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Probing Trends in Enantioinduction via Substrate Design: Palladium-Catalyzed Decarboxylative Allylic Alkylation of α -Enaminones

Douglas C. Duquette,

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

Alexander Q. Cusumano,

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

Louise Lefoulon,

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

Jared T. Moore,

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

Brian M. Stoltz

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

Abstract

Herein, we report the palladium-catalyzed decarboxylative asymmetric allylic alkylation of α -enaminones. In addition to serving as valuable synthetic building blocks, we exploit the α -enaminone scaffold and its derivatives as probes to highlight structural and electronic factors that govern enantioselectivity in this asymmetric alkylation reaction. Utilizing the (*S*)-*t*-BuPHOX ligand in a variety of nonpolar solvents, the alkylated products are obtained in up to 99% yield and 99% enantiomeric excess.

Corresponding Author stoltz@caltech.edu.

Complete contact information is available at: <https://pubs.acs.org/10.1021/acs.orglett.0c01441>

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c01441>.

Experimental procedures and characterization data (PDF)

Graphical Abstract

The development of the palladium-catalyzed decarboxylative asymmetric allylic alkylation reaction has been of longstanding interest in our group.¹ With applications in fields ranging from total synthesis² to pharmaceutical development,³ the allylic alkylation reaction has proven to be an enabling method for the asymmetric construction of all-carbon quaternary centers.^{1,4} Our initial disclosures showcased the chemistry in the context of carbocyclic ketone substrates to be utilized in this reaction (Figure 1).⁵ Employing the (*S*)-*t*-BuPHOX (**L1**) ligand, enantioselectivities of the cyclic ketone products are generally limited to a maximum of 88–92% ee. In conjunction with the development of the electron-poor (*S*)-(CF₃)₃-*t*-BuPHOX (**L2**) ligand, subsequent expansion of the substrate scope to include *N*-benzoyl lactams was realized. Interestingly, under these modified conditions, the alkylated lactam products are obtained in up to 99% ee.⁶ This finding represents a substantial improvement in enantioselectivity with respect to the carbocyclic ketone class of substrates.

Curious as to the origins of the enhanced reactivity and enantioselectivity of the *N*-benzoyl lactam substrate class, we sought to explore the underlying phenomenon through a hypothesis-driven approach to substrate design. Our approach is two-fold: (1) expand the scope of the reaction to include additional synthetically valuable substrates and (2) gain insight into the factors that dictate enantioselectivity and reactivity in the palladium-catalyzed asymmetric allylic alkylation reaction.

In comparing the previously reported carbocyclic and *N*-benzoyl lactam substrate classes, we note two potentially distinguishing features. First, assuming the intermediacy of a palladium-bound enolate,⁷ we hypothesize that the *N*-functionalized lactams afford a more electron-rich enolate than the corresponding carbocyclic ketone analogues. The mechanism through which electrophilic alkylation occurs in canonical palladium-catalyzed Tsuji–Trost reactions is considered to be strongly influenced by the electronics of the nucleophile.⁸ Experiments suggest that alkylation of stabilized “soft” nucleophiles proceed through an outer-sphere attack of the electrophilic allyl species,⁹ whereas basic “hard” nucleophiles may undergo allylic alkylation via an inner-sphere process.¹⁰ Thus, modulating the electronics of the enolate may in turn affect the propensity for the C–C bond-forming event to proceed through an inner-sphere or outer-sphere mechanism. Indeed, we believe that our prototypical asymmetric allylic alkylation proceeds via an inner-sphere-type mechanism.¹¹

To probe the hypothesis that an increasingly basic palladium enolate is driving the enhanced enantioselectivity of the lactam substrates, we previously investigated β -enaminones (i.e., vinylogous amides) as electron-rich surrogates for the carbocyclic ketone substrate.¹² Interestingly, these vinylogous amides maintain reactivity and selectivity comparable to that

of typical ketone substrates, with enantioselectivities ranging from 52 to 90% ee but not greater than 90% ee.

In addition to perturbation of the electronics of the hypothesized palladium enolate, we considered potential chelation of the Lewis basic oxygen atom of the benzoyl lactam to the palladium center in a palladium-bound enolate. In lieu of a clear trend between enolate electronics and enantioselectivity, we sought to further explore this second hypothesis through design of a carbocyclic class of substrates bearing a Lewis basic heteroatom in the α '-position. Simultaneously considering synthetic utility of such a substrate class lead us to α -enaminones (i.e., **1**).

To our delight, morpholine-containing allyl β -ketoester **1a** affords the desired product **2a** in quantitative yield and 95% ee under our previously reported conditions with **L2** (entry 9) in THF. Subsequent screening of reaction conditions reveals that enantioselectivity is a largely invariant solvent choice, and similar results are even obtained with the standard (*S*)-*t*-BuPHOX (**L1**) ligand in a variety of nonpolar solvents (Table 1). Given this, we selected ethyl acetate as an inexpensive, readily available, and environmentally benign solvent for use in subsequent development.

We then sought to explore the scope of the transformation across a variety of substitution patterns. Both yield and enantioselectivity are maintained across various α -substituents (Table 2). Interestingly, 2-methyl and 2-chloroallyl fragments also afford the desired product with high enantioselectivity, albeit with reduced yield in the 2-methyl case. It is worth noting that substitution at the 1 or 3 positions of the allyl group is not tolerated under these conditions. As previously mentioned, α -enaminones **2a–l** represent the first carbocyclic substrate class to achieve of enantioselectivities of up to 99% ee in this asymmetric allylic alkylation.

We then sought to probe further structural modifications to the carbocyclic backbone of the enolate fragment (Table 3). Piperidene-containing product **2m** was obtained in 99% yield and 99% ee, suggesting the distal oxygen of the morpholine ring is not critical for enantioinduction. Introduction of a β -methyl group to the enaminone affords a more sluggish reaction and reduced yield, whereas enantioselectivity is only slightly diminished (**2n**).¹³ We then aimed to explore the role of the potentially coordinating α -amine through cyclohexyl substrate **1o**. In accordance with our working hypothesis, product **2o** was obtained in high yield (93%) but with reduced enantioselectivity (72% ee). Considering the possibility of α -nitrogen chelation, we aimed to explore the effects of perturbations in the N–Pd–O bite angle by preparing an analogous five-membered cyclic α -enaminone substrate, **1p**. Under the optimized reaction conditions, substrate **1p** affords the desired product **2p** in 94% yield and a reduced 83% ee.

Thus far, the trends in observed product enantioenrichment with respect to substrate modification are qualitatively consistent with the proposition that enhancement in enantioselectivity of the allylic alkylation reaction may arise from secondary chelation of α -heteroatoms to the metal center in the hypothesized palladium enolate. However, we note

that these are only observations, and a thorough mechanistic study will be required to delineate the potentially numerous factors that influence enantioselectivity.

We next turned our attention to investigating the synthetic utility of the chiral quaternary-center-containing α -enaminone products for access to potential synthetic building blocks. Treatment of enaminone **2a** with hydrochloric acid in a methanol–water mixture revealed the latent 1,2-diketone functionality, providing compound **3** in 72% yield. Unfortunately, the analogous reaction of **2a** with aniline and catalytic tosic acid in toluene affords the transaminated product **4** in only modest 35% yield. However, **2a** is a competent substrate for Fisher indolization, providing indole **5** in nearly quantitative yield (over two steps). 2-Morpholine-substituted enaminones have also been utilized as precursors to pyrazole-based inhibitors of blood coagulation factor Xa by reaction with *p*-methoxyphenylchlorohydrazones.¹⁴ Accordingly, when treated with methyl (Z)-2-chloro-2-(2-(4-methoxyphenyl)-hydrazineylidene)acetate, enaminone **2a** yields the corresponding pyrazole **6** in 46% yield (Scheme 1). Further functionalization at the β -position of enaminone **2a** may be achieved through an electrophilic bromination with NBS and subsequent Suzuki–Miyaura cross-coupling with phenyl boronic acid, affording compound **7** in 58% yield over two steps.

In conclusion, we present α -enaminones as a new substrate class for the palladium-catalyzed decarboxylative allylic alkylation. Product yields of up to 99% and enantioselectivities of up to 99% ee are achieved. The quaternary-center-containing enaminone products are demonstrated to be competent precursors in a variety of postalkylation synthetic transformations. In addition to serving as useful synthetic building blocks, the α -enaminone substrate class and its derivatives offer new insight into the potential role of α -heteroatom chelation for general enhancement of enantioselectivities for the palladium-catalyzed allylic alkylation reaction. Studies to elucidate the effect of these coordinating groups are currently in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- (13). The recovered starting material (1m) of this reaction was isolated in 18% yield and 99% ee. When the reaction was stopped at 12 h, the recovered starting material was obtained in 75% yield and 16% ee. This corresponds to a modest s value of 3.3. These data indicate a small but notable relative preference for one enantiomer of the starting material as a substrate for the stereoablative decarboxylation beginning the catalytic cycle of the reaction, which to our knowledge is only observed in this specific substrate. In other cases, we have studied that there is indiscernible kinetic resolution of the starting allyl esters.
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Figure 1.

(a) Previous report of allylic alkylation in the context of carbocyclic allyl β -ketoesters.^{5a} (b) Extension of the methodology to *N*-benzoyl lactams.⁶ (c) Hypothesis-driven substrate design presented herein.

Scheme 1.
Enaminone Product Transformations

Table 1.

Solvent and Ligand Screen for the Enantioselective Decarboxylative Allylic Alkylation of Enaminone 1a^a

$(\pm)\text{-1a}$
 $\xrightarrow[\text{solvent (0.033 M), 40 }^{\circ}\text{C, 12 h}]{\text{Pd}_2(\text{dmdba})_3 \text{ (5 mol\%)}, \text{ligand (12.5 mol\%)}}$
 $(S)\text{-2a}$

entry	ligand	solvent	ee (%) ^b	entry	ligand	solvent	ee (%) ^b
1	L2	MeCN	88	8	L2	toluene	97
2	L2	dioxane	94	9	L2	EtOAc	98
3	L2	THF	95	10	L2	<i>i</i> -PrOAc	96
4	L2	2-MeTHF	96	11	L2	<i>i</i> -BuOAc	92
5	L2	Et ₂ O	97	12	L1	EtOAc	98
6	L2	DME	95	13	L1	toluene	94

$(S)\text{-t-BuPHOX (L1)}$
 $(S)\text{-(CF}_3)_3\text{-t-BuPHOX (L2)}$

^aConditions: β -ketoester (0.05 mmol), Pd₂(dmdba)₃ (5.0 mol %), ligand (12.5 mol %), solvent (1.5 mL), 40 °C, 12 h.^bDetermined by analytical chiral SFC. See Supporting Information for details.

Table 2.

Substrate Scope of the Enantioselective Decarboxylative Allylic Alkylation of Enaminones^a

entry	product	R ¹	R ²	yield (%) ^b	ee (%) ^c
1	2a	Me	H	95 (93) ^d	99 (98) ^d
2	2b	Et	H	99	98
3	2c	CH ₂ OTBS	H	96	99
4	2d	CH ₂ CH ₂ OTBS	H	93	99
5	2e	CH ₂ CH ₂ CO ₂ Me	H	98	97
6	2f	CH ₂ CH ₂ C(O)Me	H	90	94
7	2g	CH ₂ CH ₂ CN	H	99	94
8	2h	Bn	H	95	96
9	2i	<i>p</i> -(OMe)Bn	H	99	95
10	2j	<i>p</i> -(CF ₃)Bn	H	87	92
11	2k	Me	Me	92	99
12	2l	Me	Cl	58	99

^aConditions: β -ketoester (0.47 mmol), Pd₂(dmdba)₃ (5.0 mol %), (*S*)-*t*-BuPHOX (12.5 mol %), EtOAc (14 mL), 40 °C, 9 h.^bIsolated yield.^cDetermined by analytical chiral SFC. See Supporting Information for details.^dConditions: β -ketoester (12.3 mmol), Pd₂(dmdba)₃ (0.5 mol %), (*S*)-*t*-BuPHOX (1.3 mol %), EtOAc (37 mL), 40 °C.

Table 3.

Further Structural Variation of Enaminone^a

substrate	product	yield (%) ^b	ee (%) ^c
1a	2a	95	99
1m	2m	99	99
1n	2n	52	90
1o	2o	93	72
1p	2p	94	83

^a Conditions: β -ketoester (0.47 mmol), Pd₂(dmdba)₃ (5.0 mol %), (*S*)-*t*-BuPHOX (12.5 mol %), EtOAc (14 mL), 40 °C.^b Isolated yield.^c Determined by analytical chiral SFC. See Supporting Information for details. Values in red highlight deviations from those of model substrate **2a**.