

Pd-Catalyzed Redox Divergent Coupling of Ketones with Terpenols

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 Cite This: ACS Catal. 2021, 11, 6825–6834
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ABSTRACT: Redox diversity is a common and important feature of nature. Herein, a Pd-catalyzed redox divergent coupling of ketones with terpenols has been developed to access α -substituted ketones with varying degrees of unsaturation. The control of oxidation states of the product is facilitated by employing different additives. With the aid of BnOH as an external hydrogen source, a reductive coupling pathway is thermodynamically favored. The use of LiBr as the additive will reduce the reactivity of Pd–H to divert the selectivity toward α , β -unsatuated ketones. By switching the solvent from toluene to chlorobenzene, the active species Pd–H will be fully quenched to enable oxidative coupling. Gram-scale reaction with lower catalyst loading (0.5 mol %) was also accomplished to highlight the practicability of this protocol.



Challenges: Control the Redox State, Terpenols as Alkylating Agents.

Furthermore, detailed experimental studies were carried out to elucidate the reaction mechanism and the factors enabling manipulation of the redox selectivity. This redox divergent coupling protocol provides an important complement for known precedents on Tsuji–Trost allylation of ketones.

KEYWORDS: redox diversity, ketones, terpenols, reductive coupling, oxidative coupling

 ${f R}$ edox metabolism has been recognized as one of the most important metabolic pathways in organisms.¹ With the aid of various redox enzymes, this metabolite will create important bioactive metabolites with different redox states.² For example, as the primary photoreceptor molecule of vision, rhodopsin (also known as visual purple) consists of the protein opsin linked to 11-cis-retinal. A light absorption leads to the isomerization of the 11-cis-retinal group of rhodopsin to its alltrans form and the generation of a nerve impulse.³ Retinal and retinol (vitamin A) can undergo mutual conversion catalyzed by oxidoreductase.⁴ In addition, retinal can be further oxidized to retinoic acid in the presence of ALDH (aldehyde dehydrogenase, Scheme 1a).⁵ With respect to artificial processes, hydrogenation and dehydrogenation are two important methods to change the redox state of compounds. The transition-metal-catalyzed dehydrogenation has achieved rapid development in recent years. However, most of the current research focuses on monoredox transformation. Therefore, it is of great significance to realize the corresponding regulation of redox divergent couplings with artificial catalysts.

 α -Substituted carbonyl compounds are common motifs⁸ in natural products⁹ and can be widely found in most of the top 200 prescription drugs.¹⁰ In the past few decades, many elegant Pd-catalyzed Tsuji–Trost allylation reactions have been demonstrated to produce α -allyl ketones (Scheme 1b).¹¹ One of the general features of this transformation is the

formation of π -allyl palladium intermediates from substrates with leaving groups $(X_1^{12} NR_2^{13} OCO_2R_1^{14} CO_2R_1^{15} OR_1^{16})$ OH,¹⁷ etc.). On the other hand, stereo-, regio-, and chemodivergent strategies are the state-of-the-art in the generation of molecular diversity.¹⁸ Since redox diversity is ubiquitous in nature, we envisioned that the redox strategy might be also employed to expand the diversity of chemical catalytic allylation reactions. As a naturally and industrially abundant feedstock, prenol is a green precursor of terpenoids and their derivatives.¹⁹ Following our long-standing interest in pursuing divergent selective transformations of terpenes,²⁰ we sought to develop a Pd-catalyzed redox divergent coupling of ketones with terpenols (Scheme 1c). The major challenge of this proposal is the construction of C-C bond with varying degrees of unsaturation. It provides an important complement for known precedents on Tsuji-Trost allylation of ketones.

Initially, we chose 1-tetralone (1a) and prenol (2a) as the model substrates to attempt Pd-catalyzed redox divergent coupling. In the presence of $[\eta^3$ -allylPdCl]₂, N-heterocyclic

 Received:
 April 1, 2021

 Revised:
 May 12, 2021



Scheme 1. Redox Diversity-Oriented Synthesis



b) Previous Work: Palladium-Catalyzed Allylic Alkylation of Ketones



c) This Work: Pd-Catalyzed Redox Divergent Coupling of Ketones with Terpenols



carbene ligand (SIPr·HCl), and aniline, three products including reductive alkylated ketone 3a, α_{β} -unsaturated ketone 4a, and normal allylated ketone 6a were obtained in low selectivities. Of note is that aniline could be almost completely recovered, thus suggesting aniline serves as a cocatalyst (Table 1, entry 1). The yield and selectivity decreased dramatically when the reaction was performed under air atmosphere (entry 2). The use of BINAP as ligand gave low conversion of 1a (entry 3). With a view to obtain the reductive coupling product 3a, an external hydrogen source would be required. Therefore, different alcohols including MeOH, ^tBuOH, and BnOH were further examined (entries 4-6). Delightedly, when BnOH was engaged in the reaction, the yield of 3a was significantly increased to 92%, and no other products were detected (entry 6). In contrast, by varying the additives to bromide salts such as KBr, NaBr, and LiBr, 4a turned out to be predominant (entries 7-9). It may be because LiBr could decrease the hydrogenation ability of Pd-H, thereby preventing further hydrogenation of 4a. The employment of 4-aminopyridine as cocatalyst provided a better result (entry 10). The yield of 4a could be improved to 72% at an elevated temperature in the presence of precatalyst $[\eta^3$ cinPdCl]₂ (entry 11). Surprisingly, when PhCl was used as solvent, oxidative coupling product 5a was exclusively obtained (entry 12). The secondary amine piperidine was found to be a better cocatalyst (entry 13). Increasing the amount of MeONa led to a further improvement of the yield of 5a (entry 14).²¹

With the optimized conditions in hand, we subsequently explored the substrate scope of this redox divergent protocol. As demonstrated in Table 2, for reductive couplings, subjecting unsubstituted 1-tetralone **1a** to the standard conditions

Table 1. Optimization for Pd-Catalyzed Redox Divergent Coupling^a

SIPr•HCI (5 mol%)

	1:	$\mathbf{a} = [\eta^3 - \text{allylPdCl}]_2 (2.5)$	mol%) 3a	4a (<i>E/Z</i> >20:1)			
	+	Amine (50 mol MeONa (1.5 e OH Solvent, 70 °C,	9,) Q.) 16 h				
	2	la	5a (<i>E/Z</i> >2	0:1) 6 a			
		yield ^{b} (%)					
entry	amine	additive	sol	3a	4a	5a	6a
1	PhNH ₂		Tol	51	5		4
2 ^c	PhNH ₂		Tol	8		5	
3 ^d	PhNH ₂		Tol			5	15
4	PhNH ₂	MeOH	Tol	78	6		
5	PhNH ₂	^t BuOH	Tol	62	4		1
6	PhNH ₂	BnOH	Tol	92 ^h			
7 ^e	PhNH ₂	KBr	Tol	48	30		
8 ^e	PhNH ₂	NaBr	Tol	53	46		
9 ^e	PhNH ₂	LiBr	Tol	7	36		
10 ^e	4-aminopyridine	LiBr	Tol	5	56		
11 ^{f,g}	4-aminopyridine	LiBr	Tol	4	72 ^h		
12	PhNH ₂		PhCl			52	
13	piperidine		PhCl			68	
14 ^g	piperidine		PhCl			93 ^h	

^{*a*}Conditions: 1a (0.20 mmol), 2a (0.30 mmol), $[\eta^3$ -allylPdCl]₂ (2.5 mol %), SIPr•HCl (5 mol %), MeONa (1.5 equiv), additive (1.5 equiv), solvent (0.6 mL), 70 °C. ^{*b*}Determined by GC-FID analysis of the crude product mixture using mesitylene as internal standard. ^{*c*}Under air atmosphere. ^{*d*}BINAP instead of SIPr·HCl. ^{*e*}MeONa (1.0 equiv). ^{*f*}[η^3 -cinPdCl]₂ instead of [η^3 -allylPdCl]₂, 80 °C. ^{*g*}MeONa (3.0 equiv); ^{*h*}Isolated yield. Tol = Toluene; PhCl = Chlorobenzene.

Table 2. Ketone Scope for Pd-Catalyzed Reductive Coupling



^{*a*}Using (SIPr)Pd(allyl)Cl (2.5 mol%) directly. ^{*b*}BnOH (0.25 eq.). ^{*c*}**2a** (1.0 eq.). ^{*d*}Without BnOH. ^{*e*}MeOH was used as the solvent.

furnished 3a in 92% yield. 4-Me-1-tetralone 1b underwent this alkylation smoothly at 70 °C to provide 3b in 85% yield. Substrates bearing a methoxyl group on the phenyl ring, regardless of its positions, were all well tolerated (3c-e), providing the corresponding ketones in good yields. 7-Me and 7-F on the phenyl ring were also compatible with this process and gave the products (3f-g) in satisfactory yields. However, in the cases of 7-Cl- and 7-Br-derived substrates, dehalogenated products were obtained (see Scheme S1). Furthermore, this transformation could be extended to 1-indanone (1h, five-membered ring) and 1-benzosuberone (1i, sevenmembered ring). Notably, noncyclic ketones were also applicable to the current protocol, and the α -alkylated ketones could be successfully produced in 46%-93% yields (3j-1). Unfortunately, aryl ketones with ester and nitro substituents and pyridine-fused cyclohexanone were not tolerated (see Scheme S1). Additionally, the attempts to induce the enantioselectivity with chiral amine catalysts all failed (see Scheme S2).

The ketone scope for the Pd-catalyzed migratory coupling was further surveyed (Table 3). By adding LiBr, simple ketone 1a could be transformed into the α,β -unsatuated ketone 4a in 72% yield through hydrogen migration. The E-configuration of 4a was determined via two-dimensional nuclear magnetic resonance spectroscopy (NOESY). Substrates possessing electron-donating groups, such as -OMe and -Me, all reacted smoothly to produce the corresponding products in good yields (76-87%) and good selectivities (4b-4f). The fluoro group on the phenyl ring was also well tolerated and gave the ketone 4g in 74% yield with 14:1 E/Z. Moreover, the ketone bearing a 5-membered ring was applicable to the coupling as well albeit with a slightly decreased yield (4h). Notably, the 7membered ring derived ketone was efficiently converted to the corresponding product 4i in 84% yield with excellent selectivity.

Table 3. Ketone Scope for Pd-Catalyzed MigratoryCoupling



^aUsing (SIPr)Pd(cin)Cl (2.5 mol%) directly.

We next set about to assess the scope with respect to the oxidative coupling conditions (Table 4). The model substrate

Table 4. Ketone Scope for Pd-Catalyzed Oxidative Coupling



^a(SIPr)Pd(allyl)Cl (0.5 mol%), MeONa (2.0 eq.). ^bMeONa (1.5 eq.).

1a was converted into the desired product **5a** in 93% yield. It is worth noting that the process could still proceed with high efficiency (90% yield) with the catalyst loading being reduced to 0.5 mol %. Moreover, a range of 1-tetralones with substituents at the 4-, 6-, or 7-positions all worked well in this protocol to give products **5b**-**5f** in 78-94% yields. Remarkably, substrates with either a 5-membered ring or 7membered ring were all compatible with the current conditions and produced the highly unsaturated ketones (**5g**-**i**) in good to excellent yields. In all cases, the products were obtained with exclusive *E*-stereoselectivity, and the configuration was further

Table 5. Terpenol Scope for Pd-Catalyzed Redox Divergent Coupling⁴



^{*a*}Condition A: $[\eta^3$ -allylPdCl]₂ (2.5 mol %), SIPr·HCl (5 mol %), PhNH₂ (50 mol %), PhCH₂OH (25 mol %), MeONa (1.5 eq.), Tol, 70 °C. Condition B: $[\eta^3$ -cinPdCl]₂ (2.5 mol%), SIPr·HCl (5 mol %), 4-Aminopyridine (50 mol %), LiBr (1.5 eq.), MeONa (1.0 eq.), Tol, 80 °C. Condition C: $[\eta^3$ -allylPdCl]₂ (2.5 mol %), SIPr·HCl (5 mol %), Piperidine (50 mol %), MeONa (1.5 eq.), PhCl, 70 °C.





^aDetermined by GC-FID analysis of the crude product mixture using mesitylene as internal standard.

confirmed by two-dimensional nuclear magnetic resonance spectroscopy (NOESY) of product 5a.

Subsequently, we turned our attention toward the scope of various terpenols using the current redox divergent coupling strategy (Table 5). Terpenols bearing two or more isoprene units, such as geraniol (2b), farnesol (2c), and phytol (2d), all proceeded smoothly to deliver the reductive coupling products (3ab-ad) in good yields (78–87%, condition A). Under the conditions B, these substrates were also tolerated, giving the expected products (4ab-ad) in good stereoselectivity but with moderate yields, mainly because 1-tetralone 1a could not be totally consumed. For the oxidative coupling reactions, the number of isoprene units in the terpenol substrates also exhibited no significant influence on the reactive efficiency, and

all of the products (5ab-ad) were produced in good yields (83-91%).

Additional control experiments were further conducted to elucidate the mechanism of this redox divergent coupling protocol. First, the kinetic studies for the couplings under conditions A and B were carried out, and the results are shown in Scheme 2. For reductive coupling, a volcano-shaped correlation was observed between the yield of **5a** and the reaction time (Scheme 2a). In addition, the yield of $\alpha_{,\beta}$ -unsatuated ketone **4a** displayed a moderate positive correlation with the yield of **5a**. A sigmoidal kinetic curve was observed for the desired product **3a** (Scheme 2a). These results suggest that unsaturated ketones **4a** and **5a** are probably the intermediates of the reaction and can be transformed into saturated ketone **3a** through further reduction. For the coupling under

conditions B (Scheme 2b), the nearly flat yield curve of 5a indicates that its formation rate is close to its consumption rate (2-13 h). The yield of α,β -unsatuated ketone 4a increased with the reaction time under conditions B. The comparison of the reaction rate under conditions A and B reveals that the addition of LiBr greatly reduced the catalyst's turnover frequency $[k_{\text{avg}} (3a \text{ vs } 4a) = 0.14 \text{ vs } 0.02 \text{ mmol/h}]$. It is noteworthy that allylated product 6a was not detected at all under conditions B.

The interconversions of these three redox divergent products were subsequently performed (Scheme 3a). The

Scheme 3. Interchange Conversions and Gram-Scale Reaction



^{*a*}Determined by GC-FID analysis of the crude product mixture using mesitylene as internal standard.

oxidative product **5a** could be readily transformed into saturated ketone **3a** and α,β -unsaturated ketone **4a** under conditions D and E, respectively. In addition, **3a** could also be easily obtained in 90% yield from **4a** under condition E (Scheme 3a). Additionally, BnOH has no obvious effect on the interchange conversions. Remarkably, the reductive coupling still took place smoothly to furnish **3a** in gram scale (1.314 g) with 76% yield at very low catalyst loading (0.5 mol %, Scheme 3b).

The amount of MeONa had a significant effect on the selectivity of this redox divergent coupling reaction (Table 6). When the amount of MeONa was increased, the ratio of 3a/4aincreased significantly. This phenomenon indicates that in addition to a base, MeONa likely also serves as a hydrogen source in the process. This speculation was further supported by the isotopic labeling studies (Scheme 4). In the presence of CD_3ONa (2.0 equiv), the reductive coupling of prenol 2a with 1-tetralone 1a delivered deuterio-3a-d in 69% yield with deuterium being scrambled into all branched alkyl carbons (Scheme 4a, top). Under migratory coupling condition B, a similar deuterium scrambling result was observed on deuterio-4a-d (Scheme 4a, middle). The oxidative coupling product 5ad was obtained in 92% yield with 4% deuterium being incorporated at terminal methyl groups (Scheme 4a, bottom). The deuterium incorporation at terminal methyl groups of 3ad, 4a-d, and 5a-d illustrates that enol isomerization of 5a is involved during the reaction (Scheme 4b).

Table 6. Effect of MeONa on the Redox State^a



^{*a*}Determined by GC-FID analysis of the crude product mixture using mesitylene as internal standard.





For the oxidative coupling, an expected prenal 7a and an unexpected aldehyde 7b were simultaneously observed in the absence of 1-tetralone 1a (Scheme 5a). Highly unsaturated aldehyde 7b originates from the self-condensation of prenal 7a.²² This result demonstrates that prenal 7a, formed by β -H elimination, is likely the precursor of 5a, and the resulting Pd-H can be quenched by PhCl to furnish PhH. To further probe the reaction mechanism, a kinetic experiment for the oxidative coupling of 1-tetralone 1a and prenol 2a was carried out. Surprisingly, this coupling proceeded very fast and accomplished within 60 min. Meanwhile, a large amount of benzene was formed, suggesting that PhCl could quench the reductive Pd–H species to prevent further reduction of 5a (Scheme 5b). A small amount of benzene was also detected when NHC-Pd was prepared in situ with MeONa in PhCl (Scheme 5c). It indicates that benzene is partially produced from the reaction of PhCl with MeONa in the presence of palladium.

Several control experiments have been designed to interpret the role of amine during this redox-divergent coupling (Scheme 6). For the formation of ketone 5a, external amine could increase the condensation reactivity in the presence of MeONa (Scheme 6a). Compound 5a cannot be obtained when aniline was solely introduced because the strong base

Scheme 5. Mechanistic Studies for Oxidative Coupling of 1a and 2a





^{*a*}Determined by GC-FID analysis of the crude product mixture using mesitylene as internal standard.

Scheme 6. Control Studies on the Role of External Amine



^{*a*}Determined by GC-FID analysis of the crude product mixture using mesitylene as internal standard.

(MeONa) is crucial for the process. The first transfer hydrogenation of **5a** to α,β -unsatuated ketone **4a** was partially suppressed by the addition of amine (Scheme 6b). However, no negative effect of amine was observed in the second transfer hydrogenation of **4a** to saturated ketone **3a**.

In order to better clarify the role of chlorobenzene in the oxidative coupling of 1-tetralone 1a and prenol 2a, a set of aryl halides including *para*-substituted chlorobenzenes with different electronic properties, bromo- and iodobenzene were selected as the solvents (Scheme 7). All of the reactions led





"Determined by GC-FID analysis of the crude product mixture using mesitylene as internal standard.

to the formation of a large amount of dehalogenated arenes. The solvents exerted a significant influence on the outcome, and PhCl offered the best result.

On the basis of the above observations and previous work, a plausible mechanism for the redox divergent coupling was proposed (Scheme 8). Under the condition C for the oxidative coupling, the catalyst precursor undergoes reductive elimination to generate Pd(0) species **B**. A subsequent oxidative addition of chlorobenzene with B yields phenyl-Pd(II) complex C. The direct ligand exchange of Pd(II) complex C with MeONa forms a MeO-Pd-Ph species which undergoes β -H elimination and reductive elimination successively to form benzene as side product and rebound to Pd(0) species **B**. An alternative deprotonation of prenol 2a with C forms benzene as a byproduct. Meanwhile, it also generates alkoxide-Pd(II) intermediate **D** which undergoes β -H elimination to generate prenal 7a and Pd(II)-hydride E. Pd(0) species B is regenerated from a reductive elimination of E. Highly unsaturated ketone 5a could be produced from the coupling of 1-tetralone 1a with prenal 7a promoted by external amine.

Under the condition B for the migratory coupling, the alkoxide-Pd(II) intermediate D is generated from the deprotonation of prenol 2a with catalyst precursor A (Scheme 8). Then ketone 5a could be obtained via same pathway aforementioned. In the absence of chlorobenzene, Pd(II)-hydride F could be formed reversibly from the oxidation of Pd(0) species B with alcohol (prenol 2a, MeOH, or BnOH). The coordination of Pd(II)-hydride F with ketone 5a gives complex G. A subsequent hydride transfer delivers vinylogous

Scheme 8. Proposed Mechanism for Redox Divergent Coupling



enolate H. The final protonolysis of H with prenol 2a yields the migratory coupling products 4a and regenerates alkoxide-Pd(II) intermediate D. Further reduction of α,β -unsaturated ketone 4a will furnish saturated ketone 3a. The addition of LiBr can prevent further transfer hydrogenation of 4a, likely because LiBr can change the environment around the Pd center, which may have an effect on the activity of the Pd-H species.

In conclusion, a practical strategy for the redox divergent coupling of ketones with terpenols has been developed under palladium catalysis. Manipulation of the selectivity was governed by the choice of different additives. Utilization of BnOH as an additive afforded reductive coupling products with high selectivity, while LiBr additive enabled selective synthesis of migration coupling product. Moreover, using PhCl as solvent, oxidative coupling products can be obtained with high selectivity. A gram-scale reaction has also been demonstrated with lower catalyst loading (0.5 mol %) to highlight the practicality of this protocol. Furthermore, detailed experimental investigations were conducted to interpret the reaction mechanism and the factors enabling manipulation of the redox selectivity. This redox divergent coupling protocol complements traditional precedents of Tsuji-Trost allylation of ketones. Further studies on exploitation of new redox divergent couplings of terpenols are underway in our laboratory.

ASSOCIATED CONTENT

③ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c01488.

Experimental procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Prof. Yong-Gui Zhou (DICP), Prof. Vy M. Dong (UC Irvine), and Prof. Zhi-Shi Ye (DUT) for helpful discussions and manuscript revisions. Financial support from Dalian Institute of Chemical Physics (DICPI201902), Dalian Outstanding Young Scientific Talent, and the National Natural Science Foundation of China (22071239, 21801239) is acknowledged.

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