Published in final edited form as:

Org Lett. 2020 June 05; 22(11): 4272–4275. doi:10.1021/acs.orglett.0c01303.

Palladium-Catalyzed Enantioselective Decarboxylative Allylic Alkylation of Acyclic α -*N*-Pyrrolyl/Indolyl Ketones.

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Abstract

The synthesis of fully substituted α -*N*-pyrrolyl and indolyl ketones via enantioselective palladium-catalyzed allylic alkylation is described. The acyclic ketones are alkylated in high yields and enantioselectivities through the use of an electron-deficient phosphinooxazoline ligand, furnishing a highly congested and synthetically challenging stereocenter. The obtained alkylation products contain multiple reactive sites poised for additional functionalization and diversification.

Graphical Abstract

Aromatic nitrogen heterocycles, such as indoles and pyrroles, are high value motifs found in a wide range of natural products, agrochemicals, and pharmaceuticals.¹ In fact, indole is one of the most common heterocycles in FDA approved drugs.² While extensive efforts toward the functionalization of indole (or pyrrole) C2 and C3 positions have been described in the literature,³ functionalization of the N–H can be challenging due to the attenuated nucleophilicity of this position. This drawback led to N–H functionalization of such heterocycles being overlooked in the past. Recently, progress has been made in

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures and characterization data. (PDF)

intermolecular enantioselective *N*-alkylation of indoles.⁴ However, few methods have been reported for the enantioselective synthesis of fully substituted *N*-stereocenters, a motif which is found in a number of bioactive compounds (Scheme 1A).⁵ Furthermore, to the best of our knowledge, there is no report of the asymmetric synthesis of fully substituted α -*N*-pyrrolyl ketones, which is in sharp contrast to the wide utility of pyrrole in medicinal chemistry. In 2016, the Peters and Fu groups disclosed a photoinduced copper-catalyzed method for coupling racemic tertiary alkyl chloride electrophiles with carbazole and C3 protected indole derivatives to generate fully substituted *N*-stereocenters in high enantioselectivity (Scheme 1B).⁶ Due to the importance of these heterocycles, and in continuation of ongoing research from our group regarding the synthesis and utility of fully substituted acyclic enolates in palladium-catalyzed allylic alkylation,⁷ we sought to target this challenging structural motif by ultimate C–C bond formation, not C–N bond construction (Scheme 1C).

We began by investigating the synthesis of fully-substituted acyclic ketone enolates bearing an α -*N*-pyrrole substituent. Utilizing recently reported conditions,⁸ a highly selective enolization could be performed and, following enolate trapping with allyl chloroformate, provide a fully-substituted enol carbonate poised to undergo a subsequent palladium-catalyzed allylic alkylation (eq 1). This robust and operationally simple process relies on the combination of LiHMDS and dimethylethylamine (2 equiv each), and proceeds smoothly at ambient temperature.

(1)

With access to a stereodefined α -*N*-pyrrolyl enolate derivative established, we next sought to examine a subsequent palladium-catalyzed allylic alkylation to establish the desired tetrasubstituted stereocenter. Initially, a variety of ligands commonly utilized in the literature for this transformation were examined, with a representative set of these provided in Table 1 below. Use of the Trost type bisphosphine ligand **L1** in a 2:1 hexane/toluene solvent mixture led to formation of the desired product in a promising 51% ee (entry 1). Switching to the phosphinooxazoline (PHOX) ligand **L2**, ee decreased slightly to 34% (entry 2). We were pleased to find, however, that the use of the electron-deficient PHOX ligand **L3** provided the desired product in an improved 85% ee. However, no further increase in selectivity was observed through the use of even more electron-deficient ligands, such as **L4** (entry 4). Continuing with PHOX ligand **L3**, a screen of solvents and conditions revealed that a 2:1 hexane/toluene mixture was indeed the optimal solvent for this transformation, and that the catalyst loading could be significantly lowered to 0.25 mol % Pd₂(dba)₃ and 0.6 mol % **L3**. With these conditions, the alkylation product is obtained in a high 86% ee and an excellent 96% isolated yield (entry 7).

Having identified optimized reaction conditions, we next examined the scope of the transformation. A variety of substrates containing different α -alkyl and ketone aryl groups were synthesized and subjected to the optimized reaction conditions (Scheme 2). All enol carbonate substrates were prepared with excellent *E/Z* selectivity (>98:2). Substrates bearing simple α -alkyl groups such as ethyl (**2b**) and methyl (**2f**) provided the alkylation products in excellent 98% yield and 90% ee in both cases. Notably, alkylation product **2f** was prepared on gram-scale with no significant change in either yield or ee. Substrate **2c** bearing an *n*-pentyl chain and **2d** bearing a branching isobutyl substituent both proceeded well, with the alkylation products being afforded in 91% and 94% ee, respectively, both in excellent yields. A slightly decreased 84% ee was obtained with α -benzyl substrate (**2e**). Examining the electronic effects of the ketone aryl substituent revealed that both donating and withdrawing groups were tolerated (**2g–2l**). Notably, alkylation product **2k** with a *p*-Br phenyl group was obtained in 90% yield and an excellent 97% ee, and contains multiple reactive functionality that may be utilized for subsequent synthetic manipulations. We were pleased to find that sterically demanding substrate **2m** bearing an *o*-tolyl substituent performed well in the transformation, with the product obtained in 85% yield and a high 90% ee. Additionally, substitution at the 2-position of the α -*N*-pyrrole was tolerated, forging an exceedingly hindered tetrasubstituted stereocenter in a high 90% ee (i.e., **2n**). From this result, we were inspired to investigate additional, bulkier α -*N*-indole containing substrates (**2o–2r**), finding these to perform well and providing the alkylation products in excellent 90–95% ee.

With a scope of the transformation established, we next sought to examine the importance of enolate geometry on the selectivity of the transformation (eq. 2). Enol carbonate substrate **1f** was prepared as a 61:39 *E/Z* mixture via a nonselective enolization, and subjected to the optimized allylic alkylation conditions. The resultant alkylation product was obtained in an excellent 94% yield, but with a diminished 65% ee, highlighting the importance of synthesizing the starting enol carbonate as a single geometric isomer. This result runs contrary to the alkylation of acyclic ketones bearing all-carbon substituents in which we found the starting enolate geometry of acyclic ketones was inconsequential for obtaining high selectivity.^{7b} This divergence in reactivity may be due to the electron-rich nature of the α -*N*-heterocyclic substrates used herein, which may facilitate a faster reductive elimination and outcompete enolate equilibration of an intermediate Pd enolate, thereby reacting to form the C–C bond through both geometries, and with only moderate observable enantioselectivity.

(2)

Lastly, we turned toward examining product derivatizations (Scheme 3). Divergent functionalization of the ketone, terminal olefin, and pyrrole are all possible. Treatment of the alkylation product **2f** to cross metathesis conditions using methyl acrylate and Hoveyda-

Grubbs 2nd generation catalyst provided unsaturated ester **3** in an excellent 95% isolated yield. Substituted styrene **4** could be obtained in 84% yield via a Wittig olefination. Functionalization of the pyrrole could be realized by treatment with Eschenmoser's salt, providing tertiary amine containing product **5** in an excellent 93% yield.

In conclusion, we have developed a general method to access fully-substituted α -*N*-pyrrolyl and indolyl ketones. Both use of the electron-deficient phosphinooxazoline ligand **L3**, and preparation of the starting enol carbonates as single geometric isomers, are crucial for obtaining high enantioselectivity. The transformation proceeds efficiently with only 0.25 mol % of Pd₂(dba)₃ and 0.6 mol % ligand, and the resulting alkylated products could be selectively functionalized at different reactive sites in high yields.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

We thank NIH-NIGMS (R01GM080269), the Gordon and Betty Moore Foundation, and Caltech for financial support. E.J.A. thanks the National Science Foundation for a predoctoral fellowship. We thank Dr. David VanderVelde (Caltech) for NMR expertise. Dr. Scott Virgil (Caltech Center for Catalysis and Chemical Synthesis) is thanked for instrumentation and SFC assistance. Dr. Michael Takase (Caltech) and Lawrence Henling (Caltech) are acknowledged for X-ray analysis.

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A. Representative biologically active N-alkylated heterocycles

B. Asymmetric copper-catalyzed C–N cross-couplings induced by visible light

C. Pd-catalyzed decarboxylative allylic alkylation (this research)

Scheme 1.
Significance and Foundational Research

Scheme 2. Substrate Scope of Palladium-Catalyzed Allylic Alkylation^a^aReactions performed on 0.2 mmol scale unless stated otherwise. ^bYield of isolated product.^cDetermined by chiral SFC analysis. ^dAbsolute configuration of **2e** determined by single crystal X-ray diffraction, all other compounds are assigned by analogy. ^eReaction performed on 0.1 mmol scale. ^fReaction performed on 0.107 mmol scale.

Scheme 3.
Derivatization of Alkylation Products

Table 1.Optimization of Palladium-Catalyzed Allylic Alkylation^{a,b}

entry	ligand	solvent	%ee ^c (yield)
1	L1	2:1 hexane/PhMe	–51
2	L2	2:1 hexane/PhMe	34
3	L1	2:1 hexane/PhMe	85
4	L4	2:1 hexane/PhMe	84
5	L3	benzene	80
6	L3	methylcyclohexane	81
7 ^d	L3	2:1 hexane/PhMe	86 (96)

^a Conditions: 0.1 mmol **1a**, 2.5 mol % Pd₂(dba)₃, 6 mol % ligand, 2.0 mL solvent.^b Conversion over 95% if no yield from isolated product stated.^c Determined by chiral SFC analysis.^d Reaction performed with 0.2 mmol **1a**, 0.25 mol % Pd₂(dba)₃, 0.6 mol % ligand, and 2.0 mL solvent.