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Palladium-Catalyzed Intramolecular Reductive Olefin Hydrocarbonation: Benzylic Hydrogen Playing as a New Hydrogen Donor

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A palladium-catalyzed intramolecular hydrocarbonation of unactivated alkenes was achieved, in which toluene is used as hydrogen donor for the first time. The radical transfer hydrogenation is designed and realized basing on the Bond Dissociation Energy (BDE) value. Toluene derivate which is cheap, readily available and easily handled, plays as a new hydrogen donor in radical involved reactions, providing a novel and promising perspective for future reductive reactions.

The clinical success of potential drug candidates shows correlation with the carbon bond saturation as defined by fraction sp^3 -hybridized carbon atoms in the molecule.¹ Consequently, synthetic methods that enable the construction of Csp^3 - Csp^3 bonds could have a major effect on the new pharmaceuticals discovery and development. Alkyl-alkyl coupling reactions are among the most challenging of coupling processes, due in part to the potential β-hydride elimination from intermediates in the catalytic cycle.² In the past decades, substantial progress have been achieved in alkyl-alkyl coupling reactions using unactivated alkyl halides electrophiles to couple with alkyl lithium,³ alkyl Grignard,⁴ alkylznic reagents⁵ and alkylboron reagents⁶ which could be obtained from the functionalization of olefins (Scheme 1, a and b).⁷ Obviously, reductive olefin hydrocarbonation, in which to replace alkylmetallic reagents by olefins coupling with alkyl electrophiles, would present appealing advantages to traditional cross-coupling reactions, such as less expensive substrates, broader substrate availability and better functional group compatibility (Scheme 1, c). However, radical-based versions remain underestimated, probably owing to the prejudice that radical intermediates are difficult to control.

Recently, several breakthroughs on catalytic hydrogenatom-transfer-triggered transformations are achieved to



Scheme 1 Transition-metal-catalyzed alkyl-alkyl construction with unactivated alkyl electrophiles.

overcome the great synthetic challenges. Starting from the pioneering work of Mukaiyama⁸ on hydrofunctionalization reactions, hydrosilanes have been developed into a practical and milder alternative hydride source in manganese, iron, and cobalt catalyzed hydrogenation of alkenes, constructing numerous carbon-heteroatom and carbon-carbon bonds.⁹ It is worth noting that alkenes play the role of nuclephilic radical equivalents or alkylmetallic equivalents in these transformations, exhibiting a novel and promising perspective.¹⁰ However, there are few examples reported on the coupling reaction of unactivated alkyl halides and unactivated alkenes. Very recently, Fu and Liu describe a Nicatalyzed intermolecular reductive olefin hydrocarbonation between olefins and alkyl halides without using any organometallic reagent, in which silane DEMS (Diethoxymethylsilane) is used as hydrogen source and reductant (Scheme 2, a).¹¹ Considering the mechanism, the key unactivated carbon radical intermediate I caught our attentions. The traditional DEMS plays as the radical reductant whose BDE is between 83.7-94.6 kcal mol⁻¹, providing the unactivated Csp^3 -H bond whose BDE is between 95.5-106 kcal⁻¹.¹² According to our previous work on the palladium catalyzed radical reactions, a very similar carbon radical intermediate IV should exist (Scheme 2, b). It is well known that the *benzylic hydrogen of toluene*, whose BDE 88 kcal mol ¹ is closed to the Si-H, is activated easily in the radical initiating

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⁺ Electronic Supplementary Information (ESI) available: Experimental procedures, compound characterization, and copies of ¹H and ¹³C NMR spectra. See DOI: 10.1039/x0xx00000x

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conditions to generate the benzylic radical.¹³ However, almost all the attentions are focusing on the further transformation of benzylic radical, and the leaving *hydrogen radical* is totally neglected. Based on the BDE value, the *hydrogen radical* generated from toluene was potential to be used as a radical reductant instead of Si-H derivates. Herein, we discovered a new Pd-catalyzed intramolecular reductive olefin hydrocarbonation between unactivated alkenes and alkyl halides, firstly using benzylic hydrogen as radical reductant (Scheme 2, b).

We initiated our investigation to test the hypothesis by employing unactivated iodide **1a** as substrate (Table 1). In the beginning, we tried numerous reactions using Pd(OAc)₂/dppf which was reported to generated alkyl radical easily,¹⁴ however, only the iodide atom transfer radical cyclization product was obtained. Encouragingly, with the combination of PdCl₂(dppf) and Cs₂CO₃ in toluene at 130 °C, the desired cyclic

Table 1 Optimization of the reaction conditions ^a						
	(N Ts 1a	[Pd]/Ligand/E toluene, 130 °C,	Base 24 h, N ₂	9		
Entry	Catalyst	Ligand	Base/Additive	Yield (%) ^b		
1 ^{<i>c</i>}	PdCl ₂ (dppf)	-	Cs ₂ CO ₃ /-	18		
2 ^{<i>c</i>}	$PdCl_2(PPh_3)_2$	-	Cs ₂ CO ₃ /-	12		
3 ^c	Pd(PPh ₃) ₄	-	Cs ₂ CO ₃ /-	32		
4	Pd ₂ (dba) ₃	PPh₃	Cs ₂ CO ₃ /-	62		
5	$Pd_2(dba)_3$	PPh₃	Cs ₂ CO ₃ /PhB(OH) ₂	33		
6	Pd ₂ (dba) ₃	PPh_3	$Cs_2CO_3/B(OH)_3$	22		
7	Pd₂(dba)₃	PPh₃	Cs ₂ CO ₃ /H ₂ O	20		
8	Pd ₂ (dba) ₃	Ph ₂ PCy	Cs ₂ CO ₃ /-	85		
9	$Pd_2(dba)_3$	$Cy_3P \cdot HBF_4$	Cs ₂ CO ₃ /-	67		
10	Pd₂(dba)₃	(3-OMe-Ph)₃P	Cs ₂ CO ₃ /-	49		
11	Pd ₂ (dba) ₃	Ph ₂ PCy	K ₂ CO ₃ /-	18		
12^{d}	$Pd_2(dba)_3$	Ph₂PCy	Et₃N/-	11		
13	Pd₂(dba)₃	Ph₂PCy	Cy₂NMe/-	35		
14 ^e	Pd ₂ (dba) ₃	Ph ₂ PCy	Cs ₂ CO ₃ /-	73		
15 ^f	Pd ₂ (dba) ₃	Ph ₂ PCy	Cs ₂ CO ₃ /-	70		
16^g	Pd ₂ (dba) ₃	Ph₂PCy	Cs ₂ CO ₃ /-	57		

^a Reaction conditions: 1a (0.2 mmol), catalyst (5 mol%), ligand (30 mol%), additive (0.6 mmol), Cs₂CO₃ (0.4 mmol), toluene (3 mL), nitrogen atmosphere, 24 h, 130 °C.
 ^b Isolated yield. ^c Catalyst (10 mol%). ^d 1a was recovered in 63%. ^e 100 °C. ^f Ph₂PCy (20 mol%).

reductive product **2a** was isolated in 18%/ie/(entryonite) PdCl₂(PPh₃)₂ did not improve the reaction 1050167/sign1484t $Pd(PPh_3)_4$ could increase the yield to 32%, which implied the ligand PPh₃ might favor this transformation (entries 2 and 3). Furthermore, the combination of Pd₂(dba)₃ and PPh₃ greatly promoted the yield to 62% (entry 4). Employment of some proton donor additives, such as PhB(OH)₂/B(OH)₃/H₂O, did not give positive results (entries 5-7), indicating the proton did not benefit this transformation. Then we evaluated a series of ligands for this reaction (entries 8-10). To our delight, the using of Ph₂PCy increased the yield dramatically to 85%. The screening of base showed that Cs₂CO₃ kept the top status (entries 11-13). By decreasing the reaction temperature to 100 $^{\circ}$ C, the yield of **2a** fell to 73%, indicating the temperature was crucial to this transformation (entry 14). Further adjustment of Ph₂PCy offered no appreciable benefit (entries 15-16). On the basis of these results, the optimal conditions were determined to include Pd₂(dba)₃ combined with Ph₂PCy and Cs₂CO₃ in toluene at 130 °C (entry 8).

With the conditions established above, we next evaluated the substrates scope (Table 2). Firstly, the R^3 groups at

 Table 2 Results of Pd-catalyzed hydrocarbonation of unactivated alkenes^a



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C4 position were investigated. Substrates bearing alkyl group at C4 afforded the corresponding products in declining yields, indicating steric hindrance of R^3 may have a negative effect to the transformation (2b-2d), however, aryl substituents at C4 only produced the 6-endo cyclization/Heck products.¹⁵ Additionally, the substrate $\mathbf{1q}$ (R³ = H) gave an inseparable mixture of reductive product 2q and Heck product 3q (for details see SI, page S23). To our delight, the alkyl substitution at the C5 position generated the desired products in very good yields (2e and 2f), although it might undergo β -hydrogen elimination from the intermediate IV easily (Scheme 2). The C1 position showed excellent compatibility with both alkyl and aryl, providing the reductive products in good yields (2g-2j). The substitution pattern at C2 position was also explored, and the results showed that phenyl, benzyl and sterically hindered isopropyl substitutions did not affect the transformation (2k-2n). Moreover, the bicyclic compound 2o could also be obtained in 65% yield and no d.r. was obtained from the ¹H NMR. To further investigate the substrate scope of this strategy, we employed 4-nitrophenylsulfonyl as the N-protect group, and the desired product 2p was obtained smoothly in 67% yield.

To examine the transformation in the presence of stoichiometric hydrogen donor, substrate **1a** was subjected to the standard conditions with 3.0 equivalents of toluene in trifluorotoluene (Scheme 3). To our delight, this procedure also yielded the target motifs in 41% yield.

Further examination of solvents bearing benzylic hydrogen was also carried out (Table 3). The expected reductive transformation performed perfectly in xylene mixture and mesitylene, **2a** was obtained in good yields (entry 1 and 2). To our delight, the ethylbenzene could also work as the hydrogen donor and afforded **2a** successfully (entry 3), steric hindrance and lower activity of benzylic position might be responsible for



Scheme 3 Studies with stoichiometric PhMe for the reductive strategy.

Table 3 Texting experiments of solvent bearing benzylic hydrogen ^a					
I,	Pd ₂ (dba) ₃ (5 mol%) Ph ₂ PCy (30 mol%)	H			
	N Cs ₂ CO ₃ (2.0 equiv) Ts hydrogen donor, 130 °C, N ₂ , 24 1a	h Ts 2a			
Entry	Hydrogen Donor	Yield (%) ^b			
1	xylene	79			
2	mesitylene	68			
3	ethylbenzene	49			

 a Reaction conditions: 1 (0.2 mmol), Pd₂(dba)₃ (0.01 mmol), Ph₂PCy (0.06 mmol), Cs₂CO₃ (0.4 mmol), solvent (hydrogen donor) (3 mL), nitrogen atmosphere, 24 h, 130 °C. b Isolated yield.

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Scheme 4 Preliminary mechanism exploration.

the relatively declining yield.

In order to obtain direct evidence for the source of hydrogen abstraction, we performed this transformation in toluene-D8 (Scheme 4, a). The deuterated product **2a-D-I** was isolated in 77% yield with 96% deuterium. Apparently, the observation of deuterated ratio supports that the hydrogen atom is totally derived from toluene. A competition deuterium kinetic isotope effect (KIE) study was carried out by employing a mixture of toluene and tolene-D8. The deuterated product **2a-D-II** was isolated in 81% with 22% deuterium, revealing a KIE of 3.5 (Scheme 4, b). The observations show clearly that the activity of benzylic hydrogen is higher compared with benzylic deuterium, which can account for the longer reaction time in eq a, Scheme 4. These results also indicated a rate-determining step might be involved in the hydrogen abstracting from toluene.

In addition, the 1,2-diphenylethane (5) was isolated successfully from the standard reaction system (for data see SI). In order to verify 1,2-diphenylethane was the byproduct of this reaction, we performed this reaction in the absent of substrate (Scheme 4, c). As expected, no compound **5** was detected. This outcome revealed that 1,2-diphenylethane existed as a result of the reductive transformation.

Based on the preliminary investigations and prior works of other groups¹⁶, we propose the following palladium-radical involved mechanism for this reductive olefin hydrocarbonation (Scheme 5). Alkyl radical **6** could be generated from **1a** and Pd(0), which then adds to the alkene moiety to deliver a 5-*exo* cyclization intermediate **7**. Then the intermediate **7** abstracted H atom directly from the benzylic moiety of PhCH₃ to deliver the reduction product **2a**, accompanied with the release of benzyl radical **8**. Simultaneously, palladium iodine species **9** offers another benzyl radical **8'** in the course of regenerating the Pd(0) catalyst. Finally, the 1,2-diphenylethane (**5**) was afforded by coupling of two benzyl radical groups to terminate this conversion. Alternatively, both **8** and **8'** could occur self-coupling to yield 1,2-diphenylethane (**5**).



Scheme 5 Potential mechanism for the reductive cyclization.

In conclusion, we have developed a novel intramolecular hydrocarbonation of unactivated alkenes with unactivated alkyl iodides. The low-cost, readily available and safety **toluene** is employed as the hydrogen donor in radical reactions for the first time. Moreover, more solvents bearing benzylic hydrogen, such as xylene, mesitylene and ethylbenzene could serve as hydrogen-donating uneventfully. This new discovery provides us a promising perspective for future reductive reactions. The preliminary mechanistic hypothesis was established. Basing on the KIE investigation, the rate-determining step was proposed to be the hydrogen abstraction from toluene. Further efforts towards examining mechanistic possibilities and broader applications using toluene as reductant are currently underway.

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