VIP Synthetic Methods

DOI: 10.1002/ange.201207870

Palladium-Catalyzed Enantioselective Allylic Alkylations through C–H Activation**

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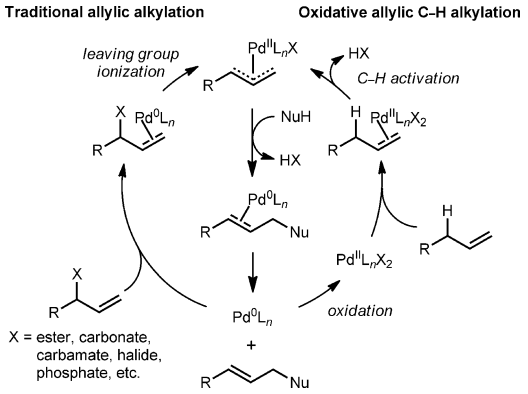
Metal-catalyzed asymmetric allylic alkylation (AAA) reactions, particularly those employing palladium,[1] copper,[2] iridium,[3] or molybdenum,[4] have found broad utility in the construction of a diverse array of enantioenriched products from achiral starting materials. Irrespective of the catalyst, however, one inviolable requirement for nearly all substrates that undergo these transformations is the presence of an allylic leaving group.[5] Such functionality permits an appropriate transition metal catalyst to transform one allylic substituent into another through a redox-neutral event (Scheme 1). One way to increase the efficiency and chemoselectivity of these reactions would be to break this paradigm



Scheme 1. Comparison of traditional and oxidative palladium-catalyzed allylic alkylations.

by developing an oxidative method to perform analogous AAA reactions with unfunctionalized alkenes. Specifically, the use of an allylic hydrogen atom as a leaving group would not only eliminate the need to install the allylic esters, carbonates, carbamates, halides, or phosphates necessary for traditional AAA reactions, but also avert the chemoselectivity issues that arise from carrying these reactive functional groups through a synthetic sequence by replacing them with relatively inert C–H bonds.

Stoichiometric palladium-mediated allylic alkylations of alkenes that proceed through insertion into allylic C–H bonds are well known,[6] but until recently, reports of metal-catalyzed allylic alkylations that did not require leaving groups were exceedingly rare.[7] In 2008, Shi and co-workers reported that $Pd(OAc)_2$, in the presence of 1,2-bis(benzylsulfinyl)ethane[8] and benzoquinone, catalyzes both the intramolecular allylic alkylation of activated and unactivated C–H bonds with β-dicarbonyl compounds and the corresponding intermolecular allylic alkylation of activated C–H bonds.[9] This latter finding was corroborated in a simultaneous disclosure by White and Young, who reported that $Pd(OAc)_2$, in the presence of 1,2-bis(phenylsulfinyl)ethane and 2,6-dimethylbenzoquinone, catalyzes the analogous intermolecular allylic C–H alkylation of activated C–H bonds with methyl nitroacetate.[10] These authors later expanded the scope of their work to include a similar intermolecular allylic C–H alkylation of unactivated C–H bonds.[11] There are, however, no reports of stoichiometric or catalytic allylic alkylations which proceed through C–H activation that are asymmetric. Herein we describe the first examples of such catalytic enantioselective allylic alkylations. These reactions are additionally noteworthy, because they stereoselectively generate quaternary carbon stereocenters, one of the most challenging feats in enantioselective catalysis,[12] and they employ prochiral nucleophiles, a class of substrates that chiral allylic alkylation catalysts often struggle to enantiodiscriminate.[13]

Given that the desired reactivity had been demonstrated, the focus of efforts to render allylic C–H alkylations enantioselective turned immediately to ligand design. Chiral phosphorus-containing compounds are the most successful class of ligands utilized in asymmetric catalysis.[14] At the outset of our program, however, there were claims about the unsuitable nature of phosphine ligands under the oxidative conditions necessary for palladium-catalyzed allylic C–H activation.[15] Nevertheless, the ubiquitous use of chiral phosphines and our success with such ligands for palladium-catalyzed AAA reactions led us to examine their use in allylic C–H alkylations, and we subsequently demonstrated that PPh_3, a common phosphine ligand, does indeed promote palladium-catalyzed allylic alkylation through C–H activation in a wide array of contexts.[16] Buoyed by this success, we evaluated many known chiral mono- and bidentate phosphorus ligand classes for analogous enantioselective reactions; all such investigations were fruitless.[17]

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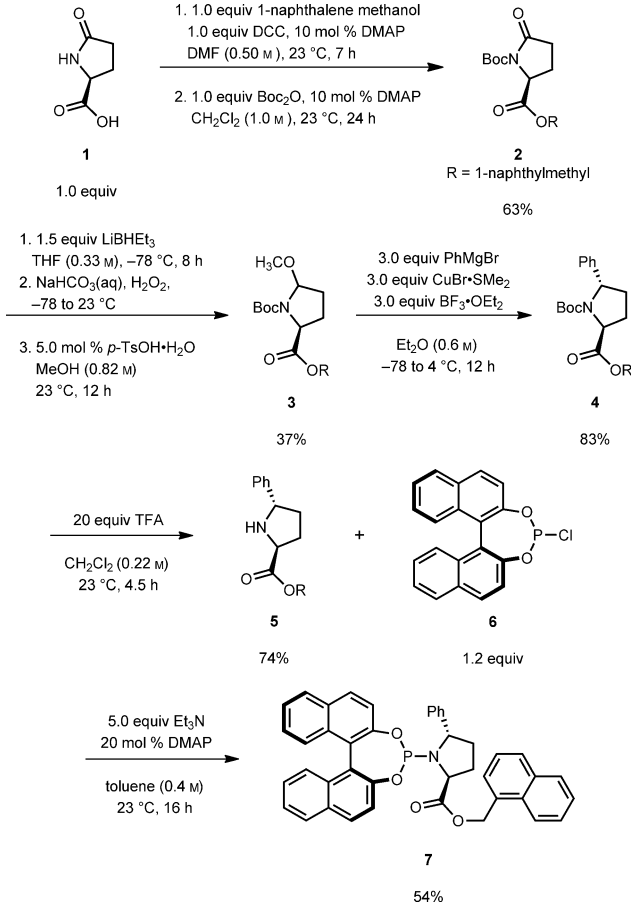
[**] We thank the National Science Foundation for their support of our programs and Johnson Matthey for generously providing us with palladium salts. D.A.T. acknowledges support from a Stanford Graduate Fellowship (The William K. Bowes, Jr. Foundation) and an Eli Lilly and Company Graduate Fellowship. E.J.D. acknowledges an Explo'ra Sup grant from CPE Lyon.

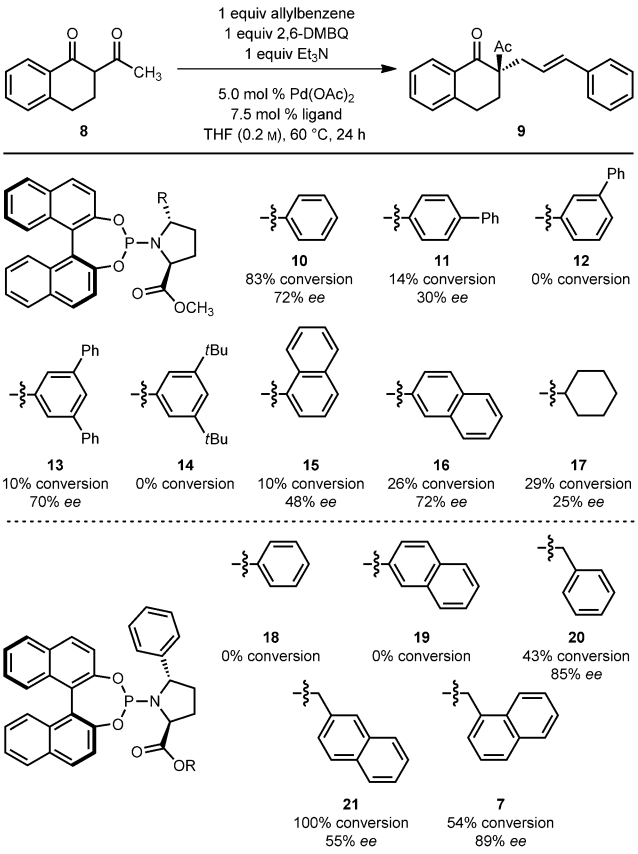
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201207870.

Ultimately, we were guided by our group's previous efforts in the design of ligands for asymmetric palladium-catalyzed trimethylenemethane cycloadditions[18] to the discovery of a novel class of pyroglutamic acid derived[19] phosphoramidite ligands that promote palladium-catalyzed allylic C–H alkylations. The preparation of this novel class of chiral phosphoramidite ligands begins with pyroglutamic acid, both enantiomers of which are readily commercially available. In a representative synthesis, esterification of L-pyroglutamic acid (**1**) with 1-naphthalene methanol using *N*,*N*′-dicyclohexylcarbodiimide (DCC) in the presence of catalytic 4-dimethylaminopyridine (DMAP) followed by carbamate formation with di-*tert*-butyl dicarbonate (Boc_2O) affords pyrrolidine **2** in 63% overall yield (Scheme 2). Chemoselective semireduction of the lactam carbonyl with lithium triethylborohydride and then treatment with methanol and catalytic amounts of *para*-toluenesulfonic acid monohydrate provides the corresponding aminal **3** in 37% yield. Copper(I) bromide dimethyl sulfide mediated addition of phenylmagnesium bromide in the presence of boron trifluoride diethyl etherate gives the desired *trans*-substituted pyrrolidine **4** in 83% yield. Notably, in every such reaction we have performed, the diastereocontrol of the cuprate addition has been complete. Cleavage of the *tert*-butyl carboxyl group with trifluoroacetic acid (TFA) liberates the unprotected pyrrolidine **5** in 74% yield; compound **5** undergoes base-promoted coupling with a slight excess of chlorophosphite **6** to afford representative ligand **7** in 54% yield. Importantly, ligands prepared with the enantiomer of **6** were inferior both with respect to reactivity and stereoselectivity. One noteworthy feature of this synthesis with particular relevance to ligand optimization is its flexibility. At the respective stages of the modular sequence, different ester, aryl, and diol pieces could be introduced, thereby allowing rapid access to a diversity of ligand structures in the service of structure–activity relationship studies. Use of (*S*)-BINOL with the (*S*,*S*)-pyrrolidine proved to be the matched case.



Scheme 2. Synthesis of chiral phosphoramidite ligands based on pyroglutamic acid.

Experiments designed to evaluate a series of ligands in this class employed equimolar amounts of 2-acetyl-1-tetralone (**8**), allylbenzene, 2,6-dimethylbenzoquinone (2,6-DMBQ), and Et_3N in the presence of $Pd(OAc)_2$ (5.0 mol%) and the ligand (7.5 mol%) in THF at 60 °C for 24 h. When the pyrrolidine subunit is substituted with a phenyl ring (**10**), allylic C–H alkylation product **9** is obtained in 83% conversion and 72% *ee* (Scheme 3).[20] Substitution on this aromatic ring is not well tolerated. A reaction with the corresponding *para*-biphenyl ligand **11** gave **9** in only 14% conversion and 30% *ee*, and the *meta*-biphenyl analogue **12** gave no desired product at all. The *meta*-terphenyl ligand **13** yielded **9** in 70% *ee*, but only at 10% conversion. Further increasing the steric bulk is deleterious, as the reaction with



Scheme 3. Palladium-catalyzed enantioselective allylic alkylations through C–H activation with selected phosphoramidite ligands.

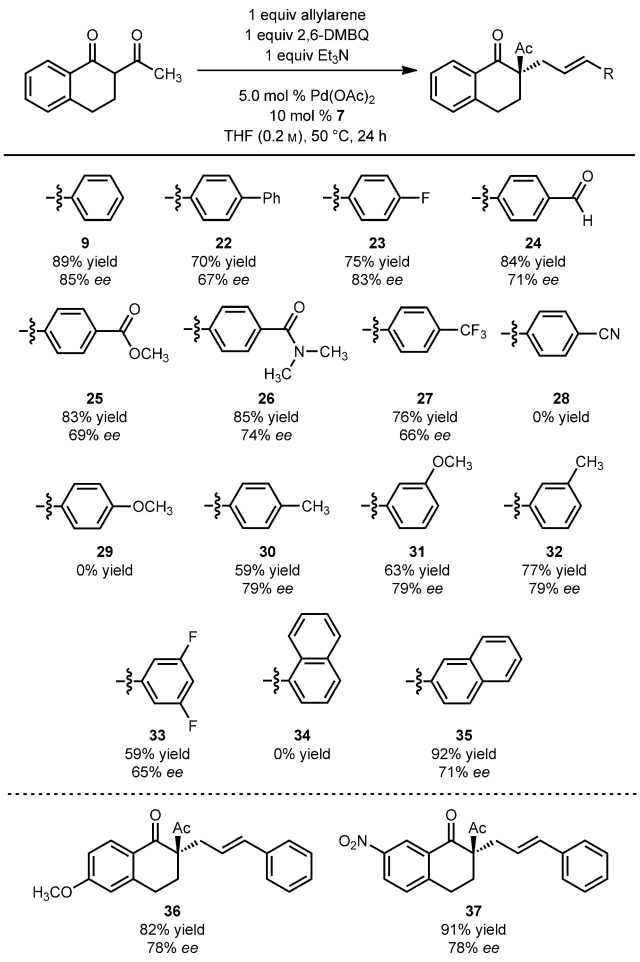
the 3,5-di-*tert*-butylphenyl ligand **14** gave no desired product. Neither the 1-naphthyl (**15**) or 2-naphthyl (**16**) ligands offered improvement in terms of conversion or enantioselectivity, and replacement of the aromatic ring with cyclohexane (**17**) provided **9** in only 29% conversion and 25% *ee*.

The effect of the ester substituent of **10** on both the reactivity and enantioselectivity of the allylic C–H alkylation was next examined (Scheme 3). Replacing the methyl with either a phenyl (**18**) or 2-naphthyl (**19**) group gave inactive catalysts, presumably because these sterically demanding groups inhibit the C–H activation event. However, substitution with a benzyl group (**20**) yielded **9** in 43% conversion and 85% *ee*. The reaction conversion increased to 100% with the corresponding benzylic 2-naphthyl ligand **21**, and the product was obtained in 55% *ee*. With a benzylic 1-naphthyl ester (**7**), the reaction gave **9** in 54% conversion and 89% *ee*.

Although the palladium-catalyzed allylic C–H alkylation could be conducted with high enantioselectivity, incomplete conversion was a significant problem, and it was attributed at least in part to catalyst decomposition. An extensive screen of 11 solvents from methylene chloride through to DMSO and DMF showed THF to be superior. At 40 °C, *ee* values as high as 97% but only 53% conversion were observed, while at 80 °C complete conversion occurred but the *ee* dropped to 76%. Varying concentration and substrate ratios beyond 1:1 showed no beneficial effect. Through such optimization studies, it was found that when the ligand loading was increased to 10 mol%, the temperature decreased to 50 °C, and the catalyst dosed in two portions at the beginning of the reaction and after three hours, the desired product **9** could be isolated in 89% yield and 85% *ee* (Scheme 4).

Conducting the reaction with the corresponding allyl-*para*-biphenyl electrophile gave **22** in 70% yield and 67% *ee*, while the *para*-fluoro analogue provided **23** in 75% yield and 83% *ee*. In a demonstration of the mildness of the reaction conditions, **24** was obtained in 84% yield and 71% *ee* despite the presence of an aldehyde. The corresponding methyl ester and dimethyl amide gave **25** in 83% yield and 69% *ee* and **26** in 85% yield and 74% *ee*, respectively. Though the *para*-trifluoromethyl derivative provided **27** in 76% yield and 66% *ee*, the corresponding nitrile electrophile fails to react, presumably because palladium coordination to the nitrogen lone pair is inhibitory.

Highly electron-rich aromatic rings, such as that present in **29**, disfavor the C–H activation event, but moderately electron-rich substrates are tolerated, as **30** was isolated in 61% yield and 79% *ee*. When the *para*-methoxy group is replaced with a *meta*-methoxy group, the strong π-donating nature of the substituent is overwhelmed by its σ-withdrawing ability, and the correspondingly electron-deficient ring participates in the desired reaction to provide **31** in 63% yield and 79% *ee*. The *meta*-methyl substrate gave **32** in 77% yield and 79% *ee*, and the corresponding 3,5-difluoro substrate provided **33** in 59% yield and 65% *ee*. Steric bulk in the *ortho*-position relative to that undergoing C–H activation is generally not tolerated, as the failure to obtain **34** shows, but 2-allylnaphthalene reacted to give **35** in 92% yield and 71% *ee*. Electron-rich and electron-poor 2-acetyl-1-tetralones also participate in the allylic C–H alkylation: reaction with 2-acetyl-6-methoxy-1-tetralone provided **36** in 82% yield and 78% *ee* and 2-acetyl-7-nitro-1-tetralone analogously gave **37** in 91% yield and 78% *ee*. Notably, when the reaction was conducted in the absence of a phosphoramidite ligand, no desired product was observed, thus highlighting the essential role of the ligand in both enabling the desired reactivity and controlling the stereochemical course of the reaction.



Scheme 4. Substrate scope of palladium-catalyzed enantioselective allylic alkylations through C–H alkylation. Catalyst added in two portions: 2.5 mol% $Pd(OAc)_2$ and 5 mol% **7** at the beginning of the reaction and 2.5 mol% $Pd(OAc)_2$ and 5 mol% **7** after 3 h; reactions performed on a 0.100 mmol scale. The absolute stereochemistry of the products was assigned by analogy to **9**, the configuration of which was determined to be *S* by a comparison of its optical rotation to that reported in a previous synthesis.[21] See the Supporting Information for details.

In conclusion, we report the first examples of catalytic enantioselective allylic C–H alkylations, a transformation to date unknown with any metal and one that now provides a complementary approach to traditional methods for the synthesis of enantioenriched allylic substitution products. This achievement was enabled by the discovery of a new class of phosphoramidite ligands, which promote both the palladium-catalyzed C–H activation and the subsequent alkylation event. Investigations into other C–H activation reactions employing this unique ligand class are ongoing.

Experimental Section

General procedure for the palladium-catalyzed enantioselective allylic alkylation through C–H activation (1.00 mmol scale): A reaction vial equipped with a stir bar was charged with the $Pd(OAc)_2$ (5.60 mg, 0.030 mmol) and **7** (32.3 mg, 0.050 mmol). To a second reaction vial equipped with a stir bar was added 2-acetyl-1-tetralone (**8**, 188 mg, 1.00 mmol), 2,6-dimethylbenzoquinone (136 mg, 1.00 mmol), $Pd(OAc)_2$ (5.60 mg, 0.030 mmol), and **7** (32.3 mg, 0.050 mmol). The vials were sealed, connected with a cannula, and evacuated and filled with Ar three times. THF (2.44 mL) was added to the latter vial, followed by Et_3N (0.139 mL, 1.00 mmol) and 4-allyltoluene (0.132 mL, 1.00 mmol). The yellow solution was heated to 50 °C and stirred for three hours, at which point THF (2.44 mL) was added to the remaining vial and the catalyst solution added through a cannula to the reaction, which was stirred at 50 °C for additional 21 h. After cooling to room temperature, the solution was concentrated and the crude material was purified by flash chromatography on silica gel ($CH_2Cl_2/Et_2O = 9:1$) to give the product (**30**, 194 mg, 59 % yield, 79 % *ee*) as a colorless oil.

Received: September 29, 2012
Revised: November 27, 2012
Published online: December 11, 2012

Keywords: allylic alkylation · C–H activation · enantioselectivity · homogeneous catalysis · palladium

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