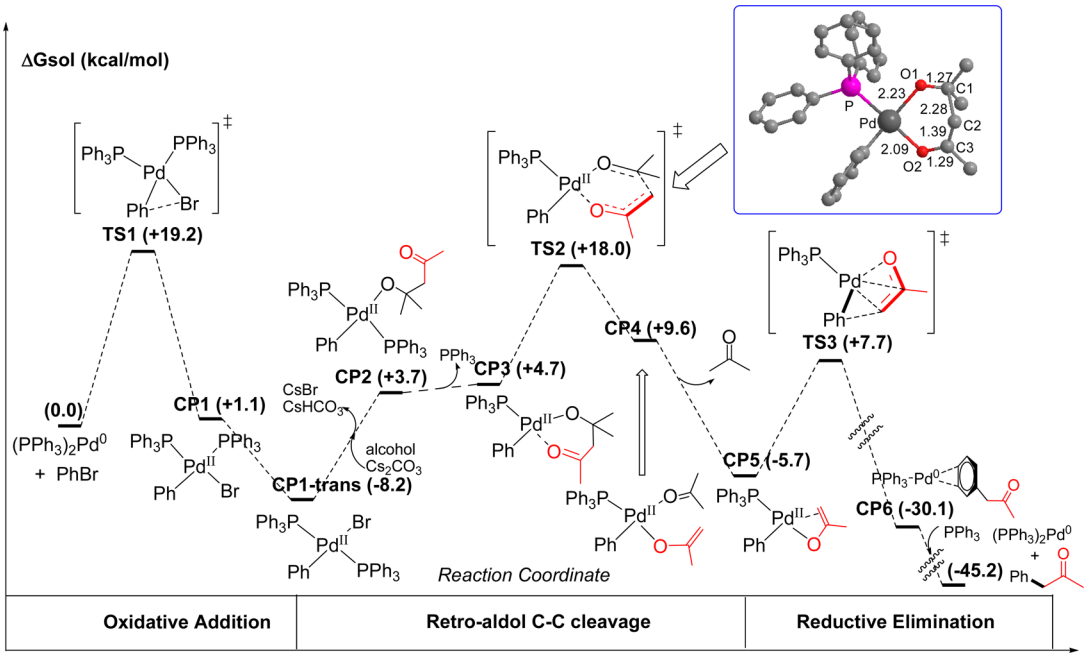


Figure 1. Catalytic cycle calculated for this retro-aldol reaction at the M06/SDD-6-311+G(d,p) level. Values in parentheses are relative free energies in kcal/mol in toluene.

of only 13.4 kcal/mol, and is significantly exergonic by 39.5 kcal/mol.

As shown in Figure 1, retro-aldol C−C cleavage is the rate-determining step in the full catalytic cycle, with an apparent activation barrier of 26.2 kcal/mol, the magnitude of which is in good agreement with the experimental conditions that the reactions were conducted in refluxing toluene. This relatively large activation barrier is contributed mainly by two components: the energy required for deprotonation of the alcohol and the activation energy for the retro-aldol C−C cleavage. These computational results not only provide strong evidence supporting the mechanistic proposal shown in Scheme 6 but also reveal more detailed mechanistic insights into this reaction, including the structures and energetics of the key intermediates and transition states along the reaction coordinate.

3. CONCLUSIONS

A general and efficient Pd-catalyzed coupling of two β-hydroxy ketone or ester compounds with aryl halides and triflates to produce mono-α-arylated ketones and esters in good yields has been reported. This reaction is compatible with various aryl iodides, bromides, chlorides, and triflates and can tolerate an array of useful functional groups on the aromatic ring. It can be readily scaled up to produce the desired α-arylated ketones on a gram level without a significant decrease in the reaction yield. By means of this reaction, biologically active isocoumarin and indole derivatives could be readily prepared from readily available alcohols and aryl halides, which demonstrates the synthetic potential of this reaction. Finally, the mechanism of this reaction has been discussed on the basis of experimental observations and DFT computational studies. The retro-aldol C−C cleavage of β-hydroxy carbonyls is proposed to be the rate-determining step in a full catalytic cycle and involves a key regulated six-membered transition structure to produce the key aryl-Pd(II) enolate intermediate. Further studies on the expansion of the substrate scope and the application of this retro-aldol reaction are ongoing in our group.[27]

EXPERIMENTAL SECTION

General Information. All of the reactants and reagents were used as received from commercial suppliers without further purification. All of the reactions were performed under an atmosphere of N_2 using conventional evacuation/backfill techniques. NMR spectra were recorded on a 400 MHz spectrometer using TMS as the internal standard. GC analyses were performed by comparison with authentic samples.

General Procedure for the Retro-Aldol Reaction of β-Hydroxy Ketone 2a with Aryl Halides or Triflates. Palladium acetate (6.0 mg, 0.025 mmol), PPh_3 (26 mg, 0.10 mmol), aryl halide or triflate **1** (0.5 mmol), and cesium carbonate (244 mg, 0.75 mmol) were added to an oven-dried Schlenk tube equipped with a stir bar. The tube was then sealed, evacuated, and backfilled with nitrogen three times using standard Schlenk techniques. Toluene (3.0 mL) and 4-hydroxy-4-methyl-2-pentanone (**2a**) (348 mg, 3.0 mmol) were sequentially added by syringe at ambient temperature. The resulting mixture was vigorously stirred and heated at 120 °C (oil bath) for 5 h. After the mixture was cooled to room temperature, water (20 mL) was added. The resulting mixture was extracted with ethyl acetate (5 mL × 3). The combined organic layers were then washed with brine, dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (eluting with 10:1−5:1 (v/v) petroleum ether/ethyl acetate) to provide the desired product **3**.[13,28]

1-(2-Nitrophenyl)propan-2-one (3a). Yield: 72 mg, 80%. Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (dd, J = 8.2, 1.3 Hz, 1H), 7.62 (td, J = 7.5, 1.3 Hz, 1H), 7.53−7.44 (m, 1H), 7.30 (dd, J = 7.6, 1.1 Hz, 1H), 4.14 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 203.5, 148.6, 133.6, 133.5, 130.4, 128.4, 125.2, 48.5, 30.0. Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.51; H, 5.10; N, 7.72.

1-(4-Nitrophenyl)propan-2-one (3b). Yield: 58 mg, 65%. Yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 3.87 (s, 2H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.0, 147.2, 141.4, 130.5, 123.8, 50.1, 29.9. Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.58; H, 5.16; N, 7.70.

DOI: 10.1021/acs.joc.5b02098
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1-(4-Methyl-2-nitrophenyl)propan-2-one (3c). Yield: 80 mg, 83%. Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.41 (dd, J = 7.7, 1.1 Hz, 1H), 7.17 (d, J = 7.7 Hz, 1H), 4.08 (s, 2H), 2.45 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 203.8, 148.4, 138.9, 134.3, 133.3, 127.4, 125.6, 48.2, 29.9, 20.8. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.25; H, 5.78; N, 7.22.

1-(2-Nitro-4-trifluoromethylphenyl)propan-2-one (3d). Yield: 79 mg, 64%. Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 4.24 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 202.4, 148.7, 134.4, 134.2, 131.4, 131.0, 129.9, 124.1, 122.6, 121.4, 48.4, 30.1. Anal. Calcd for $C_{10}H_8F_3NO_3$: C, 48.59; H, 3.26; N, 5.67. Found: C, 48.66; H, 3.29; N, 5.64.

1-(4-Methoxy-2-nitrophenyl)propan-2-one (3e). Yield: 80 mg, 76%. Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 2.5 Hz, 1H), 7.23−7.12 (m, 2H), 4.06 (s, 2H), 3.90 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.0, 159.2, 149.0, 134.4, 134.2, 130.0, 128.0, 122.3, 120.3, 109.9, 55.9, 47.9, 29.9. Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.68; H, 5.42; N, 6.56.

1-(1-Naphthyl)propan-2-one (3f). Yield: 65 mg, 71%. Light-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (ddd, J = 6.9, 3.6, 1.8 Hz, 2H), 7.84 (d, J = 8.2 Hz, 1H), 7.54 (ddd, J = 7.2, 3.9, 1.7 Hz, 2H), 7.51−7.45 (m, 1H), 7.42 (d, J = 6.9 Hz, 1H), 4.18 (s, 2H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 206.8, 133.9, 132.2, 131.1, 128.8, 128.2, 128.1, 126.6, 125.9, 125.6, 123.8, 49.2, 28.9. Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.84; H, 6.60.

1-(2-Phenylphenyl)propan-2-one (3g). Yield: 69 mg, 66%. Yellow liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.49−7.16 (m, 9H), 3.72 (s, 2H), 1.96 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 206.5, 142.4, 141.4, 133.1, 131.5, 130.1, 129.2, 128.8, 127.8, 127.6, 127.3, 48.1, 30.1. Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.74; H, 6.73.

3-Methyl-1*H*-isochromen-1-one (3h). Yield: 55 mg, 70%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 8.5 Hz, 1H), 7.69 (td, J = 7.7, 1.3 Hz, 1H), 7.46 (t, J = 8.2 Hz, 1H), 7.35 (d, J = 7.9 Hz, 1H), 6.28 (s, 1H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.9, 154.6, 137.7, 134.7, 129.5, 127.5, 124.8, 120.0, 103.5, 19.6. Anal. Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 75.06; H, 5.05.

1-(3-Acetylphenyl)propan-2-one (3i). Yield: 36 mg, 41%. Yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (dt, J = 7.4, 1.5 Hz, 1H), 7.81 (s, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.44−7.40 (m, 1H), 3.80 (s, 2H), 2.62 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 205.5, 197.9, 137.5, 134.7, 134.2, 129.2, 128.9, 127.2, 50.4, 29.6, 26.7. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.18; H, 6.95. ESI-MS m/z: $[M + H]^+$ calcd 177.1, found 177.1.

1-(4-Acetylphenyl)propan-2-one (3j). Yield: 53 mg, 60%. Yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 3.79 (s, 2H), 2.60 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 205.1, 197.6, 139.5, 136.0, 129.7, 128.7, 50.6, 29.6, 26.6. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.10; H, 6.92.

1-(4-Formylphenyl)propan-2-one (3k). Yield: 40 mg, 50%. Yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 7.88 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 3.83 (s, 2H), 2.23 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.8, 191.8, 141.0, 135.3, 130.2, 130.1, 50.8, 29.7. Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.28; H, 6.35. ESI-MS m/z: $[M + Na]^+$ calcd 185.1, found 185.1.

1-(3-Nitrophenyl)propan-2-one (3m). Yield: 48 mg, 54%. Yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20−8.12 (m, 1H), 8.08 (s, 1H), 7.55−7.52 (m, 2H), 3.88 (s, 2H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.3, 148.4, 135.9, 135.8, 129.5, 124.5, 122.2, 49.7, 29.8. Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.60; H, 5.18; N, 7.68.

General Procedure for the Retro-Aldol Reaction of β-Hydroxy Acetic Ester 2b with Aryl Halides. $Pd(TFA)_2$ (8.0 mg, 0.025 mmol), PCy_3 (14 mg, 0.05 mmol), aryl halide **1** (0.5 mmol), and Cs_2CO_3 (244 mg, 0.75 mmol) were added into an oven-dried Schlenk tube equipped with a stir bar. The tube was then sealed, evacuated, and backfilled with nitrogen three times using standard Schlenk techniques. Xylene (3.0 mL) and **2b** (219 mg, 1.5 mmol) were sequentially added by syringe at ambient temperature. The resulting mixture was vigorously stirred and heated at 120 °C (oil bath) for 15 h. After the mixture was cooled to room temperature, water (20 mL) was added. The resulting mixture was extracted with ethyl acetate (5 mL × 3). The combined organic layers were then washed with brine, dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (eluting with 20:1 (v/v) petroleum ether/ethyl acetate) to provide the desired product **4**.[15,29]

Ethyl 2-(2-Nitrophenyl)acetate (4a). Yield: 74 mg, 71%. Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (dd, J = 8.2, 1.2 Hz, 1H), 7.62 (td, J = 7.5, 1.3 Hz, 1H), 7.50 (td, J = 8.1, 1.4 Hz, 1H), 7.38 (dd, J = 7.5, 0.9 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.04 (s, 2H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 148.9, 133.5, 133.3, 129.9, 128.5, 125.3, 61.3, 39.8, 14.1. Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.60; H, 5.38; N, 6.56.

Ethyl 2-(Naphthalen-1-yl)acetate (4b). Yield: 76 mg, 71%. Light-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44−7.33 (m, 7H), 4.11 (q, J = 7.1 Hz, 2H), 3.62 (s, 2H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.9, 142.5, 141.2, 131.9, 130.3, 130.2, 129.3, 128.2, 127.5, 127.1, 60.7, 39.0, 14.1. Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.80; H, 6.65.

Ethyl 2-(4-Methyl-2-nitrophenyl)acetate (4c). Yield: 70 mg, 64%. Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.41 (d, J = 7.7 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.98 (s, 2H), 2.45 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.1, 148.6, 139.0, 134.2, 133.1, 126.9, 125.6, 61.2, 39.5, 20.8, 14.1. Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.30; H, 5.92; N, 6.16.

Methyl 2-(2-Ethoxy-2-oxoethyl)benzoate (4d). Yield: 42 mg, 38%. Light-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (dd, J = 7.8, 1.3 Hz, 1H), 7.50 (td, J = 7.5, 1.5 Hz, 1H), 7.38 (td, J = 7.7, 1.3 Hz, 1H), 7.28 (dd, J = 7.1, 1.1 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.03 (s, 2H), 3.89 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.5, 167.6, 136.0, 134.7, 132.3, 132.2, 131.0, 127.3, 60.7, 52.0, 40.7, 14.2. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.12; H, 6.08.

Procedure for the Synthesis of 6. Zinc dust (0.131 g, 2 mmol) and glacial acetic acid (0.240 g, 4 mmol) were added to a reaction tube. MeOH (2 mL) and **3a** (0.090 g, 0.5 mmol) were sequentially added by syringe at ambient temperature. The mixture was stirred at room temperature for 90 min. Water (20 mL) was then added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were then washed with brine, dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (eluting with 10:1 (v/v) petroleum ether/ethyl acetate) to provide 2-methyl-1*H*-indole (**6**) as a white solid in 45% yield (0.030 g, 0.227 mmol).

2-Methyl-1*H*-indole (6). Yield: 30 mg, 45%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.58 (d, J = 7.4 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.21−7.10 (m, 2H), 6.27 (s, 1H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.1, 135.1, 129.1, 120.9, 119.7, 110.2, 100.4, 13.7. Anal. Calcd for C_9H_9N: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.56; H, 6.94; N, 10.50.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02098.

^{1}H and ^{13}C NMR spectra for all of the products and DFT computational results (PDF)

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DOI: 10.1021/acs.joc.5b02098
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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This study was supported by the National Natural Science Foundation of China (21472068 and 21202062) and the Natural Science Foundation of Jiangsu Province (BK2012108).

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DOI: 10.1021/acs.joc.5b02098
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