

Palladium-Catalyzed Homocoupling Reactions between Two Csp³–Csp³ Centers

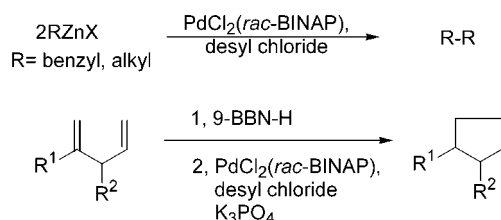
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ABSTRACT



A novel palladium-catalyzed coupling reaction between two Csp³–Csp³ centers has been investigated. This protocol is initiated by the oxidative addition of an α -halo carbonyl compound to a palladium(0) species, followed by the double transmetalation. The key dialkyl palladium intermediate undergoes reductive elimination to form the desired coupling product.

During the last several decades, palladium-catalyzed carbon–carbon bond formations have been extensively studied for organic synthesis.¹ Generally, these reactions involve the oxidative addition of a RX to a Pd(0) species as the initial step, followed by transmetalation and reductive elimination. However, most coupling reactions reported involve at least one sp- or sp²-hybridized carbon. The coupling reactions between two sp³-hybridized carbon centers are rare.² The possible reasons are that the oxidative addition of a sp³-alkyl halide to a palladium species is slow and the competitive β -H elimination of the alkyl–Pd–X is fast.³

Development of coupling reactions between two sp³-hybridized carbon centers bearing a β -H atom remains a great challenge in organic synthesis. Knochel et al. have developed an efficient Ni-catalyzed cross-coupling reaction of primary alkyl iodides and organozinc reagents in the presence of an assisting functional group^{2c,2f} or cocatalysts.^{2a,e} Fu's group reported the highly efficient palladium-catalyzed cross-coupling reactions of alkyl bromides bearing β -H atoms using PCy₃ as the ligand.^{2b}

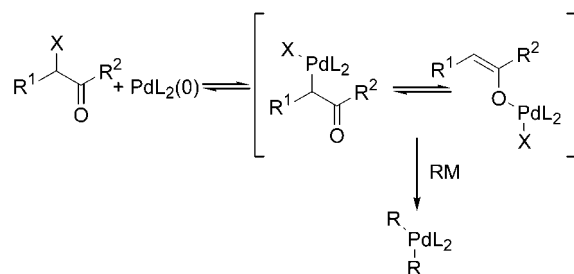
Recently, we have developed a novel double transmetalation process that introduces two R groups from RM onto a palladium center (Scheme 1).⁴ The reactions were initiated by the oxidative addition of α -halo carbonyl compounds and

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Scheme 1



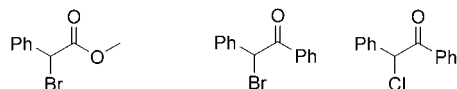
followed by an isomerization to an O-bound palladium enolate. In this paper, we report our strategy to construct a Csp³–Csp³ bond through this double transmetalation process.⁵ Since a Csp³–Pd–Csp³ intermediate can form from the double transmetalation of a Csp³–M to a palladium(II)

Table 1. Homocoupling Reactions Involving the sp³-Hybridized Carbon–Palladium Bond via Double Transmetalation^a

entry	substrate	method	yield (%) ^b
1		A	50
2		B	99
3		C	99
4		A	62
5		C	89
6		A	62
7		C	88
8		C	95
9		D	42 ^c
10		C	92
11		D	20 ^d
12		C	81
13		A	67
14		D	82 ^e

^a Method A: Reactions were performed using 0.25 mmol of methyl α -bromophenyl acetate, 0.025 mmol of PdCl₂(rac-BINAP), and 0.7 mmol of zinc reagent at room temperature for 16 h. Method B: reactions were performed using 0.25 mmol of desyl bromide, 0.025 mmol of PdCl₂(rac-BINAP), and 0.7 mmol of zinc reagent at 60 °C. The reactions were done when desyl bromide had been completely consumed from TLC. Method C: It is the same as Method B except desyl chloride was used instead of desyl bromide. Method D: it is the same as method C except room temperature was used. ^b Isolated yields. ^c 42% conversion. ^d 20% conversion. ^e 100% conversion in 4 h.

α -halocarbonyl compounds:



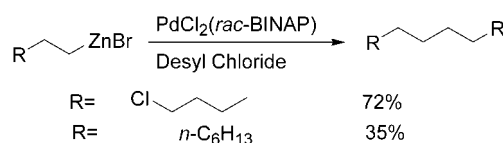
methyl- α -bromophenylacetate Desyl Bromide Desyl Chloride

center, we envisioned that the new Csp³–Csp³ coupling reaction can offer some advantages compared with the classic carbon–carbon coupling reactions.

The reaction of benzyl zinc bromide formed from the benzylmagnesium bromide and ZnBr₂, PdCl₂(rac-BINAP) and methyl α -bromophenylacetate in THF was carried out. Moderate yield (55%) was obtained for this Csp³–Csp³ homocoupling reaction. After screening different α -halo carbonyl compounds, we found that desyl chloride was an excellent reagent to initiate the oxidative addition and facilitate the isomerization from a C-bound palladium enolate to an O-bound palladium enolate. Double transmetalation of the organozinc reagents and the reductive elimination yielded Csp³–Csp³ homocoupling products. The results of these homocoupling reactions with different benzyl zinc reagents are shown in Table 1. Moderate to excellent yields have been achieved for many organozinc reagents. The results with α -methylbenzyl zinc bromide (Table 1, entries 13 and 14) were encouraging since it showed that the system could tolerate β -H atoms.

Under the optimized conditions, we have explored the coupling reaction of two sp³-hybridized carbon centers bearing β -H atoms. Moderate yields were obtained (Scheme 2). In one case, low yield (35%) was observed, and this

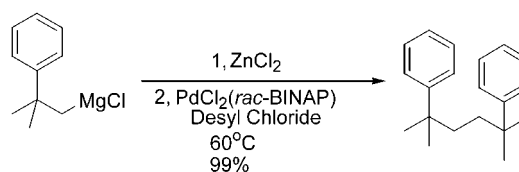
Scheme 2



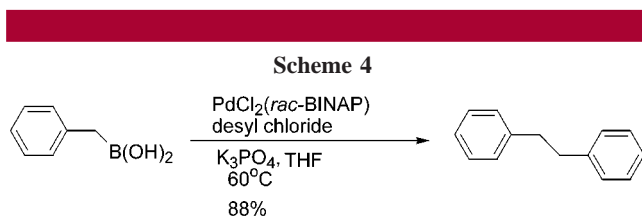
problem still needs to be addressed. Presumably, β -H elimination remains a key competitive side-reaction, and in this case it is responsible for the low yield while the higher yield obtained from the other reaction may be due to the presence of heteroatoms.^{2c,f}

To examine the influence of the β -hydrogen in the Csp³–Csp³ coupling reaction, we explored the coupling reaction of 2-methyl-2-phenylpropylmagnesium chloride in the presence of ZnCl₂. The high yield obtained under our coupling conditions indicated that the reductive elimination between two alkyl Csp³–Csp³ centers without β -H atoms could proceed smoothly (Scheme 3).

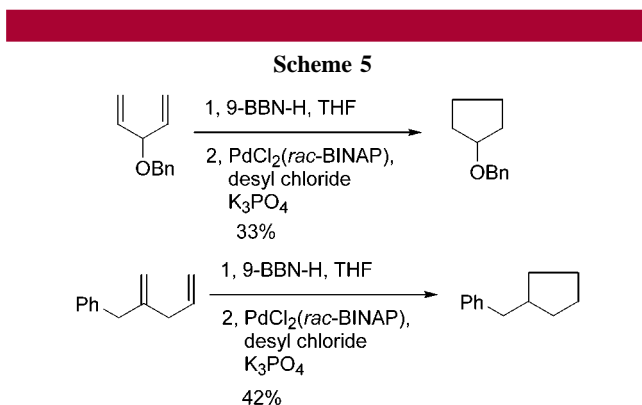
Scheme 3



In addition to homocoupling of organozinc reagents, we have also established the homocoupling reaction of organo boronic acids to form carbon–carbon bonds.^{4b} For example, the coupling reaction of benzyl boronic acid led to the desired product in 88% yield in the presence of desyl chloride and a palladium catalyst (Scheme 4).



On the basis of this result, we explored the hydroboration of alkenes and the coupling reactions to construct carbocyclic compounds. It is known that organoboranes derived from hydroboration of alkenes using 9-BBN-H as the reagent can be used to carry out Csp³–Csp² and Csp³–Csp³ Suzuki-coupling reactions.^{6,2b} We wish to extend the scope of this reaction to examine intramolecular Csp³–Csp³ coupling reaction with β -H atoms at both ends. Hydroboration of 1,4-dienes using 9-BBN-H produced a key intermediate, which can be coupled with a palladium catalyst in the presence of desyl chloride. These one-pot reactions generate cyclopentane products as shown in Scheme 5. These results

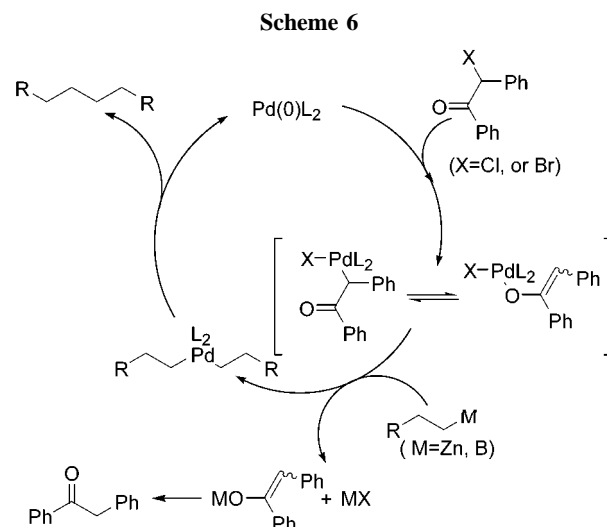


are significant for exploration of the Csp³–Csp³ coupling reaction. Further modification may inhibit the β -H elimination process, and a fundamentally useful coupling method can be generated.

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On the basis of our experimental results, we propose that the oxidative addition of desyl chloride to a palladium center is the initial step. Double transmetalation leads to a key dialkylpalladium intermediate, and reductive elimination forms the coupling product and regenerates the catalyst (Scheme 6). The intermediate formed from oxidative addition of desyl chloride to a palladium species contains a palladium–halide bond and a palladium–carbon bond. Although transmetalation between organometallic reagent and a palladium–halide bond is well documented, the transmetalation between organometallic reagent and a palladium enolate bond is novel. A carbon anion serving as the leaving group for transmetalation step is not common. While the transmetalation is well-known between organometallic reagent and a palladium–oxygen bond.^{1a,c,h} Therefore we propose that the tautomerization of a palladium enolate between the C-bound and the O-bound palladium enolate is a key process for our reaction,⁷ the first transmetalation occurs between an O-bound palladium enolate and an organozinc or organoborane reagent, and an alkyl–Pd–X (X = halide) intermediate is obtained.⁸ In the following step, X (X = halide) may be displaced in the second transmetalation to form an alkyl–Pd(II)–alkyl species. In contrast to other palladium-catalyzed coupling reactions, this process employs desyl chloride as a surrogate to perform the oxidative addition. Subsequently, the first transmetalation can form the intermediate alkyl–Pd–X (X = halide) which can then undergo a second transmetalation.

We have achieved some success in performing both inter- and intramolecular Csp³–Csp³ coupling reactions of substrates bearing β -H atoms. Further efforts will focus on

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(8) We observed the reductive elimination of an alkyl–Pd–X (X = halide) to form an alkyl–X species in high selectivity. We did not detect any arylation product from the reductive elimination of an alkyl–Pd–enolate. This leads us to believe that an alkyl–Pd–enolate intermediate was not formed in this reaction. A. Lei, X. Zhang, *Abstr. Pap. Am. Chem. Soc.* **2001**, *222*, 602-ORGN.

identifying a more efficient ligand that will promote reductive elimination and inhibit the β -H elimination.

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Supporting Information Available: Spectroscopic data and experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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