

Palladium-Catalyzed Enantioselective Decarboxylative Allylic Alkylation of Protected Benzoin-Derived Enol Carbonates

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Dedicated to our friend Professor Eric N. Jacobsen on the occasion of his 60th birthday.

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Abstract: The enantioselective palladium-catalyzed decarboxylative allylic alkylation of fully substituted α -hydroxy acyclic enol carbonates providing tetrasubstituted benzoin derivatives is reported. Investigation into the transformation revealed that preparation of the starting material as a single enolate isomer is crucial for optimal enantioselectivity. The obtained alkylation products contain multiple reactive sites that can be utilized toward the synthesis of stereochemically rich derivatives.

Keywords: allylic alkylation; palladium catalysis; benzoin; asymmetric catalysis

Benzoins are a preeminent motif in organic chemistry that are used as synthetic intermediates to access a variety of useful structures.^[1] As a result, extensive efforts toward the asymmetric synthesis of benzoin derivatives have been reported, including enantioselective benzoin condensations,^[2] reductions of α diketones,^[3] and enzyme-catalyzed kinetic resolutions.^[4] However, the direct synthesis of a fullysubstituted a-carbonyl stereocenter in an enantioselective manner has only recently been developed. In 2008, the Glorius group reported the palladiumcatalyzed direct C-allylation of benzoins, as well as a tandem benzoin-allylation process.^[5] They note, however, that performing the transformation in an asymmetric fashion proved to be challenging, likely due to nonselective formation of a mixture of enolates. Several years later, the Hartwig group reported the use of iridium-catalysis for the diastereo- and enantioselective synthesis of branched a-alkoxy ketones via a

stereodefined enolate, formed by enolization in the presence of a copper additive (Scheme 1A).^[6] Recently, the Trost group has reported a unique strategy toward the asymmetric alkylation of benzoins via a 1,3-dioxaborole intermediate (Scheme 1B).^[7] Due to the importance of this structural motif, and in continuation of recent research from our group regarding the synthesis and utility of fully-substituted acyclic enolates for palladium-catalyzed allylic alkylation,^[8] we hypothesized that preformation of a benzoin-derived enolate precursor as a single geometric isomer would allow for an enantioselective alkylation process. (Scheme 1C).

We began our investigations by examining the enolization selectivities obtained from various protected benzoins when treated with recently reported

A. Iridium catalyzed allylation with acyclic *a*-alkoxy ketones (Hartwig 2016)



B. Pd-catalyzed allylation of 1,3-dioxaborole intermediates (Trost 2019)



C. Pd-catalyzed allylation of MOM-protected benzoins (this research)



Scheme 1. Asymmetric strategies toward tertiary α -hydroxy ketones.

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selective enolization conditions (Table 1).^[9] While a 2,2,2-trichloroethoxycarbonyl (Troc) carbonate protecting group (entry 1) decomposes under the reaction conditions, a variety of alternative groups were found to be stable. When benzoin is protected with a TBS group, enolization selectivity is poor providing the enol carbonate in only a 56:44 ratio (entry 2). This could be improved slightly to 75:25 by switching to a benzoyl (Bz) group (entry 3). The use of methoxyacetal protecting group variants provided an additional boost to enolization selectivity with a benzyloxymethyl (BOM) group resulting in a 86:14 ratio (entry 4) and a MOM group (entry 5) providing access to a > 98:2isomeric ratio. While certain chelating protecting groups provide higher levels of enolization selectivity, we note that deviation from the standard selective enolization conditions (i.e. omission of Me₂NEt) results in decreased enolization selectivity.

With ready access to a stereodefined benzoin enolate precursor established, we next examined conditions for performing an enantioselective palladium-catalyzed allylic alkylation (Table 2). We began our investigations by examining a variety of ligands commonly used in the literature for this transformation. The electron deficient phosphinooxazoline ligand (S)- $(CF_3)_3$ -t-BuPHOX (L1) was found to provide the desired product in a low 25% ee (entry 1). Switching to bisphosphine ligands developed by Trost and coworkers, product ee could be improved. Both the (R, R)R)-DACH–Ph (L2, entry 2) and (R,R)-DPEN–Ph (L3, entry 3) ligands provided the desired product in promising levels of ee (64% and 67% respectively). Switching to the (R,R)-ANDEN-Ph ligand (L4, entry 4) resulted in an increase to 80% ee, and was carried forward as the optimal ligand. A screen of solvents revealed that methylcyclohexane (entry 7) was the optimal solvent for the transformation, affording the desired product in a good 88% ee and an

 Table 1. Impact of protecting group on enolization selectivity.

 [a]

		LiHMDS, Me ₂ NEt toluene, 25 °C hen allylchloroformate	OCO ₂ Allyl Ph Ph
entry	R	2	Z/E ratio
1	Tr	oc –	-
2	TE	BS 5	6:44
3	Bz	z 7	/5:25
4	BC	OM 8	6:14
5	M	OM 2	>98:2

^[a] Conditions: ketone (2.0 mmol), LiHMDS (2 equiv), Me₂NEt (2.0 equiv), PhMe (5.0 mL), 23 °C; then allyl chloroformate (2.0 equiv), 25 °C. E/Z ratio and assignment of olefin stereochemistry was determined by NMR analysis.

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Table 2. Optimization of acyclic, decarboxylative allylic alky-lation of benzoin-derived enol carbonate.

	OCO ₂ Allyl Ph Ph 1a	Pd₂(dba)₃ (2.5 mol %) ligand (6 mol %) Solvent (0.05 M) 25 °C, 12h	O OMOM Ph 2a
entry	ligand	solvent	%ee (yield) ^{b,c}
1 2 3 4 5 6 7 ^d	L1 L2 L3 L4 L4 L4 L4 L4 L4	3:1 hexane/PhMe 3:1 hexane/PhMe 3:1 hexane/PhMe 3:1 hexane/PhMe PhMe Et ₂ O methylcyclohexane F ₃	25 64 67 80 79 82 (97) 88 (99)
		F_{3} $HN - F_{3}$ $HN - F_{$	$ \begin{array}{c} $

^[a] Conditions: 0.1 mmol 1a, 2.5 mol% Pd₂(dba)₃, 6 mol% ligand, 2.0 mL solvent.

^[b] Determined by chiral supercritical fluid chromatography (SFC) analysis.

^[c] Conversion over 95% if no yield from isolated product stated.

^[d] Reaction performed with 0.2 mmol of **1 a**, 1 mol% Pd₂(dba)₃, 2.4 mol% ligand, and 4.0 mL solvent.

excellent 99% isolated yield. Notably, the catalyst loading could be lowered to 1 mol% of $Pd_2(dba)_3$ and 2.4 mol% of ligand with no deleterious results.

With optimal conditions identified, we next sought to examine the importance of enolate geometry on the transformation (Scheme 2). Under the standard conditions, the desired product is obtained in a 99%



Scheme 2. Importance of substrate enolate geometry

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isolated yield and 88% ee favoring the R-absolute stereochemistry when the starting material consists of a > 98:2 Z/E ratio of enolates. Even when a relatively high 93:7 Z/E mixture of enolates is used, the alkylation product is obtained in a significantly decreased 75% ee, highlighting the importance of forming the starting enol carbonate in as high geometric purity as possible.

Having identified optimized reaction conditions, we examined the scope of the transformation for accessing various benzoin derivatives (Figure 1). In all cases, the starting enol carbonate is prepared as a single enolate isomer. A variety of substrates were examined showing that both electronic and steric changes were tolerated leading to excellent yield and good enantioselectivity. Substitution at the *para*-position showed that both electron rich and electron deficient rings performed well, with para-Me (2b), para-OMe (2f), and parafluoro (2d) substrates yielding the products in 98–99% yield and 82-88% ee. The presence of other halides at

> Pd₂(dba)₃ (1 mol %) L4 (2.4 mol %) OMOM .OMOM MeCy (0.025 M) 25 °C, 12 h Å٢ 2a-k омом омом CI Ńе ĊI 2b 2c 89% yield, 73% ee 99% vield, 88% ee омом омом MeO **ÔMe** 20 2f 99% yield, 74% ee 99% vield^d, 84% ee 22 OMOM омом

> > 2i

99% Yield, 81% ee

омом

Figure 1. Substrate scope of asymmetric, decarboxylative allylic alkylation of benzoin derivatives. ^b Yield of isolated product. ^c Determined by chiral SFC analysis. ^d Reaction performed for 48 h.

2h

90% yield, 78% ee

омом

2j 74% yield^d, 80% ee

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2g 97% yield, 79% ee

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2k

97% vield. 72% ee

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the para-position lead to a decrease in enantioselectivity down to 71% ee for *para*-chloro (2c) and 73% ee for a *para*-bromo substituent (2e). Substitution at the *meta*-position led to consistent results, proceeding with excellent yield and modest enantioselectivity for meta-Me (2g) and *meta*-chloro (2h) alkylation products obtained in 79% and 78% ee respectively. More hindered substrates such as the bis-Me substrate (2i), and (2j) derived from piperonal showed promising results, providing the products in 80% ee and 81% ee, respectively. However, a naphthyl ring (2k) showed the limit of steric hindrance on this system with a diminished 72% ee. Notably, both electron rich substrates (2 f) and (2 j) required longer reaction times to reach full conversion (i.e., 48 h).

With a scope of the transformation examined, we next sought to demonstrate the utility of the produced a-tetrasubstituted benzoins toward further functionalizations (Scheme 3). Direct treatment of the standard alkylation product 2a to cross metathesis conditions using methyl acrylate provided ester 3 in 93% isolated yield. Deprotection of the MOM group to afford the corresponding enantioenriched tertiary alcohol 4^[10] was achieved using acidic Dowex-50W-X8 resin^[11] in quantitative yield. Notably, no erosion of enantiomeric excess of 4 was observed, a process that might theoretically occur via an α -ketol rearrangement. Alcohol 4 could be further derivatized via alkylation with allyl bromide and subsequent ring-closing metathesis using Grubbs' second generation catalyst, yielding dihydropyran 5 in 88% yield over two steps. Alternatively, acylation with acryloyl chloride followed by ring-closing metathesis yields α,β -unsaturated lactone 6 in 94% yield over two steps.



ray diffraction, all other compounds are assigned by analogy. Conditions: a) NaH then allyl bromide, DMF, 0 °C. b) Grubbs II (1 mol %), CH₂Cl₂, 40 °C. c) *n*-BuLi then acryloyl chloride, THF, −78 °C.

Scheme 3. Derivatization of alkylation products.

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In conclusion, we have developed an asymmetric palladium-catalyzed decarboxylative allylic alkylation of enol carbonates derived from protected benzoins. Both the use of the hindered bisphosphine (R,R)-ANDEN-Ph ligand and the preparation of the starting enol carbonate in high isomeric purity are necessary for obtaining high enantioselectivity. The obtained tetrasubstituted benzoin products can be derivatized to afford chiral building blocks containing several differentiated reactive sites poised to undergo additional transformations.

Experimental Section

General Procedure:

In a nitrogen-filled glovebox, a solution of $Pd_2(dba)_3$ (1.8 mg) and L4 (3.9 mg) in MeCy (4 mL) was stirred for 30 minutes at 25 °C, then the resulting solution was added to a vial containing allyl enol carbonate substrate (0.2 mmol) in MeCy (4 mL). The vial was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 25 °C for 12 h. The crude reaction mixture was concentrated then purified by silica gel flash chromatography to provide the desired alkylation product.

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