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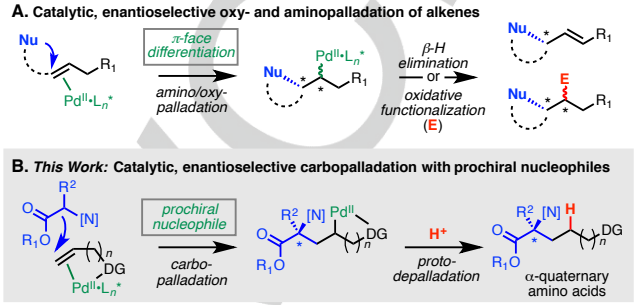
Catalytic, Enantioselective α-Alkylation of Azlactones with Non-Conjugated Alkenes via Directed Nucleopalladation

Sri Krishna Nimmagadda[†,§], Mingyu Liu[†,§], Malkanthi K. Karunananda[†,§], De-Wei Gao[†], Omar Apolinar[†], Jason S. Chen[†], Peng Liu[‡,], Keary M. Engle[†,*]*

Abstract: A palladium(II)-catalyzed enantioselective α-alkylation of azlactones with non-conjugated alkenes is described. The reaction employs a chiral BINOL-derived phosphoric acid as the source of stereoinduction and a cleavable bidentate directing group appended to the alkene to control the regioselectivity and stabilize the nucleopalladated alkylpalladium(II) intermediate in the catalytic cycle. A wide range of azlactones were found to be compatible under the optimal conditions to afford products bearing α,α-disubstituted α-amino acid derivatives with high yields and high enantioselectivity.

Palladium(II)-catalyzed Wacker-type nucleopalladation of alkenes is a synthetically enabling mode of reactivity to conjoin alkenes and various oxygen and nitrogen nucleophiles.[1,2] Stereocontrol in such reactions has been actively studied, most typically focused on stereodifferentiation of the two faces of the C=C bond (Scheme 1A).[2] Carbon (pro)nucleophiles, such as 1,3-dicarbonyls, also participate in nucleopalladation, though such reactions have been less extensively studied. In 1965, Tsuji described an early example of stoichiometric carbopalladation of 1,5-cyclooctadiene with sodium dimethyl malonate. The synthetic utility of stoichiometric carbopalladation was later demonstrated by Holton and Hegedus.[3] In the early 2000s, Widenhoefer reported a series of seminal studies on catalytic intramolecular redox-neutral cyclization of 1,3-dicarbonyl moieties and alkenes.[4] In 2016, our laboratory described substrate-directed hydrocarbofuntionalization of non-conjugated alkenes with various carbon (pro)nucleophiles.[5] He, Peng, and Chen recently identified a monodentate chiral oxazoline ligand to render this transformation enantioselective with internal alkenes.[6]

With *prochiral* nucleophiles, carbopalladation presents the opportunity for stereocontrol in a manner that is distinct from cases with oxygen and nitrogen nucleophiles, namely establishing the absolute configuration of the nucleophilic carbon atom. α-Alkylation of carbonyl-based pronucleophiles is an extraordinarily enabling synthetic technology; however, non-conjugated alkenes have only been rarely employed as electrophiles despite their clear advantages over alkyl (pseudo)halides in terms of cost and availability.[7,8] The use of non-conjugated alkenes and carbonyl pronucleophiles as reaction partners in a Wacker-type manifold would represent a powerful approach towards enantioselective α-alkylation yet remains unknown to the best of our knowledge.[9] The goal of the present study was to demonstrate this concept in the context of a synthetically significant problem, the α-alkylation of masked amino acids to form α-quaternary amino acid products (Scheme 1B).



Scheme 1. Background and Project Synopsis

We envisioned that such an approach could offer an appealing approach to access α-quaternary amino acids bearing a variety of substitution patterns. α-Quaternary amino acids are sought-after target compounds owing to their unusual conformationally constrained nature compared to natural α-amino acids, which imparts unique biological activity,.[10] The widespread interest of α-quaternary amino acids has inspired the development of different synthetic methods, including (a) chiral-auxiliary-controlled electrophilic alkylation of amino acid enolate equivalents (b) asymmetric Strecker-type reactions, and (c) ring-opening reactions of chiral quaternary oxazolones.[11] Herein, we report a catalytic system to promote the stereocontrolled carbopalladation of a prochiral amino acid equivalent followed by protodepalladation of the resulting chelation stabilized alkylpalladium(II) intermediate to produce diverse α-quaternary amino acids.

To reduce this idea to practice, we elected to explore the combination of azlactones[12] as the masked amino acid pronucleophiles and chiral phosphoric acids (CPAs)[13] for stereoinduction. Several important precedents informed this choice. Specifically, multiple groups have previously described CPA-catalyzed enantioselective α-functionalization of azlactones with a variety of electrophiles.[14] Additionally, stereocontrol in an assortment of mechanistically distinct palladium(II)-catalyzed reactions has been achieved using CPAs as chiral ligands/promoters.[15] In our proposed transformation, we envisioned the stereoinduction to occur through coordination of the CPA as an X-type ligand to palladium(II), with enantioselectivity thus manifested in either the nucleopalladation step or subsequent protodepalladation step.

We initiated the investigation by examining the reaction between alkene **1** and azlactone **2** with different palladium precatalysts using (*R*)-TRIP (**PA6**) as chiral ligand. After extensive optimization of reaction conditions (see SI), we found that by using **2** (3 equiv) in benzene (0.2 M) at 70 °C we were able to obtain the desired product **3** in 72% with 86:14 *er*. A notable finding from the optimization experiments was that the use of a non-polar solvent medium was critical for stereoinduction. We then explored a range of BINOL-derived phosphoric acids with different substituents at the 3 and 3' positions, as shown in Table 1. Screening of various chiral phosphoric acids **PA1**–**PA4** gave the product with moderate *er* (entries 1–4, Table 1). Upon modulating the steric bulk on the 3, 3' substituents of the phosphoric acid promoter (**PA5**–**PA7**), we observed that TCYP (**PA7**), which contains cyclohexyl

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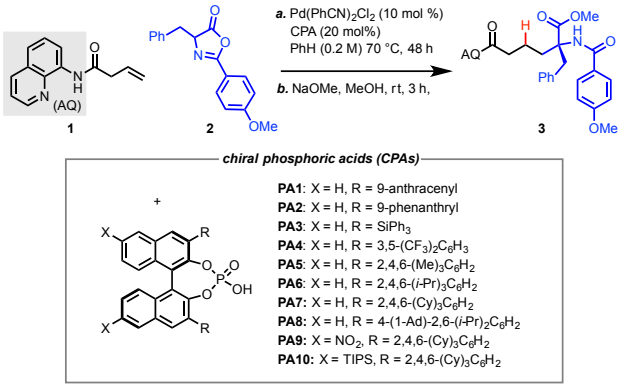
substituents, improved the *er* to 91:9 with 90% yield (Table 1, entry 8). Further increasing the level of steric encumbrance around the phosphoric acid by using **PA8** gave 87:13 *er* and 79% yield (Table 1, entry 9). Additional optimization revealed that 55 °C temperature and 0.1 M concentration were optimal for this reaction, improving the *er* to 93:7 with 74% yield (Table 1, entry 11). Tuning the electronic properties of the CPA in order to perturb the pK_a of the O–H bond did not significantly impact the reaction, with both electron-donating and -withdrawing groups showing similar *er* (Table 1, entries 12 and 13).

Table 1. Optimization of the Reaction Conditions[a]

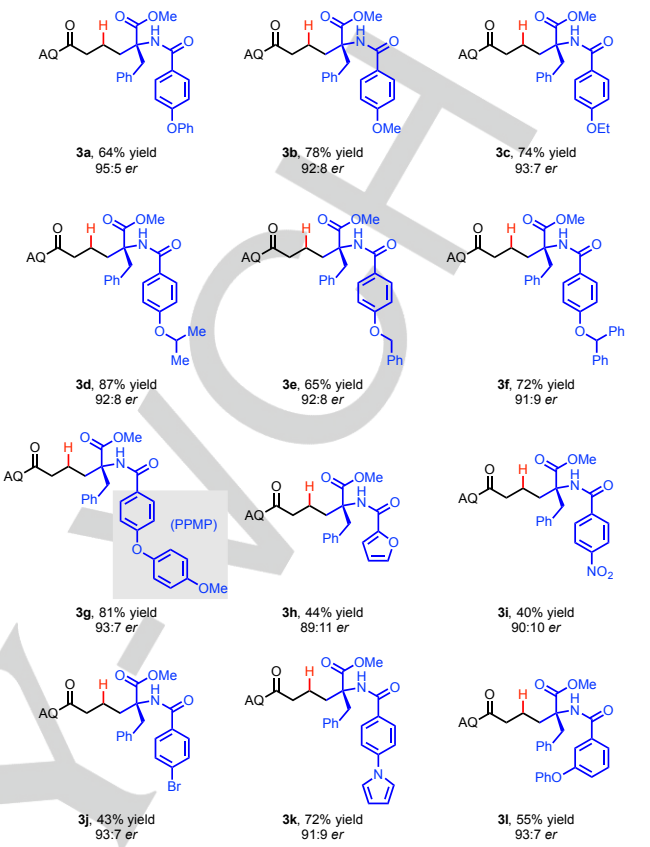


Entry	Promoter (20%)	Yield[b] (%)	Enantiomeric Ratio (*er*)[c]
1	-	12	50:50
2	**PA1**	74	83:17
3	**PA2**	69	75:25
4	**PA3**	29	55:45
5	**PA4**	69	65:35
6	**PA5**	73	80:20
7	**PA6**	72	86:14
8	**PA7**	90	91:9
9	**PA8**	79	87:13
10[d]	**PA7**	75	92:8
11[d, e]	**PA7**	**74**	**93:7**
12[d, e]	**PA9**	65	91:9
13[d, e]	**PA10**	71	94:6

[a]Reaction conditions: **1a** (0.05 mmol), **2a** (3.0 equiv), $Pd(PhCN)_2Cl_2$ (10 mol %), ligand (20 mol%), anhydrous benzene (0.2 M), 70 °C, 2 days. [b]Isolated yield. [c]Enantiomeric ratio determined by chiral SFC. [d]At 0.1 M concentration. [e]At 55 °C, 4 days.

We next probed the effect of different substituent at the C-2 position, with the aim of identifying a generally useful azlactone protecting group that would provide high yield and *er* with various amino acid nucleophiles bearing different side chains.[16] In general, electron-donating groups on the *para* position of the aryl group provided the highest yield and enantiomeric ratio (**3a**–**3g**, Table 2; for additional examples, see Figure S2 in the SI). In particular, we identified the 4-phenoxybenzoyl group in **3a** as highly effective, providing 95:5 *er* and 64% yield. We speculated that the 4-OPh group could be involved in π–π-stacking with the chiral phosphoric acid.[17] Based on this idea, we then tested the 4-methoxyphenoxyphenyl (PPMP) group, which led to further improvement in yield, while maintaining high enantioselectivity. Gratifyingly, using the PPMP-containing nucleophile, **3g** was formed with 81% yield and 93:7 *er*. Notably, the 3-OPh group also afforded product **3l** with a high *er* of 93:7 and 55% yield. Substrates bearing electron-withdrawing groups on the *para* position of the aryl group led to diminished yields (**3i**, Table 2 and Figure S2).

Table 2. Examination of Different C-2 Substituents on the Azlactone Nucleophile[a–c]



[a]Reaction conditions: **1a** (0.05 mmol), **2a** (3.0 equiv), $Pd(PhCN)_2Cl_2$ (10 mol %), **PA7** (TCYP) (20 mol%), anhydrous benzene (0.1 M), 55 °C, 4 days. [b]Isolated yield. [c]Enantiomeric ratio determined by chiral SFC.

We then examined different C-4 substituents on the azlactone using the PPMP protecting group. Azlactones derived from phenylalanine containing electron-releasing groups (-CH_3, -OCH_3) or weak electron-withdrawing groups (-Br, -Cl and -F) on the aryl ring showed high yields and excellent *er* values (**4a**–**4g**, Table 3). Stronger electron-withdrawing groups (-CF_3 and -NO_2) gave products with slightly diminished yields and *er* values (**4h** and **4i**), presumably due to attenuated nucleophilicity. Azlactones containing heterocyclic groups (indole, thiophene and furan) (**4k**–**4l**) and naphthyl groups (**4m** and **4n**) were also effective. Interestingly, with azlactones bearing α-substituents other than benzyl moieties, high yields were maintained (**4p**–**4s**), though enantioselectivity was more modest. The alkene scope proved to be rather limited. When an α-Me-substituted alkenyl AQ amide was tested, the reaction was low-yielding, even at 70 °C,[18] Internal alkenes were unreactive in this system. Taken together, these results speak to the sensitivity of the overall coordination assembly to subtle steric perturbations.

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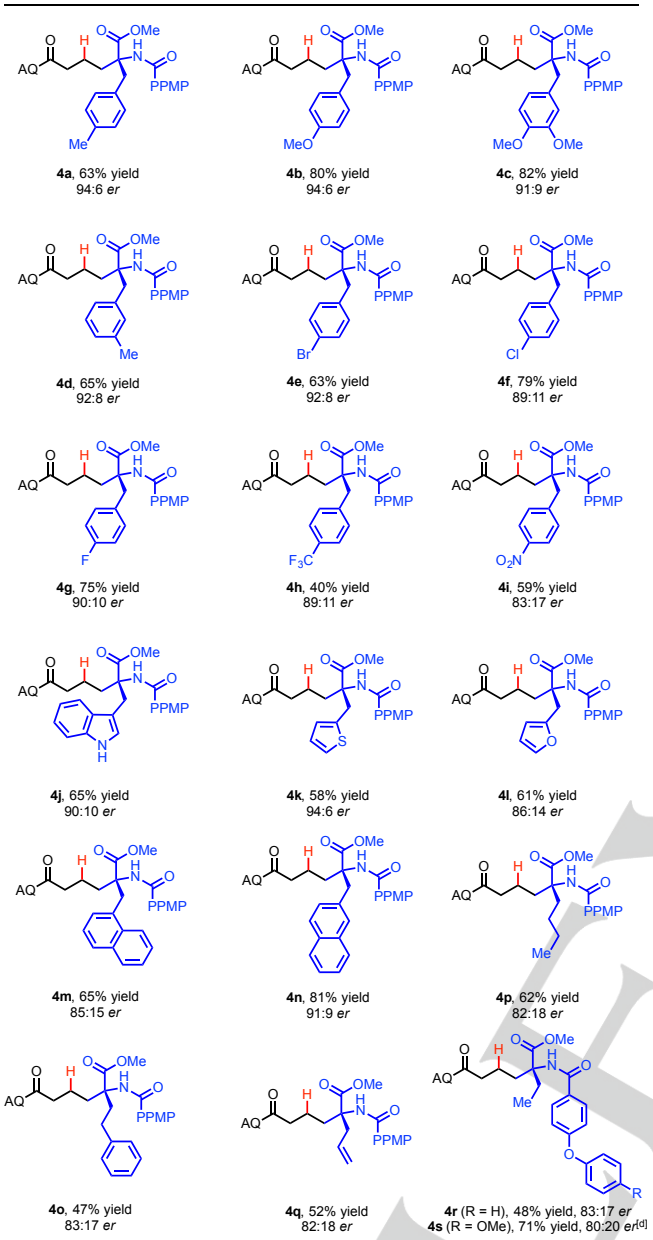
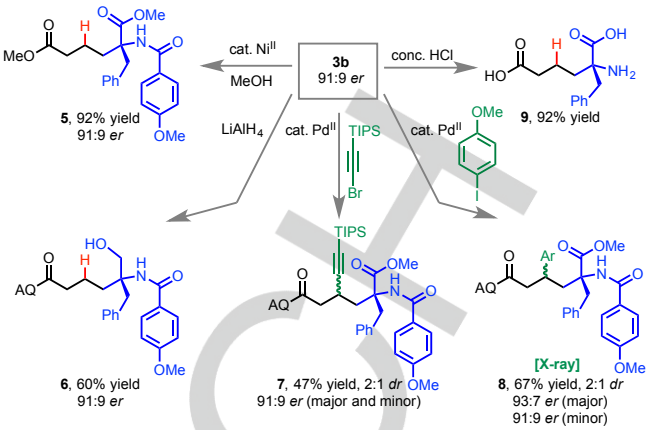
Table 3. Scope of Azlactones with Different C-4 Substituents[a–c]



[a]Reaction conditions as in Table 2. [b]Isolated yield. [c]Enantiomeric ratio determined by chiral SFC. [d]70 °C, 2 d. [e]The relative stereochemistry could not be assigned.

To demonstrate the synthetic utility of this method, we carried out a series of diversification reactions with representative enantioenriched product (**3b**), and in all cases the stereochemical integrity of the newly formed chiral center was maitained (Scheme 2). Firstly, the 8-aminoquinoline directing group could be selectively cleaved using Ohshima's alcoholysis protocol catalyzed by Ni(tmhd)$_2$ (tmhd = 2,2,6,6,-tetramethyl-3,5-heptanedionate) to give product **5**.[19] Additionally, the ester functional group could be reduced selectively to afford chiral aminoalcohol **6**.[20] We also found that product **3b** could undergo Daugulis-type alkynylation (**7**)[21] and arylation (**8**)[22] in 2:1 *dr* without erosion of stereochemical purity, thereby effecting a net two-step alkene 1,2-dicarbofunctionalization. The absolute configuration of the α-position for all of products was assigned as *S* by analogy to compound **8,** the structure of which was confirmed by single-crystal X-ray crystallography (see SI). Lastly, we were also able to perform global deprotection with 6 M HCl to obtain free amino acid **9**.[23]



Scheme 2. Derivatization Reactions of **3b**

To elucidate the stereoinduction model in this unique enantioselective carbo-Wacker α-alkylation, we carried out a series of experimental and computational studies. We first subjected enantioenriched product to the reaction conditions and found that it did not undergo racemization (see SI). Next, we sought to determine the number of CPA molecules involved in the enantiodetermining step. To this end, we examined how the *ee* of a representative reaction changed as a function of the *ee* of the CPA. Using TRIP as a model CPA, we found strong linear correlation between TRIP *ee* and product *ee* (Figure 1). The absence of a non-linear effect is consistent with 1:1 Pd:CPA ratio in the enantiodetermining step, which informed subsequent computational studies.

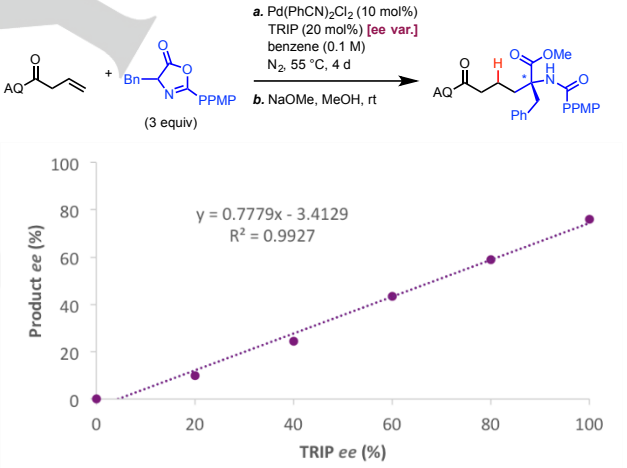


Figure 1. Correlation between CPA *ee* and Product *ee*.

Armed with this information, we performed density functional theory (DFT) calculations to probe the reaction mechanisms and the origins of enantioselectivity using **1** as the model substrate, **PA5** as the CPA ligand, and **2** as the azlactone (see SI: Figure S5 and Figure S6). For nucleopalladation, the activation free energy barrier for the (*S*)-nucleopalladation pathway (**TS1_S**, 10.3 kcal/mol) is lower than that of the (*R*)-pathway (**TS1_R**, 11.2 kcal/mol). However, the subsequent protodepalladation step has a higher activation energy, indicating that the nucleopalladation step is reversible[5,24] and therefore, the reaction is under Curtin–Hammett control. The CPA-assisted protodepalladation step to form the (*S*)-enantiomer (**TS2_S**) has a lower activation free energy (13.5 kcal/mol) than the protodepalladation to form the (*R*)-enantiomer (**TS2_R**, 14.9 kcal/mol). **TS2_R** is destablized by steric repulsions between the chiral azlactone and the CPA ligand.

The kinetic preference to form the (*S*)-enantiomer at the enantioselectivity-determining protodepalladation step is consistent with experimental selectivity.[25]

In conclusion, we have demonstrated a catalytic, enantioselective α-alkylation of azlactones with a non-conjugated alkenes that proceeds via stereoselective carbopalladation. The resulting products can be conveniently deprotected to reveal useful α-quaternary amino acid derivatives.

Acknowledgements

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Keywords: palladium • directing group • chiral phosphoric acid (CPA) • enantioselective • C–C bond formation

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[16] Across several representative examples, we found that yields and *er* values were consistent in reaction performed on 0.05-mmol scale to 0.3-mmol scale. On larger scale (1.0 mmol), the reaction progressed more slowly, leading to slightly lower yields, while maintaining similar *er*. We elected to perform the examples in Tables 2 and 3 on 0.05-mmol scale due to the valuable nature of **PA7** and because all of the reaction components have high formula weights, allowing for accurate measurement even on small scale.

[17] The 4-OPh group appears to be relatively close to the CPA ligand in the calculated enantioselectivity-determining transition state, **TS2_S,** supporting this explanation.

[18] Over several trials, yields ranged from 10–35%, with d.r. values ranging from 2:1 to >20:1.

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[25] The alternative diastereomeric palladium π-alkene intermediate and the corresponding nucleopalladation and protodepalladation transition states were also located computationally but were found to be higher in energy (see SI).

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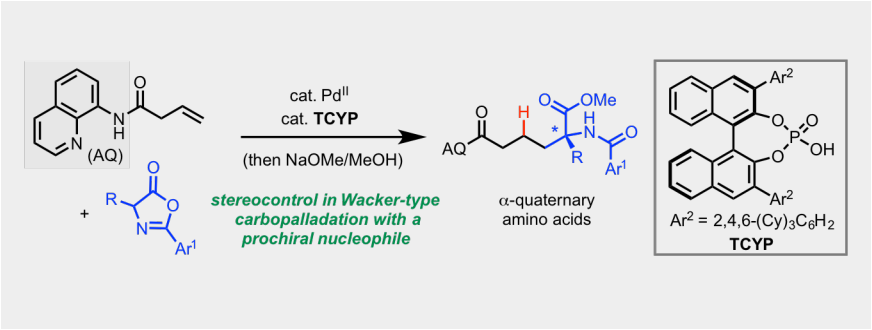

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Catalytic, Enantioselective α-Alkylation of Azlactones with Non-Conjugated Alkenes via Directed Nucleopalladation

C–C Bond Formation. A method to achieve asymmetric α-alkylation of azlactones with non-conjugated alkenes through the dual catalytic action of Pd(II) and a chiral phosphoric acid. The reaction enables expedient access to quaternary α-amino acid products.