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C-Acylation of Cyclopropanols: Preparation of Functionalized 1,4-Diketones

Bibhuti Bhusan Parida, Pragna Pratic Das, Mathilde Niocel, and Jin Kun Cha*

Department of Chemistry, Wayne State University, 5101 Cass Avenue, Detroit, Michigan 48202, United States

jcha@chem.wayne.edu

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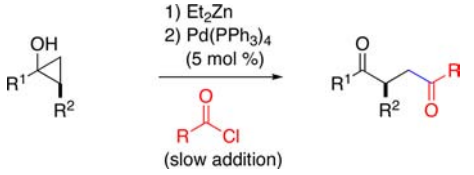
ABSTRACT



A convenient method for preparing attractively functionalized 1,4-diketones has been devised by palladium-catalyzed cross-coupling of cyclopropanols and acyl chlorides. The utility of this method has been demonstrated in an enantioselective synthesis of (+)-myrmicarin 217.

As part of our research program directed at total synthesis of bioactive natural products containing five- and six-membered heterocycles, we required easy access to functionalized 1,4-diketones. 1,4-Diketones have been shown to be useful building blocks for the preparation of cyclopentenones and five-membered hetereocycles.[1] There are various synthetic methods available, including (*a*) several types of conjugate addition reactions of acyl radicals or acyl anion equivalents to α,β-enones, in addition to carbonylative 1,4-addition,[2] (*b*) addition of homoenolate equivalents to acyl derivatives,[3] (*c*) alkylation of enolates,[4] (*d*) oxidative coupling of enolates,[5] (*e*) one-carbon extension of 1,3-diketones,[6] and (*f*) other approaches (Scheme 1).[7] A wide variety of these known methods notwithstanding, a practical and versatile coupling reaction of two functionalized subunits (segment coupling) under mild conditions is highly desirable. Taking advantage of the ready availability of enantiopure cyclopropanols, we report herein the palladium-catalyzed cross-coupling of cyclopropanols and acyl chlorides for the convenient preparation of attractively functionalized 1,4-diketones.

In conjunction with our ongoing studies on ring-opening reactions of cyclopropanols, we were particularly interested in approach *b*. One direct route to ketones involves acylation of several types of organometallics with acyl

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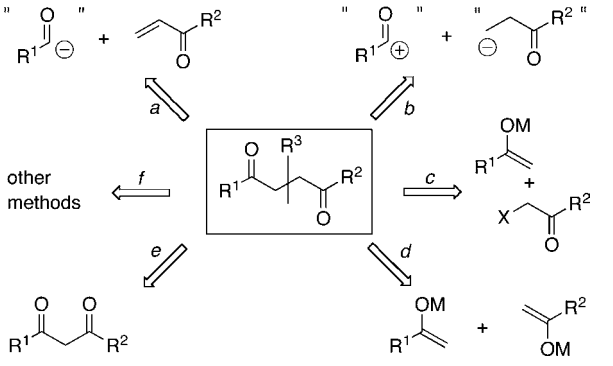
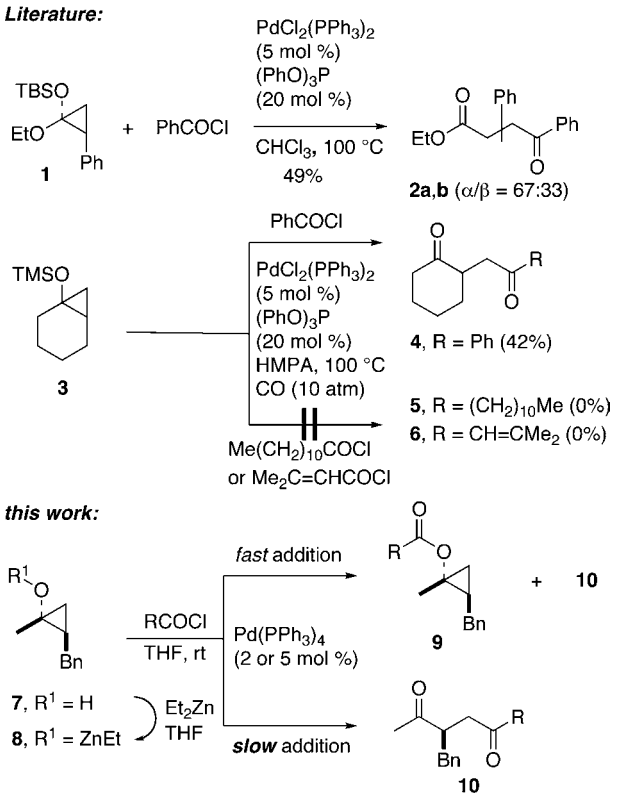
Scheme 1. Synthetic Methods for 1,4-Diketones



Scheme 2. Acylation of Cyclopropanols and Silyl Ethers



chlorides or derivatives, and a useful method is the copper- or palladium-catalyzed acylation of organozinc reagents.[8,9] Despite pioneering studies on cyclopropanone hemiacetals (R^2 = alkoxy) as homoenolates by the Kuwajima group, acylation met with limited success: preformed zinc ester homoenolates were necessary for the preparation of 4-keto esters via Pd(0)- or Cu(I)-catalyzed coupling.[10] Extension to the preparation of 1,4-diketones via keto homoenolates was by no means straightforward due to their known proclivity to cyclize to the corresponding cyclopropoxides in contrast to the corresponding metal homoenolates of weakly electrophilic esters and derivatives.[11] Previous methods involved the use of siloxycyclopropanes under harsh conditions: this protocol was limited to aroyl chlorides (Scheme 2).[3] Aliphatic acyl chlorides gave no desired product, and decarbonylation became problematic. We hypothesized that the use of a suitable metal cyclopropoxide could offer a simple, yet effective solution to this challenging problem.

As recently utilized in another transition-metal-mediated C−C bond forming reaction of cyclopropanols,[12] addition of diethylzinc to a THF solution of (racemic) cyclopropanol **7** gave the corresponding zinc alkoxide **8**. When a Pd(0) catalyst[13] and benzoyl chloride (R = Ph) were added in one portion (fast addition), an ∼1:1 to 1:1.9 mixture of *O*-acylation product **9** and *C*-acylation product **10** was isolated (49−52%). On the other hand, slow (over 1 h via syringe pump) addition of benzoyl chloride allowed clean *C*-acylation to afford **10** in 71% yield, free from the competing ethyl transfer. Also noteworthy is the regiospecificity of the coupling reaction. In the absence of a catalyst, treatment of **8** with benzoyl chloride resulted in *O*-acylation (i.e., **9** in 35% yield), in addition to recovered **7** (∼25%).

Initial screening indicated that both THF and Et_2O were suitable as solvent, whereas significant amounts of starting materials were recovered unreacted when 5:1 THF−DMA was employed. In contrast, *C*-acylation of preformed zinc ester homoenolates was reported to require the use of HMPA−TMSCl in ether, whereas only *O*-acylation was observed in $CHCl_3$.[10] We next examined the acylation reaction of cyclopropanols **7**, **11**, and **12** with a bevy of acyl chlorides to establish a broad substrate scope (Figure 1). A full range of acyl chlorides gave satisfactory yields, and substituents were well tolerated at α- or distal positions. Small amounts of benzyl ethyl ketone (**27**) were isolated as side products from the coupling reactions of cyclopropanol **12** (R^2 = H), whereas the corresponding ring-opened ketones **28** were not found from those of **7** and **11** ($R^2 \neq$ H).

Additional examples involving nonracemic substrates underline the synthetic utility of the key methodology in rapidly building up molecular complexity via segment coupling (Figure 2, wherein the keto segments on the right side are derived from acyl chlorides).[14] As seen in the preparation of **32**, the coupling reaction is compatible with

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(13) A brief survey revealed that several Pd(0) catalysts [e.g., $Pd(OAc)_2$/Ph_3P, $Pd_2(dba)_3$/4 Ph_3P, or $Pd(dba)_2$/4 Ph_3P] were equally effective.

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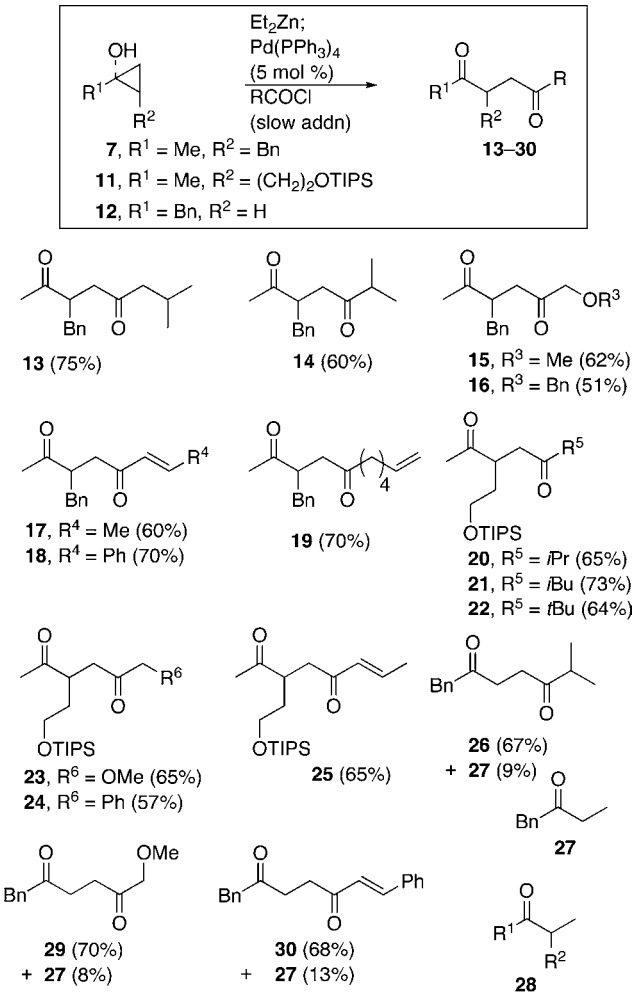


Figure 1. Cross-coupling of cyclopropanols and acyl chlorides.

the presence of a free hydroxyl group (2 equiv of Et_2Zn used) in the cyclopropanol partner.

As an initial foray into synthetic applications, (+)-myrmicarin 217 (**37**) was chosen as the first target (Scheme 3).[15−17] We envisioned an intramolecular Paal−Knorr synthesis from 1,4-diketone **40** and subsequent ring closing metathesis (RCM) of the resulting pyrrole to afford tricycle **39**. An enantioselective route to the key intermediate **40** would be available by

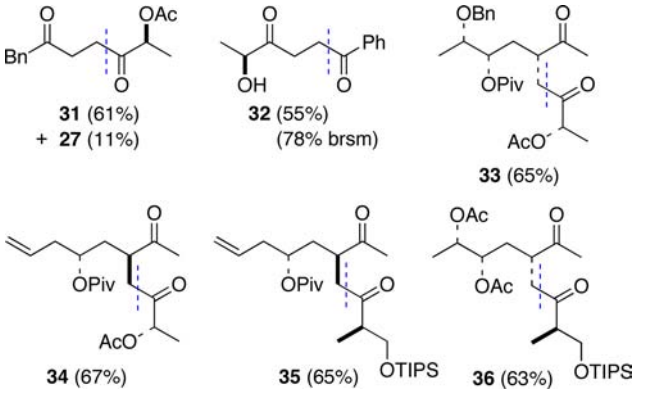
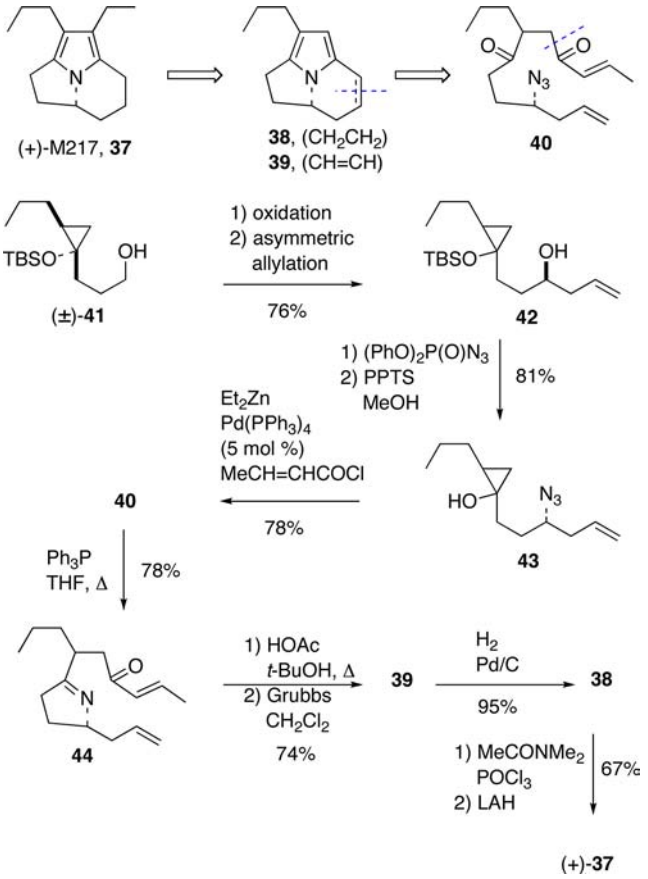


Figure 2. Cross-coupling of nonracemic substrates.

Scheme 3. Retrosynthetic Analysis and Total Synthesis of (+)-**37**



cross-coupling between cyclopropanol **43** and crotonoyl chloride. Our synthesis commenced with readily available (±)-**41**.[18] Dess-Martin oxidation of alcohol **41** and asymmetric allylation by Keck's method[19] [using (*S*)-BINOL)] afforded homoallylic alcohol **42** as an inconsequential 1:1 mixture of two diastereomers. Azide **43** was next prepared

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(18) Prepared by the Kulinkovich cyclopropanation of γ-butyrolactone with *n*-pentylmagnesium chloride, followed by straightforward functional group manipulation: For reviews, see: (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (b) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597. (c) Cha, J. K.; Kulinkovich, O. G. *Org. React.* **2012**, *77*, 1.

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in 81% overall yield by clean displacement of the secondary alcohol of **42** with diphenylphosphoryl azide,[20] followed by desilylation. The key cross-coupling reaction of **43** with crotonoyl chloride proceeded cleanly to provide **40** in 78% yield. Subsequent conversion of **40** to the corresponding pyrrole started with initial treatment with triphenylphosphine, followed by gentle heating of the resulting intermediate **44** in *tert*-butanol (containing 5 equiv of HOAc).[21] Isolation of **44** (albeit fully characterized) was unnecessary for the Paal–Knorr pyrrole synthesis. RCM of the crude pyrrole product with Grubbs' second-generation catalysis delivered **39**, which was converted by catalytic hydrogenation to labile **38** (which was used immediately for next step). Finally, Vilsmeier–Haack acylation of **38** and subsequent LAH reduction according to literature precedents completed an enantioselective synthesis of (+)-**37**.

In conclusion, a straightforward cross-coupling reaction between cyclopropanols and acyl chlorides offers a versatile method for preparing attractively functionalized 1,4-diketones. Segment coupling allows a rapid buildup in molecular complexity due to an expedient bond connection. In view of the ready availability of nonracemic substrates, broad substrate scope, operational simplicity, and mild reaction conditions, this method should find use in natural product synthesis. Mechanistic and synthetic studies are in progress.

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Supporting Information Available. Experimental details and spectroscopic data for key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(20) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett*. **1977**, *18*, 1977.

(21) A protic solvent containing 3–5 equiv of HOAc (to promote the imine to enamine tautomerization) was necessary for clean formation (89–95%) of the pyrrole. With methanol as solvent, the Michael reaction took place to afford the pyrrole bearing the corresponding β-methoxy side chain in 95% yield.