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Palladium-catalyzed atom transfer radical cyclization of unactivated alkyl iodide†

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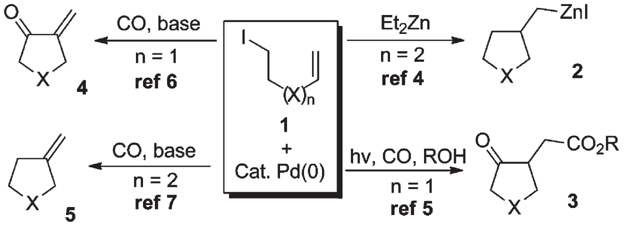
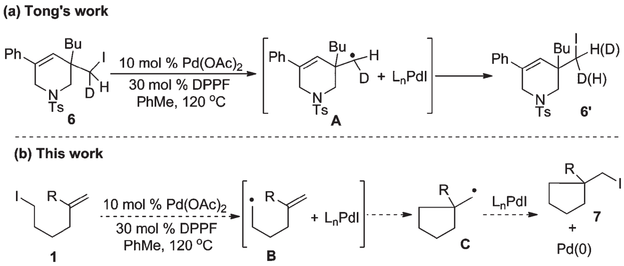
A palladium-catalyzed atom transfer cyclization of unactivated alkyl iodide has been developed. A radical chain mechanism has been proposed for this transformation, which might not involve an alkylpalladium intermediate.

Alkyl halides, especially those with β hydrogen atoms, are a class of challenging substrates for palladium-catalyzed transformations. The challenges mainly stem from the reluctant oxidative addition[1] of aliphatic C–X bond to Pd(0) species and the facile β-H elimination[2] for alkylpalladium intermediate.

Despite the formidable challenges, several new catalyst systems have been established to enable the use of alkyl halides as the starting material.[3] Among those elegant developments, the palladium-catalyzed reactions of alkenyl iodide **1** have received increasing attention (Scheme 1). In 1996, Knochel and co-workers demonstrated that 5-hexenyl iodide can be readily converted into cyclopentylmethylzinc iodide **2** in the presence of catalytic Pd(0) species and a dialkylzinc reagent.[4] For 4-pentenyl iodide, two different protocols have been developed. Ryu and co-workers established a Pd/light system to promote multiple carbonylative cyclization with the assistance of alcohol, resulting in the formation of keto ester **3**.[5] Later, Alexanian and co-workers realized a carbonylative Heck-type reaction of 4-pentenyl iodide to yield α,β-unsaturated ketone **4** when the above mentioned light condition and alcohol additive are removed.[6] Interestingly, when almost identical reaction conditions were employed to 5-hexenyl iodide, an intramolecular Heck-type product **5** was steadily isolated.[7] It should be emphasized that a common hybrid organometallic-radical mechanism has been proposed for the above mentioned transformations. Some metal-catalyzed atom transfer radical cyclization (ATRC) reactions have been reported in the past,[8] including the radical formation mechanism.[9] However, as shown above, subtle changes in reaction conditions may result in very different outcomes, indicating there might be many possible pathways in palladium-catalyzed transformations of unactivated alkyl iodide.



Scheme 1 Pd(0)-catalyzed transformations of alkenyl iodides.



Scheme 2 Design plan for Pd(0)-catalyzed ATRC of alkenyl iodide.

Recently, both the Tong[10] and Lautens[11] groups have described the carboiodination of alkenes and the Houk group reported the theoretical study of Pd(0)-catalyzed carbohalogenation of alkenes.[12] During Tong's study on Pd(0)-catalyzed iodide atom transfer cyclization of (*Z*)-1-iodo-1,6-diene, they have found that the Pd(0) catalyst (10 mol% Pd(OAc)$_2$ and 30 mol% DPPF) may transfer single electron to alkyl iodide **6** to form alkyl carbon-centered radical **A** and L$_n$PdI species, responsible for the observation of stereochemistry loss in **6** (Scheme 2a). These findings lead us to envision that this palladium catalyst system might be also workable toward 5-hexenyl iodide to form radical intermediate **B** which would be followed by 5-*exo* addition and iodide transfer to yield cyclic product **7** (Scheme 2b). Herein we report a Pd(0)-catalyzed iodide atom transfer radical cyclization (ATRC) of alkenyl iodide (Scheme 2b). To the best of our knowledge, this is the first example related to Pd(0)-catalyzed ATRC of unactivated alkyl iodide.[13]

To validate our hypothesis outlined in Scheme 2, alkenyl iodide **1a** was subjected to the conditions of Pd(OAc)$_2$ (10 mol%), DPPF (30 mol%) in toluene at 120 °C (Table 1). To our delight,

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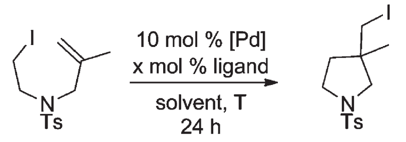
Table 1 Optimization of reaction conditions[a]

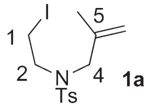
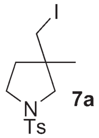
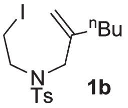
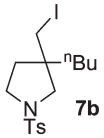
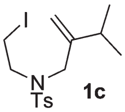
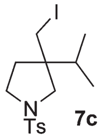
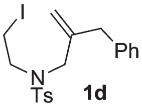
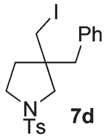
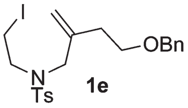
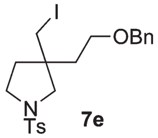
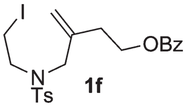
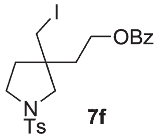
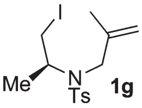
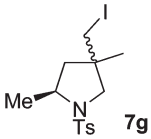
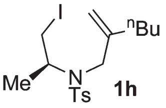
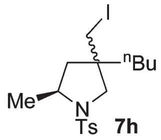
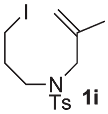
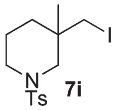
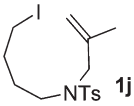
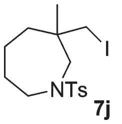


1a **7a**

Entry	[Pd]	Ligand-x	Solvent	*T* (°C)	Yield[b]
1	$Pd(OAc)_2$	dppf-30	PhMe	120	54%
2[c]	$Pd(OAc)_2$	P^tBu_3-60	PhMe	120	Trace
3	$Pd(OAc)_2$	PPh_3-60	PhMe	120	13%
4	$Pd(OAc)_2$	binap-30	PhMe	120	48%
5	$Pd(PPh_3)_4$	—[d]	PhMe	120	49%
6	$Pd_2(dba)_3$	dppf-30	PhMe	120	47%
7	—[e]	dppf-30	PhMe	120	ND[f]
8	$Pd(OAc)_2$	dppf-30	DMF	120	ND[f]
9	$Pd(OAc)_2$	dppf-30	DCE	120	ND[f]
10	$Pd(OAc)_2$	dppf-30	Xylene	120	36%
11	$Pd(OAc)_2$	dppf-30	MeCN	120	32%
12	$Pd(OAc)_2$	dppf-30	PhH	120	Trace[g]
13	$Pd(OAc)_2$	dppf-30	PhMe	130	82%
14	$Pd(OAc)_2$	dppf-30	PhMe	150	62%
15	$Pd(OAc)_2$	dppf-20	PhMe	130	66%
16	$Pd(OAc)_2$	dppf-40	PhMe	130	78%

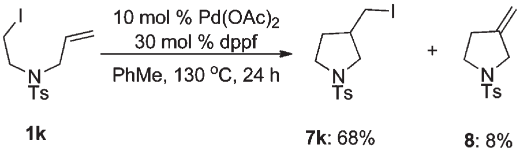
[a] Reactions were carried out using 0.2 mmol **1a**. [b] Isolated yield. [c] $P^tBu_3 \cdot HBF_4$ + K_2CO_3 were used. [d] Without ligand. [e] Without palladium. [f] ND = not detected. [g] 92% of **1a** was recovered.

Table 2 Pd(0)-catalyzed IATC[a]

Entry	Substrate	Product	Yield[b]
1	 **1a**	 **7a**	82%
2	 **1b**	 **7b**	70%
3	 **1c**	 **7c**	68%
4	 **1d**	 **7d**	35%
5	 **1e**	 **7e**	72%
6	 **1f**	 **7f**	58%
7	 **1g**	 **7g** (d.r. = 4:1)	81%
8	 **1h**	 **7h** (d.r. = 10:1)	76%
9	 **1i**	 **7i**	NR[c]
10	 **1j**	 **7j**	NR[c]

[a] Reactions run 0.05 M in PhMe at 130 °C with the use of $Pd(OAc)_2$ (0.02 mmol, 4.6 mg) and dppf (0.06 mmol, 34 mg) for 24 h. [b] Isolated yield. [c] No reaction.

iodide atom transfer cyclization (IATC) product **7a** was indeed isolated in the yield of 54% (Table 1, entry 1). An extensive screening of catalysts showed that other palladium catalyst systems were also workable albeit with decreased efficiency (Table 1, entries 2–6), no product was formed without palladium source (Table 1, entry 7). The solvent screening proved that toluene was the optimal one (Table 1, entries 8–11). To our delight, the yield was improved to be 82% when the reaction was conducted in a closed vessel at 130 °C (Table 1, entry 13). Higher reaction temperature, for example 150 °C, was found to be negative in terms of yield (Table 1, entry 14). It was found that the quantity of DPPF was an important factor, but its influence on the product yields is not monotonous (Table 1, entries 15–16).

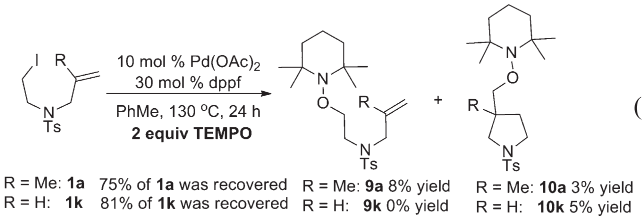


1k **7k**: 68% **8**: 8% (1)

With the optimized conditions in hand, we then turned our attention to the reaction scope and the results are summarized in Table 2. In general, the palladium-catalyzed IATC can be efficiently achieved with a wide range of 5-hexenyl iodides, delivering alkyl iodide derivatives **7** in moderate to high yields. Substitution on C5-position shows wide tolerance; even the bulky isobutyl group is compatible in terms of reaction rate and yield (Table 2, entry 3). An oxygen-functionalized tether could also be introduced into C5-position (Table 2, entries 5 and 6). However, substrate **1d** with benzylic substituent at C5-position exhibits relative worse reactivity, leading to 35% isolated yield (Table 2, entry 4). The transformation is also tolerant with 2-substituted substrate, such as **1g** and **1h**, delivering the corresponding IATC products **7g** and **7h** in the yields of 81% and 76%, respectively

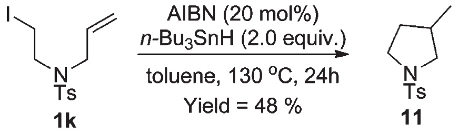
(Table 2, entries 7 and 8). Unfortunately, the six- and seven-member ring could not be obtained in this reaction (Table 2, entries 9 and 10). Interestingly, the reaction of the substrate **1k** with no substituent at C5-position afforded not only IATC product **7k** in 68% yield, but also Heck-type byproduct **8** in 8% yield (eqn (1)).

To investigate the mechanism of the Pd(0)-catalyzed IATC, two deuterium-labeled substrates **(*Z*)-1k-D** and **(*E*)-1k-D** were tested under the optimized conditions. The same product **7k-D**[14] was obtained from either **(*Z*)-1a-D** or **(*E*)-1a-D**, with similar yields.



(2)

These outcomes strongly indicated that the IATC might involve radical intermediate(s). Thus, TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) was added into the optimized conditions to probe the potential intermediacy of carbon-centered radicals. Indeed, the reaction of substrate **1a** with 2 equiv of TEMPO yielded adducts **9a** and **10a** in the yields of 8% and 3%, respectively (eqn (2)). While substrate **1k** was tested under the same conditions, only **10k** was isolated in the yield of 5% (eqn (2)). No detection of compound **9k** implied that the corresponding 5-*exo* radical addition might be a fast step due to less steric hindrance.

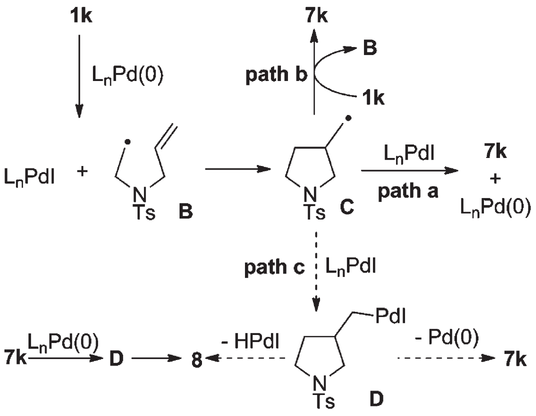


(3)

If this process is a radical mechanism, we expect this reaction should be promoted by the normal radical cyclization conditions. So we tested the substrate **1k** in the presence of AIBN (20 mol%) and *n*-Bu$_3$SnH (2.0 equiv.), and compound **11** was obtained in 48% yield (eqn (3)). This result implied that this kind of cyclizations could be realized by radical process.

On the basis of these observations, our proposed mechanism is depicted in Scheme 3, although the detailed mechanism for this process remains uncertain at this stage. Single-electron transfer between Pd(0) catalyst and substrate **1k** produces LnPdI species and a carbon-centered free radical **B**. The latter undergoes intramolecular radical addition to form a second carbon-centered free radical **C**. According to the related findings on metal-catalyzed atom transfer radical cyclization,[15] intermediate **C** is believed to abstract iodide atom from LnPdI species to deliver the IATC product **7k** with concomitant regeneration of the catalyst (Scheme 3, path a). Alternatively, intermediate **C** might abstract iodide atom from substrate **1k**, resulting in the formation of product **7k** and intermediate **B** (Scheme 3, path b). For path b, Pd(0) catalyst just serves as a radical initiator.[16]

Besides these two possible reaction pathways, a hybrid organometallic-radical mechanism should be considered (Scheme 3, path c), as has been reported in previous work.[4–7] Interception of intermediate **C** by the LnPdI species might lead to the formation of alkylpalladium intermediate **D**. Given the fact that the alkylpalladium complex rapidly undergoes β-H elimination, intermediate **D** barely has a chance to reductively eliminate alkyl iodide to generate **7k**, indicating that the Pd(0)-catalyzed ATRC might not proceed *via* the hybrid organometallic-radical mechanism, *i.e.* path c is unlikely. Alternatively, intermediate **D** could be generated *via* oxidative addition of **7k** to Pd(0) species, which undergoes β-H elimination to yield the Heck-type[17] byproduct **8** and IPdH species. Without the assistance of base additive, IPdH species can not regenerate Pd(0) catalyst, rendering compound **8** being isolated only in 8% yield.[18]



Scheme 3 Proposed mechanism.

In summary, we have found that the combination of 10 mol% Pd(OAc)$_2$ and 30 mol% DPPF is an efficient catalyst system to promote ATRC of unactivated alkyl iodide. A radical chain mechanism has been proposed for this transformation on the basis of the fact that TEMPO additive can readily trap the involved carbon-centered radicals. A proposal has also been suggested to account for the isolation of Heck-type byproduct **8**, which might provide a complementary understanding for hybrid organometallic-radical mechanism. Further studies of the reaction mechanism and employment of this catalyst system to other types of unactivated alkyl iodides are currently underway and will be reported in due course.

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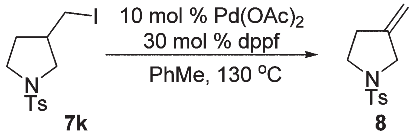
18 Indeed, the reaction of **7k** under the optimized conditions afforded compound **8** in the yield of 7%. When 2 equiv triethylamine was added as base, the yield of **8** was improved to be 85%



7k **8**

without base: 7% yield
with 2 equiv NEt$_3$: 85% yield