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Palladium-Catalyzed Carbocyclizations of Unactivated Alkyl Bromides with Alkenes Involving Auto-Tandem Catalysis

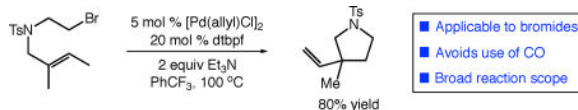
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Abstract

The development of a general catalytic system for the palladium-catalyzed carbocyclization of unactivated alkyl bromides with alkenes is described. This approach uses a commercially available bisphosphine ligand, and avoids the use of carbon monoxide atmosphere present in prior studies involving alkyl iodides. Detailed mechanistic studies of the transformation are performed, which are consistent with auto-tandem catalysis involving atom-transfer radical cyclization followed by catalytic dehydrohalogenation. These studies also suggest that reactions involving alkyl iodides may proceed through a metal-initiated, rather than metal-catalyzed, radical chain process.

Graphical Abstract



INTRODUCTION

The Mizoroki-Heck reaction is a premier method for catalytic C–C bond construction across a wide range of synthetic contexts.¹ The reactions commonly use aryl or vinyl halides (or sulfonates) as substrates in inter- or intramolecular cross couplings with alkenes. Extension to widely available alkyl electrophiles containing β -hydrogens has been a longstanding challenge in catalysis.² Two issues to be addressed include the relative reluctance of sp^3 -hybridized versus sp^2 -hybridized electrophiles to participate in oxidative addition³ and the susceptibility of alkylmetals to β -hydride elimination.⁴ Despite early studies demonstrating potential cross couplings with limited scope (e.g., styrenes),⁵ the need for a general solution to this problem remained.

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ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.

In recent years, several studies have demonstrated the ability of a variety of metals to catalyze formal alkyl-Mizoroki-Heck reactions, including Ti, Co, Ni, Au, and Pd. The Ti- and Co-catalyzed processes significantly increased the substrate scope of these carbocyclizations, but required highly reducing alkyl-magnesium reagents for catalyst turnover, limiting their broader use in the synthesis of complex targets.⁶ Recent studies involving Ni, Au, and Co catalysts provided useful Mizoroki-Heck-type reactions of unactivated alkyl halides that proceed under mild conditions.⁷ Pioneering work from the Fu group detailed the first examples of Pd-catalyzed alkyl-Mizoroki-Heck-type reactions to construct cyclopentanes with primary alkyl halides and terminal alkenes (Figure 1).⁸

Our prior studies towards a general, Pd-catalyzed carbocyclization encompassed both primary and secondary alkyl halides and a diverse range of alkenes.⁹ However, a major limitation was the requirement of alkyl iodides as substrates. Furthermore, reactions involving primary alkyl iodides required a CO atmosphere (10 atm) to maximize reaction yield (Figure 1). Thus, while the substrate scope was attractive, these system limitations served to hinder potential applications.

Another major question that remained was the role of the metal catalyst in these carbocyclizations. Fu demonstrated the presence of alkylpalladium(II) intermediates formed from S_N2-type oxidative addition.⁸ While our initial mechanistic studies provided evidence for radical intermediates in reactions involving alkyl iodides, it was unclear whether these reactions were *palladium-initiated*, *innate chain reactions* or *palladium-catalyzed* transformations.¹⁰ These questions have important consequences regarding the potential for catalyst control in reaction development.

Herein, we report a second-generation catalytic system for the palladium-catalyzed carbocyclization of unactivated alkyl halides with alkenes that significantly increases the reaction scope and practicality of the transformation. This new catalytic process constitutes the first general carbocyclization of alkenes involving unactivated alkyl bromides. Importantly, this system also removes the requirement for CO atmosphere present in our previous studies. The mechanistic analysis of the hybrid organometallic-radical reactivity involved uncovered some intriguing insights into these reactions, consistent with an auto-tandem catalysis pathway for the present reaction, while suggesting that reactions involving alkyl iodides may proceed via metal-initiated, innate chain processes.

RESULTS AND DISCUSSION

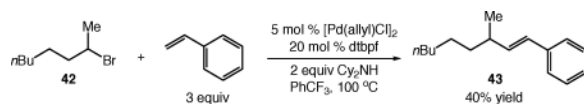
Our studies commenced with the carbocyclization of unactivated alkyl bromide **1** (Table 1). The use of catalytic systems previously developed in our laboratory for the carbonylation of alkyl bromides (entry 1)¹¹ or aromatic C–H alkylation using alkyl bromides (entry 2)¹² did not lead to successful carbocyclization. The ligand screen was then expanded to bidentate ferrocenyl ligand systems, as this class of ligands has proven useful in previous carbocyclizations involving alkyl electrophiles. The dtbdppf ligand recently used by Gevorgyan in an endo silyl-methyl Mizoroki-Heck-type process¹³ provided carbocyclization product **2** in poor yield (entry 3). The use of 1,1'-bis(dialkylphosphino)ferrocene ligands dcypf or dippf failed to improve reactivity (entries 4–5). Switching the ligand to 1,1'-bis(di-

tert-butylphosphino)ferrocene (dtbpf) provided a promising result, with a significantly increased reaction yield (33%, entry 6). Substituting [Pd(allyl)Cl]₂ as precatalyst (entry 7) and Et₃N as base (entry 8) further increased the yield and selectivity of the reaction. The use of trifluorotoluene as solvent further increased the reaction efficiency by limiting reductive dehalogenation (entry 9). Interestingly, the use of the prepared Pd(dtbpf)Cl₂ as catalyst was less successful (entry 10).

With optimized conditions in hand, a comparison of the previously reported carbocyclizations of alkyl iodides to the current system using alkyl bromides was performed (Table 2). Each carbocyclization proceeded with similar or increased yields across a range of primary and secondary alkyl halides with diverse alkene substitution, as compared to our previous report.⁹ Importantly, the carbocyclizations of primary alkyl bromides using the second-generation catalytic system avoids the 10 atm CO previously required in cyclizations of alkyl iodides, increasing the practicality of the current system.¹⁴

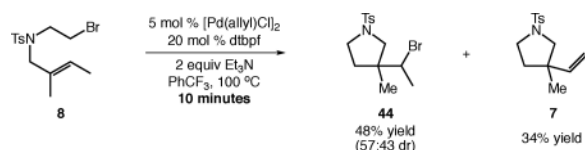
We next studied the carbocyclization of a range of substrates to assess the full reaction scope (Table 3). The 5-exo cyclizations of primary alkyl bromides were successful with di- and trisubstituted alkenes (entries 1–3), styrenes (entry 4), and terminal alkenes (entry 5). Simple substitution of the tether unit provides access to important heterocycles (e.g., pyrrolidines, tetrahydrofurans) or carbocycles, as desired. Importantly, this approach is not limited to five-membered ring synthesis, as demonstrated by the 6-exo cyclizations of entries 6–8. Secondary alkyl bromides also undergo efficient cyclization, as demonstrated by the 5-exo and 6-exo cyclizations of substrates **38** and **40**, respectively (entries 9–10).

In addition to carbocyclization, the present system is also effective in promoting intermolecular couplings. As an initial demonstration, we have studied the intermolecular cross coupling of secondary alkyl bromide **42** with styrene (eq 1), which delivers product **43** in moderate yield (40% by ¹H NMR analysis). Previous reports of such palladium-catalyzed, intermolecular couplings required the use of alkyl iodides as substrates, used directly or formed in situ via Finkelstein reactions with iodide salts.¹⁵



(1)

To glean insight into the reaction mechanism of the carbocyclization, we began by attempting to isolate intermediates at short reaction times and low conversion. Surprisingly, the reaction of primary alkyl bromide **8** proceeded to near full conversion after only 10 minutes, and the major product was alkyl bromide **44**—the product of atom-transfer radical cyclization (ATRC, eq 2). In addition, the expected carbocyclization product **7** was isolated in 34% yield.



(2)

A number of other representative substrates were studied to determine the role of ATRC in these carbocyclizations (Table 4). In order to maximize the potential for observing ATRC products, these reactions were performed at a slightly lower temperature (80 °C) with a decreased amount of base added (0.5 equiv). In each case, the formation of the ATRC product was significant. The low yield observed in the production of tertiary ATRC product **47** is attributed to the high propensity towards elimination to the alkene product. Interestingly, these results represent a rare example of ATRC processes involving unactivated alkyl halides,¹⁶ and the first involving unactivated alkyl bromides.

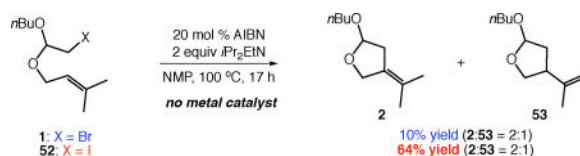
Preliminary mechanistic investigations of the carbocyclizations of alkyl iodides were consistent with the presence of free radical intermediates in the reaction pathway.⁹ Two major mechanistic questions remained: 1) whether or not the carbocyclizations of alkyl iodides and alkyl bromides proceeded via the same pathway, and 2) the role of the palladium as either an initiator or a catalyst.

The reactions of alkyl bromide **17** and alkyl iodide **15** afforded bicyclic product **16** in 77% and 48% yield, respectively (Table 5, entries 1–2). Reaction of alkyl bromide **17** in the presence of single electron transfer inhibitor 1,4-dinitrobenzene resulted in a complete return of starting material (<2% conversion, entry 3). On the other hand, the reaction of alkyl iodide **15** went to complete conversion, and **16** was actually formed in higher yield (78%, entry 4). Similar results were observed upon the addition of persistent radical TEMPO. The reaction of alkyl bromide **17** proceeded with low conversion, and neither the ATRC nor the Heck-type product were observed (entry 5). Conversely, the reaction of the corresponding iodide delivered **16** in moderate yield with complete consumption of starting material.

We next studied the dehydrohalogenation of ATRC intermediates **48** and **51** in a similar manner (Table 6). Both substrates underwent high yielding dehydrohalogenation under the reaction conditions (entries 1–2).¹⁷ In the presence of 1,4-dinitrobenzene, the reaction of alkyl bromide **48** was significantly inhibited, while the dehydrohalogenation of iodide **51** was unaffected (entries 3–4). In the absence of metal catalyst or ligand, no dehydrohalogenation of bromide **48** occurred, while the elimination of iodide **51** still proceeded to a significant extent (entries 5–6).

ATRC reactions may be initiated by transition metals or other simple radical initiators. We hypothesized that particularly in the case of alkyl iodides, palladium could be functioning as an initiator for an innate chain reaction, rather than as a catalyst. Alkyl iodides are known to participate in ATRC with alkenes in chain fashion.¹⁸ The carbocyclizations of alkyl bromide **1** and iodide **52** were studied *in the absence of palladium* using 20 mol % AIBN as a

representative radical initiator (eq 3). While the reaction of alkyl bromide **1** proceeded with low conversion, a good yield of the Heck-type products **2** and **53** was achieved using alkyl iodide **52**.



(3)

A plausible mechanism consistent with our observations is depicted in Scheme 1. We hypothesize that palladium is serving as a true catalyst, rather than a simple initiator, in the carbocyclization of unactivated alkyl bromides. The catalytic cycle commences with a bromine atom abstraction by the palladium catalyst, producing a carbon-centered radical and a putative palladium(I) intermediate. Facile radical cyclization forms the desired C–C bond and generates a new radical intermediate. At this stage, the ATRC product **48** is formed by bromine atom transfer from the catalyst.

Following the formation of the ATRC product, the palladium catalyst reengages bromide **48** to form the secondary alkyl radical once again. This is followed by formation of an alkylpalladium(II) intermediate, which upon β -hydride elimination delivers the product **16**. As a single catalyst promotes two different transformations (ATRC and dehydrohalogenation), we hypothesize that this is an example of auto-tandem catalysis.¹⁹ While our results are consistent with ATRC as the major pathway for most substrates, it is possible that the direct formation of an alkylpalladium(II) species could also occur preferentially to bromine atom transfer, leading directly to product.²⁰

Our results involving the reactions of alkyl iodides in the presence of inhibitors, and in the absence of palladium, suggest that an alternative mechanistic scenario may be involved. While palladium is required to abstract an iodine atom to begin the reaction, upon radical cyclization chain transfer with another equivalent of substrate is viable (Scheme 2). Furthermore, palladium is not necessarily required for the dehydrohalogenation of ATRC iodide products. While other pathways may contribute overall, in reactions of alkyl iodides involving palladium the role of the metal as an initiator, rather than catalyst, must be considered.

CONCLUSIONS

In conclusion, we have developed an efficient second-generation system for the carbocyclization of unactivated alkyl halides with alkenes. This catalytic system promotes a general carbocyclization of unactivated alkyl bromides for the first time, and avoids the undesired use of the CO atmosphere previously required. This reaction efficiently transforms an array of primary and secondary alkyl bromides in cyclizations with diverse alkenes to form valuable 5- and 6-membered carbo- and heterocycles. We propose the reactions of alkyl bromides involve auto-tandem catalysis, involving the first examples of ATRC with

unactivated alkyl bromides. We anticipate this work will significantly expand the use of these catalytic cyclizations in chemical synthesis and provide important insights into the reactivity of palladium catalysts with unactivated alkyl halides in new reaction development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

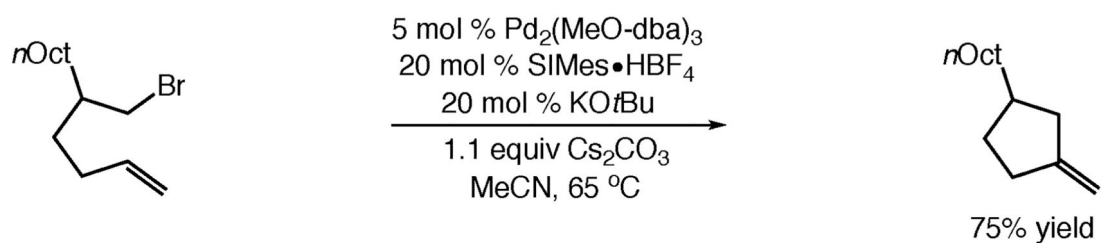
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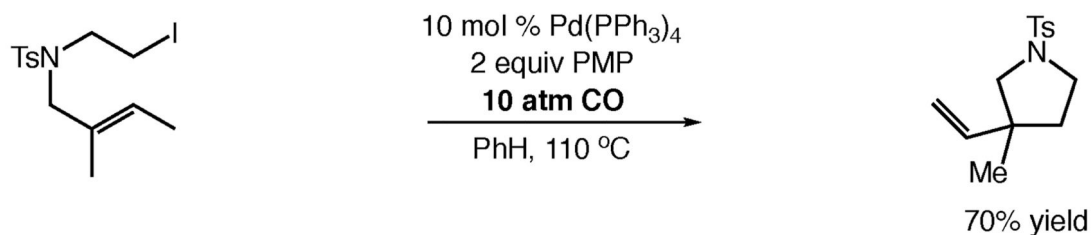
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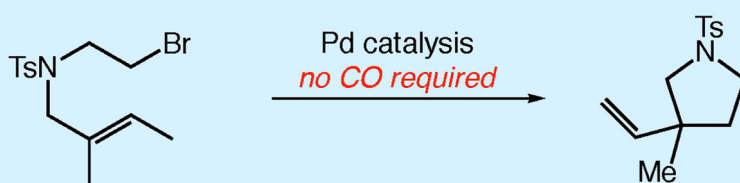
■ *Palladium-catalyzed alkyl-Mizoroki-Heck methylenecyclopentane synthesis: Fu (2007)*



■ *Palladium-catalyzed carbocyclizations of alkyl iodides with alkenes: Alexanian (2011)*

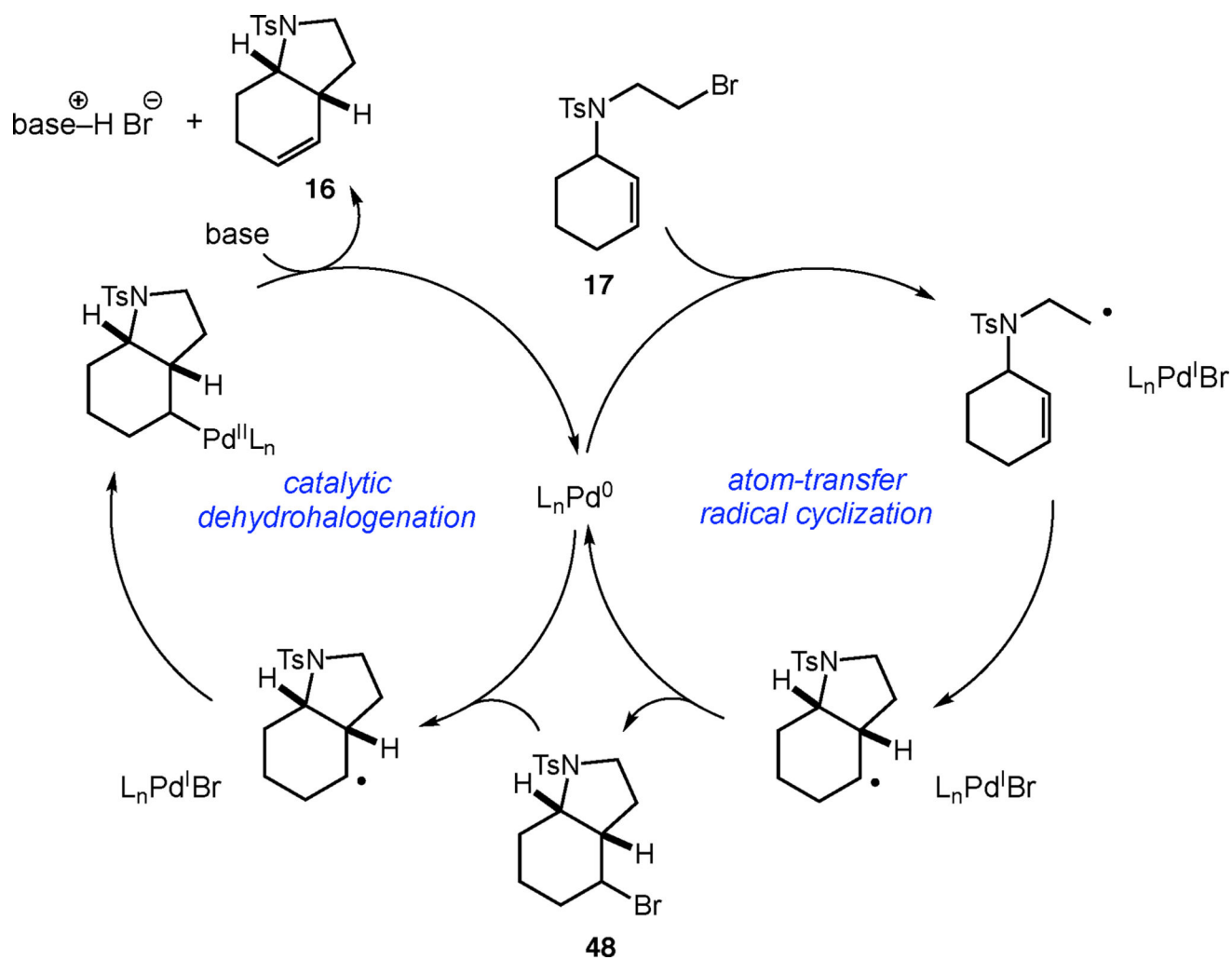


■ **This work:** *Palladium-catalyzed carbocyclizations of alkyl bromides with alkenes*

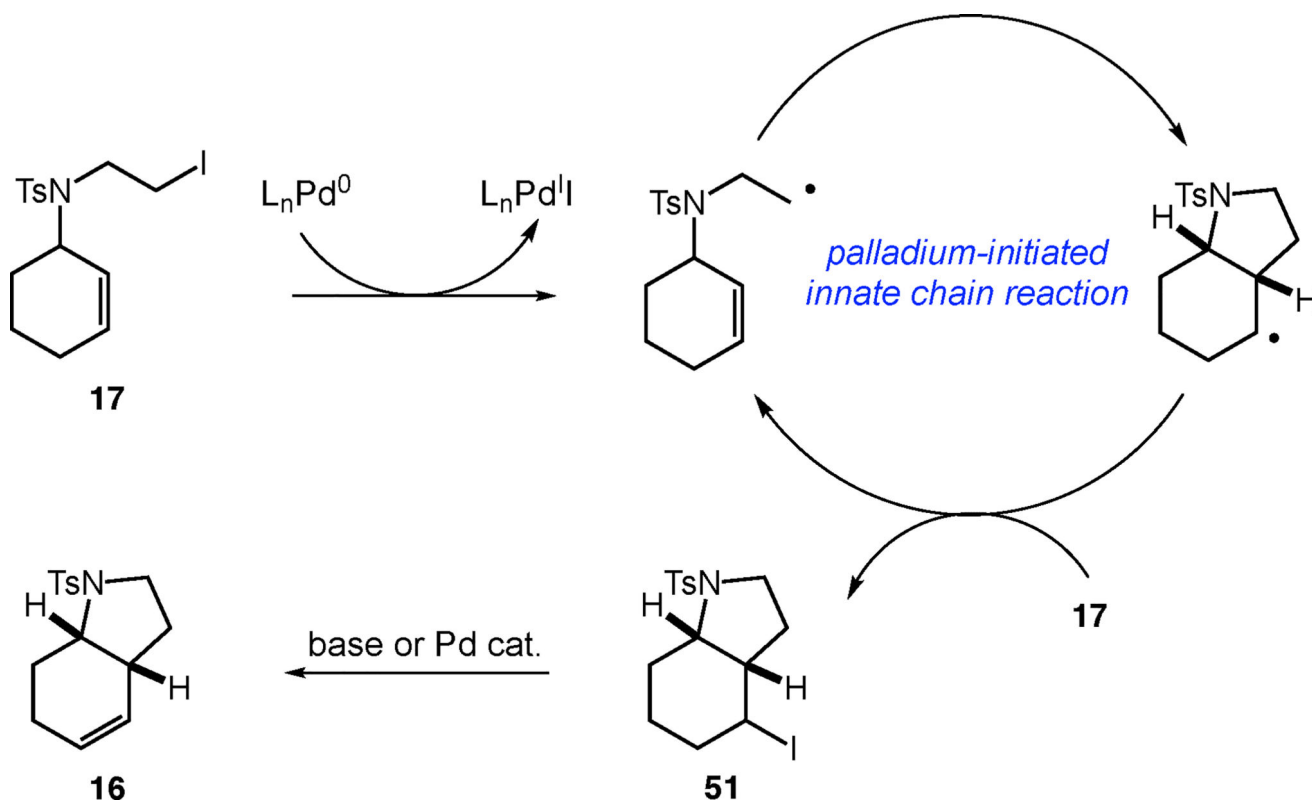


- Alkyl bromides viable substrates
- Broad reaction scope
- Avoids use of CO
- Auto-tandem Pd catalysis

Figure 1. Carbocyclizations of unactivated alkyl halides with alkenes involving palladium.

**Scheme 1.**

Plausible mechanism for the palladium-catalyzed carbocyclization of unactivated alkyl bromides with alkenes involving auto-tandem catalysis.

**Scheme 2.**

Plausible mechanism for the palladium-initiated carbocyclization of alkyl iodides involving an innate chain reaction.

Table 1

Identification of a catalytic system for the carbocyclization of unactivated alkyl bromides.

entry	catalyst	ligand	base	solvent	yield (%) ^a
1	[Pd(allyl)Cl] ₂	IMes	<i>i</i> Pr ₂ NEt	PhMe	<2
2 ^b	Pd(PPh ₃) ₄	–	PMP	Ph <i>n</i> Bu	<2
3	Pd(OAc) ₂	dtbdppf	<i>i</i> Pr ₂ NEt	PhMe	5
4	Pd(OAc) ₂	dcyppf	<i>i</i> Pr ₂ NEt	PhMe	<2
5	Pd(OAc) ₂	dpppf	<i>i</i> Pr ₂ NEt	PhMe	<2
6	Pd(OAc) ₂	dtbpf	<i>i</i> Pr ₂ NEt	PhMe	30(3)
7	[Pd(allyl)Cl] ₂	dtbpf	<i>i</i> Pr ₂ NEt	PhMe	65(12)
8	[Pd(allyl)Cl] ₂	dtbpf	Et ₃ N	PhMe	73(5)
9	[Pd(allyl)Cl] ₂	dtbpf	Et ₃ N	PhCF ₃	85(5)
10	Pd(dtbdppf)Cl ₂	–	Et ₃ N	PhCF ₃	14(2)

^aYield determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. Yield in parenthesis is that of a minor regioisomer, see Supporting Information for details.

^bReaction temperature 130 °C.

Table 2

Comparison of previously reported first-generation catalytic systems (alkyl iodides)⁹ with current protocol (alkyl bromides).

entry	substrate	product	yield (%) ^a
1			80
2			90
3			70
4			80
5			73 (83:17 dr)
6			73 (89:11 dr)
7			70 ^b
8			82 ^b
9			74 ^b
10			77 ^b
11			66% (>95:5 dr)
12			93% (>95:5 dr)

Reactions of alkyl iodides as reported in ref. 9. All reactions of alkyl bromides were performed with [substrate]₀ = 0.25 M in PhCF₃ at 100 °C with 5 mol % [Pd(allyl)Cl]₂, 20 mol % dtbpf, and 2 equiv Et₃N as base.

^a Isolated yield.

^b Isolated with minor regioisomers, see Supporting Information for details.

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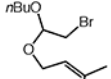
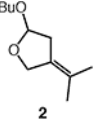
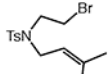

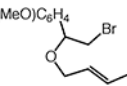
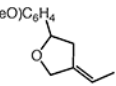
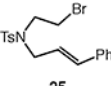

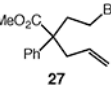

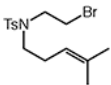
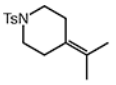
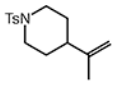
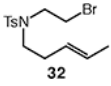
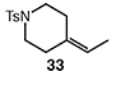
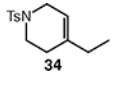
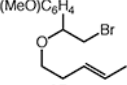
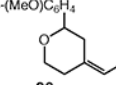
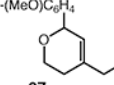
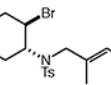
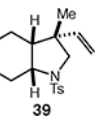
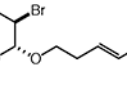
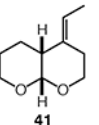
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Table 3

Catalytic carbocyclization of diverse unactivated alkyl bromides.

entry	substrate	product	yield (%) ^a	
1			86 ^b	
2			81 ^b	
3			71 (1:1 <i>E:Z</i>)	
4			65 (1:1 <i>E:Z</i>)	
5 ^c			65	
6 ^d				92 (30:31 = 1.9:1)
7 ^d				70 (33:34 = 3.3:1)
8 ^d				40 (36:37 = 7.0:1)
9			63 (>95:5 dr)	
10			75 (>95:5 dr) (1.5:1 <i>E:Z</i>)	

Reactions were performed with [substrate]₀ = 0.25 M in PhCF₃ at 100 °C with 5 mol % [Pd(allyl)Cl]₂, 20 mol % dtbpf, and 2 equiv Et₃N as base.^aIsolated yield.

^b Isolated with minor regioisomers, see Supporting Information for details.

^c DBU used as base instead of Et₃N.

^d Reactions were performed at 120 °C with 5 mol % [Pd(allyl)Cl]₂, 20 mol % dtbpf, and 2 equiv Cy₂NMe as base.

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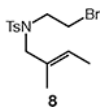
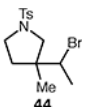
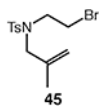
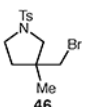
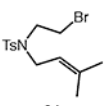
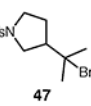
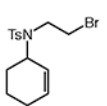
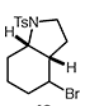
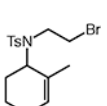
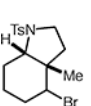
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Table 4

Palladium-catalyzed atom-transfer radical cyclizations of unactivated alkyl bromides.

entry	substrate	product	yield (%) ^a
1	 8	 44	45 (57:43 dr)
2	 45	 46	30
3	 21	 47	26
4	 17	 48	60 (50:50 dr)
5	 49	 50	84 ^b (60:40 dr)

Reactions performed with [substrate]₀ = 0.25 M in PhCF₃ at 80 °C with 5 mol % [Pd(allyl)Cl]₂, 20 mol % dtbpf, and 0.5 equiv Et₃N as base.

^aIsolated yield.

^bYield determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

Table 5

Comparing reactions of alkyl bromides and iodides in the presence of radical and electron-transfer inhibitors.

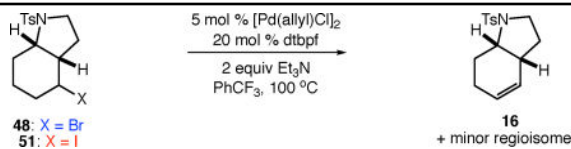
Reaction scheme: C1=CC=C(C=C1)N(C)CCX (17: X = Br, 15: X = I) $\xrightarrow[20 \text{ mol } \% \text{ dtbpf}]{5 \text{ mol } \% [\text{Pd}(\text{allyl})\text{Cl}]_2}$ C1=CC=C(C=C1)N(C)C2CC1C=C2 (16) + minor regioisomers. Conditions: 2 equiv Et_3N , PhCF_3 , 100°C .

entry	conditions	conversion (%) ^a	yield (%) ^a
1	X = Br, no additive	100	77
2	X = I, no additive	100	48
3	X = Br, with 10 mol % dinitrobenzene	<2	<2
4	X = I, with 10 mol % dinitrobenzene	100	78
5	X = Br, with 1 equiv TEMPO	31	<2
6	X = I, with 1 equiv TEMPO	100	55

^aDetermined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. For details regarding the distribution of minor regioisomers, see Supporting Information.

Table 6

Comparing the dehydrohalogenation of alkyl bromide and iodide ATRC intermediates.



entry	conditions	conversion (%) ^a	yield (%) ^a
1	X = Br, no additive	100	100
2	X = I, no additive	100	97
3	X = Br, with 10 mol % dinitrobenzene	22	9
4	X = I, with 10 mol % dinitrobenzene	100	100
5	X = Br, no metal or ligand	<2	<2
6	X = I, no metal or ligand	56	37

^aDetermined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. For details regarding the distribution of minor regioisomers, see Supporting Information.