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Construction of Seven-Membered Carbocycles via Cyclopropanols

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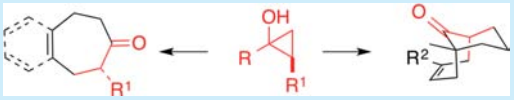
Supporting Information

ABSTRACT: A new method for seven-membered ring annulation has been devised by an intramolecular cross-coupling of cyclopropanols and aryl/alkenyl halides. This cyclization reaction is broad in scope and provides easy access to not only fused but also bridged bicyclic compounds.



Development of a general method for the construction of medium-sized (seven- and eight-membered) carbocycles has been an active area of research, in part owing to a wide occurrence of structurally complex hydroazulene, guaiane, and pseudoguaiane sesquiterpenes.[1] For example, the isolation and potent anticancer activity of (−)-englerin A has drawn renewed interest in guaiane sesquiterpenoids.[2,3] Annulation of medium-sized rings presents unique challenges. An efficient method for direct cyclization is attractive and complements those based on ring expansion or fragmentation.[1,4]

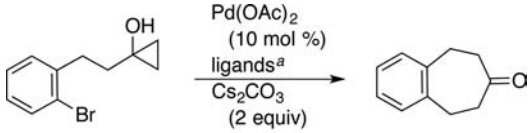
As part of our research program on ring-opening reactions of cyclopropanols,[5−8] we report herein a modular assembly of functionalized seven-membered carbocycles by intramolecular cross-coupling between cyclopropanols and aryl/alkenyl halides or triflates.

X = I, Br, OTf

Palladium-catalyzed cross-coupling of the silyl ethers of cyclopropanone hemiacetals and cyclopropanols with aryl triflates was first reported by Kuwajima and co-workers in their pioneering application of cyclopropanone hemiacetals as homoenolate equivalents.[9] As reported independently by the Orellana and Walsh groups,[10,11] the analogous coupling of unprotected cyclopropanols with aryl halides was found to proceed under milder conditions. Inspired by Uemura's attractive cross-coupling reactions of cyclobutanols with aryl halides,[12] we previously developed palladium-catalyzed oxidative ring-opening of cyclopropanols for the preparation of α,β-enones.[13] As a logical progression, we subsequently examined a cross-coupling reaction, which closely paralleled successful examples of the Orellana and Walsh groups: cross-coupling between bromobenzene and the cyclopropanol, which was obtained by the Kulinkovich reaction of allylbenzene with ethyl acetate,[5,14a] afforded the β-hydride elimination product as the major product under several conditions.[15] This unfortunate result appeared to be limited specifically to this particular substrate, presumably as a consequence of the phenyl group. Prompted by the aforementioned successful cross-coupling reactions by the Orellana and Walsh groups,[10,11] we recently revisited not only intermolecular but also intramolecular variants. Surprisingly, the intramolecular counterpart has received scant attention, except for a sole example of five-membered spirocyclization.[10a] Additionally, no example has appeared on the use of synthetically more versatile alkenyl halides or pseudohalides in place of aryl derivatives. Unlike the latter, the former reactants could become susceptible to β-elimination.

Cyclopropanol **1**[16] was selected as the first substrate for palladium-catalyzed cyclization with the tethered aryl bromide. Treatment of **1** with $Pd(OAc)_2$ and Ph_3P in toluene furnished the desired seven-membered ring ketone **2** in 60% yield (Table 1, entry 3). Optimization studies of temperature, solvents, and phosphine ligands resulted in formation of **2** in up to 95% yield (entry 5), where bidentate ligands were generally more effective than Ph_3P. Solvent effects were negligible (entries 1−4), and

Table 1. Palladium-Catalyzed Cyclization of Cyclopropanol 1



1 2

entry[a]	solvent	ligand	temp (°C)	time (h)	yield (%)
1	toluene	PPh_3	60	6	18
2	THF	PPh_3	60	6	25
3	toluene	PPh_3	80	3	60
4	CH_3CN	PPh_3	80	2	59
5	CH_3CN	dppb	80	1	95
6[b]	CH_3CN	dppb	80	1	92
7[c]	CH_3CN	dppb	80	2	84
8	CH_3CN	dppp	80	1	67
9	CH_3CN	dppe	80	1	79

[a]Unless noted otherwise, $Pd(OAc)_2$ (10 mol %), ligands [Ph_3P (40 mol %) or bidentate (20 mol %), Cs_2CO_3 (2 equiv) were used. [b]Cs_2CO_3 (1 equiv) was used. [c]$Pd(OAc)_2$ (5 mol %) and dppb (10 mol %) were used.

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acetonitrile was chosen as the solvent for operational convenience for the reactions with bidentate ligands (entries 5−9). With regard to base (Cs_2CO_3), little difference in yield was observed between the use of 1 and 2 equiv (entries 5 and 6).

Under optimized conditions (entry 5), we next established a broad scope with respect to cyclopropanols and aryl bromides/triflates (Figure 1); aryl bromides were employed, unless

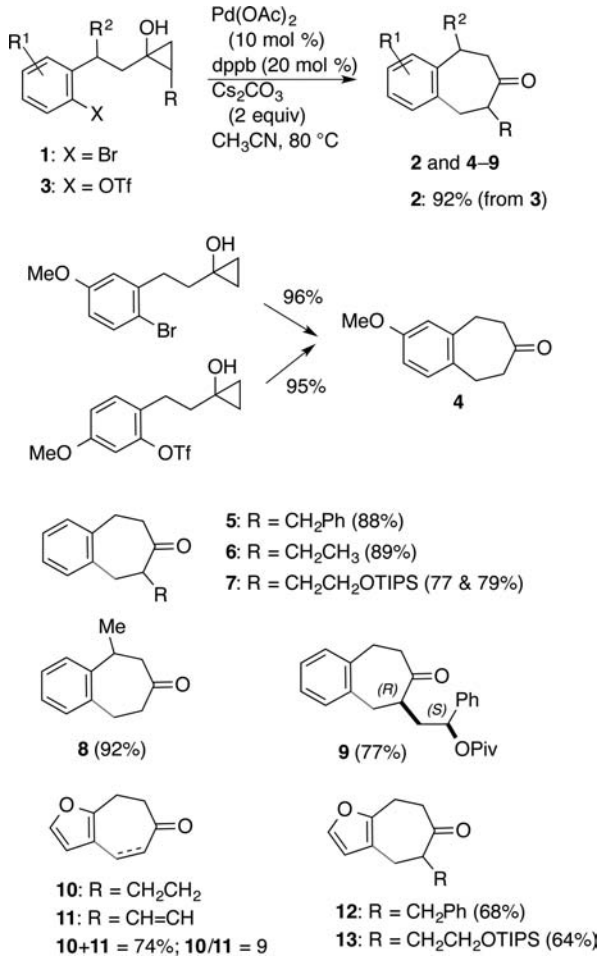


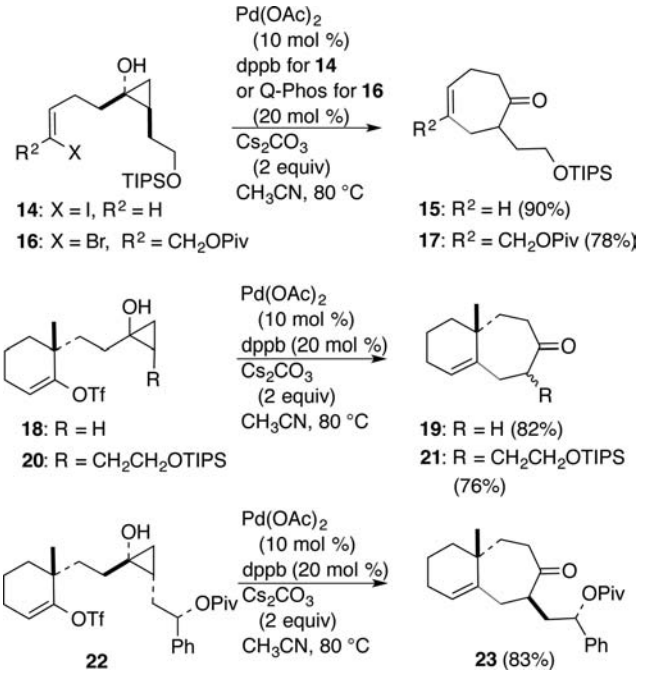
Figure 1. Intramolecular cross-coupling reactions of aryl halides.

indicated otherwise. The corresponding triflates were equally amenable to the cross-coupling reactions.[17] Electron-rich substituents (e.g., OMe) on the aryl ring, as well as substituents on the spectator skeleton of the cyclopropanol partner, were well tolerated, as shown for formation of **4** and **5**−**9**. As expected, the identical ketone **7** was obtained in comparable yields from the *cis*- and *trans*-dialkyl cyclopropanols. Taking advantage of the hydroxyl-directed cyclopropanation of the corresponding homoallylic alcohol,[14b] enantiopure **9** was obtained as a single diastereomer (free from potential epimerization) in 77% yield.

The use of a 3-furyl bromide bearing a tethered cyclopropanol at C2 was examined, as the furan functionality offers a useful handle for elaboration. Cross-coupling of the 3-furyl bromide substrates proved to be more demanding, and a screening of phosphine ligands revealed that satisfactory yields were possible by employing P(*o*-Tol)$_3$ or Q-Phos.[15] An inseparable 9:1 mixture of **10** and **11** was obtained in 74% yield from the corresponding monosubstituted cyclopropanol. On the other hand, disubstituted cyclopropanols afforded the desired bicyclic ketones **12** and **13**, free from the enone byproduct.

It was surprising that no cross-coupling reaction between alkenyl halides and cyclopropanols was documented in the literature, despite the synthetic utility of the resulting coupling products. We thus investigated the use of alkenyl halides having tethered cyclopropanols in place of aryl halides. The requisite substrates were readily prepared by the Kulinkovich cyclopropanation of the corresponding esters or lactones,[14a] followed by Stork−Zhao *Z*-olefination.[18] Under the aforementioned coupling reaction conditions for aryl bromides, cross-coupling of **14** proceeded cleanly to provide **15** in 90% yield (Scheme 1) and took only 15 min for completion. However,

Scheme 1. Intramolecular Cross-Coupling Reactions of Alkenyl Iodides and Triflates



the respective coupling reaction of **16** gave a complex mixture in the presence of dppb. A satisfactory solution was found in the use of Q-Phos, which afforded **17** in 78% yield. Similarly, the key methodology was effective for enantioselective formation of bicyclic seven-membered ketones **19**, **21**, and **23**, starting from nonracemic keto esters.[19] For convenience, cyclopropanol **20** was prepared as a 1:1 mixture of two *cis*-dialkyl diastereomers and yielded **21** (76%) in the identical ratio. The corresponding *trans*-alkyl cyclopropanol **22**, which was prepared (a 6:1 dr) by the hydroxyl-directed cyclopropanation,[14b] delivered **23** cleanly in 83% yield. Thus, the fomation of **21** and **23** was accompanied by little or no epimerization at the α-carbon of the keto group. The cross-coupling of alkenyl bromides or triflates took place slightly faster than the aryl counterparts.

Finally, the underlying method was applied to cyclopropanol **24** for an efficient construction of bridged bicyclo[4.3.1] ketones, and **25** was obtained in 66% and 72% yield in the presence of dppb or Q-Phos, respectively (Scheme 2). Ketone **25** represents a [4 + 3] cycloadduct of 1,3-butadiene with a six-membered oxyallyl.[20,21] Despite the well-proven utility of the [4

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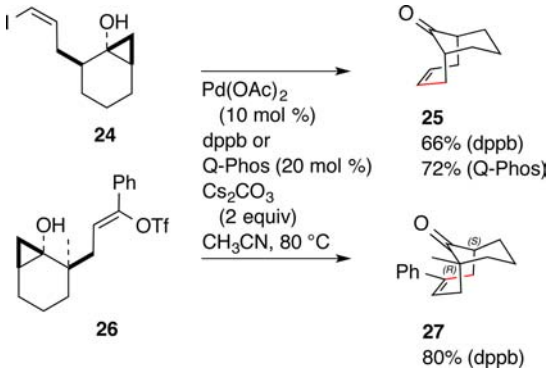
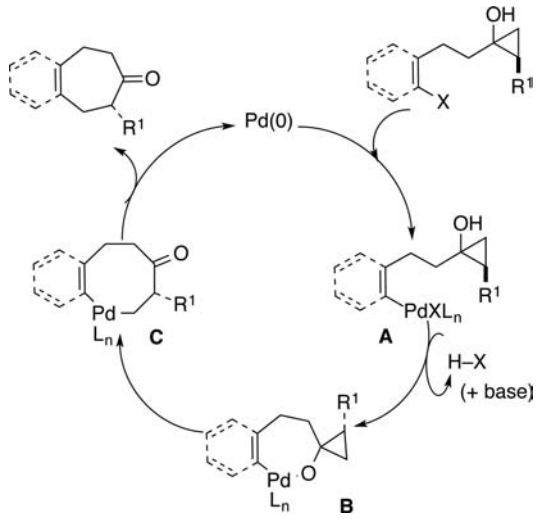
Scheme 2. Facile Construction of Bicyclo[4.3.1] Ketones



+ 3] cycloaddition of oxyallyls, an enantioselective preparation is difficult, especially with acyclic 1,3-dienes.[20h,i] In this connection, it is noteworthy that enantiopure **27** was readily accessible in a satisfactory yield. This method provides a convenient entry to attractively functionalized and enantiopure bicyclo[4.3.1]decanones, thus offering a conceptually new and effective alternative to the challenging enantioselective [4 + 3] cycloaddition of oxyallyls.

It is likely that the overall mechanism of the key methodology is conceptually related to that proposed for palladium-catalyzed *C*-acylation of cyclopropanols with acid chlorides.[8b] A plausible catalytic cycle begins with oxidative addition of Pd(0) to an aryl or alkenyl halide substrate, followed by ligand exchange between **A** and the tethered cyclopropanol in the presence of base (Scheme 3). Subsequent

Scheme 3. Plausible Mechanism



β-carbon elimination of the resulting palladium cyclopropoxide **B** would deliver **C**. Finally, reductive elimination of **C** would afford the desired cross-coupling product.

In conclusion, an intramolecular cross-coupling reaction of cyclopropanols with the tethered aryl or alkenyl bromides (or triflates) offers new access to seven-membered carbocycles. Both fused and bridged seven-membered ring compounds are readily accessible by the key cyclization. The latter cross-coupling adducts embody enantioenriched [4 + 3] cycloadducts of oxyallyls. Extension to the cognate preparation of eight-membered carbocycles is in progress, as well as applications to natural product synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02978.

Experimental procedures and spectroscopic data for key intermediates (PDF)

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Notes

The authors declare no competing financial interest.

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