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A New Class of Non-C_2-Symmetric Ligands for Oxidative and Redox-Neutral Palladium-Catalyzed Asymmetric Allylic Alkylations of 1,3-Diketones

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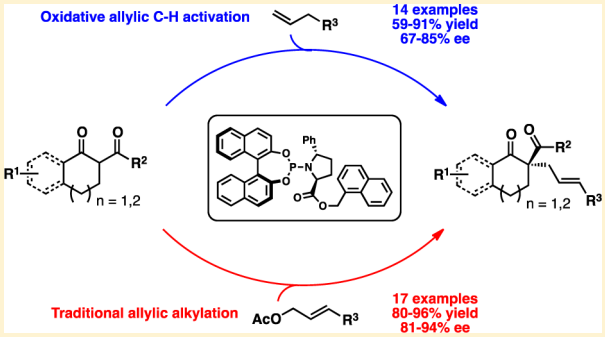
Supporting Information

ABSTRACT: We report the discovery, synthesis, and application of a new class of non-C_2-symmetric phosphoramidite ligands derived from pyroglutamic acid for use in both oxidative and redox-neutral palladium-catalyzed asymmetric allylic alkylations of 1,3-diketones. The resulting chiral products are typically obtained in high yield with good to excellent levels of enantioselectivity.



INTRODUCTION

The ability to construct C−C bonds in an asymmetric fashion continues to challenge synthetic chemists. Catalytic processes are particularly effective to address this challenge because they assemble molecules in the most atom-economical way possible.[1] Nevertheless, challenges persist even in such a developed field, particularly in the area of asymmetric bond formation. More precisely, the stereoselective construction of C−C bonds, especially those of all-carbon quaternary stereocenters, remains a challenge that continues to receive broad attention from the organic chemistry community.[2]

Within the class of asymmetric transformations that can be utilized to generate C−C bonds, transition-metal-catalyzed asymmetric allylic alkylation (AAA) reactions, principally those employing palladium,[3] copper,[4] iridium,[5] or molybdenum,[6] have emerged as powerful tools for the synthesis of complex molecules. The widespread use of AAA reactions speaks to not only their ability to complete chemo-, regio-, diastereo-, and enantioselective catalytic processes, but also the broad scope of substrates that can be employed and the catalysts' tolerance for a variety of other functional groups.

There are three general characteristics of AAA reactions that differentiate them from other asymmetric transition-metal-catalyzed methods. First, in contrast to processes such as asymmetric oxidations and reductions, AAA reactions exhibit several mechanisms through which asymmetric induction can be realized.[7] These include the differentiation of enantiotopic leaving groups or π-allyl termini and the preferential reaction of one prochiral face of either the nucleophile or the electrophile. Second, both reacting partners can simultaneously be prochiral, allowing for the concurrent formation of multiple stereocenters using a single catalytic species. Third, the asymmetric bond-breaking or -forming event typically occurs outside the coordination sphere of the metal and therefore distal to the chiral ligands.

A common design element of widely applicable chiral catalysts, including those employed in AAA reactions, is a C_2-symmetric scaffold around the metal.[8] Conceptually, this style of ligand is attractive because the inherent symmetry reduces the number of potential catalyst−substrate arrangements, simplifying the mechanistic rationale of the transformation and minimizing the number of possible reaction pathways. Generally, reducing the number of competing processes that may lead to enantiomeric products can increase the catalyst's enantioselectivity.[9] This basic strategy has been leveraged to create countless metal complexes for asymmetric catalysis, many of which are based on common ligands derived from cinchona alkaloids,[10] bis(oxazoline)s,[11] salens,[12] DIOPs,[13] BINAPs,[14] and BINOLs[15] (Figure 1).

Our group was thus attracted to the advantages afforded by C_2 symmetry when we developed diphenylphosphinobenzoic acid (DPPBA)-based ligands for palladium-catalyzed AAA reactions (Figure 2). These modular ligands, derived from derivatization of readily accessed chiral building blocks, have been used over a broad variety of substrates and transformations that is unmatched by any other family of chiral catalysts in the field of palladium-catalyzed AAA reactions (Figure 3).[16]

However, despite all the progress that has been made in catalyst design, DPPBA ligands are not universally applicable.

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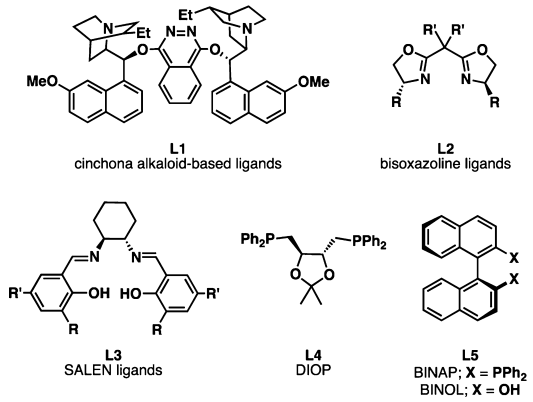

Figure 1. Common C_2-symmetric ligands used for asymmetric catalysis.

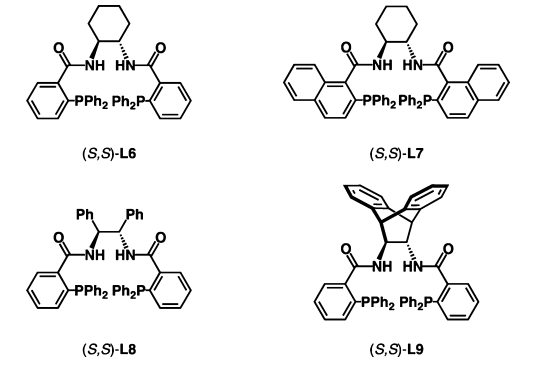

Figure 2. C_2-symmetric DPPBA ligands.

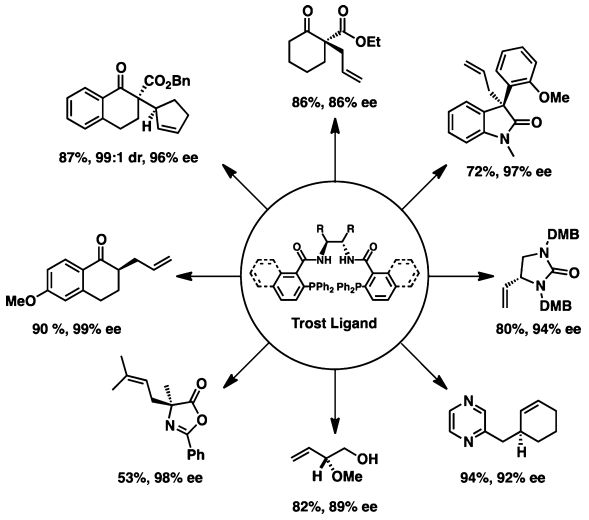

Figure 3. DPPBA ligands in palladium-catalyzed AAA reactions.

One prominent limitation is that for nearly all substrates that undergo metal-catalyzed allylic alkylations, a leaving group is required on the electrophile.[17] Such functionality allows the catalyst to convert one allylic substituent into another via a redox-neutral event (Figure 4). One way to increase the efficiency, chemoselectivity, and scope of these reactions would be to eliminate this limitation by developing an oxidative method to perform analogous AAA reactions with unfunctionalized alkenes. The use of a relatively inert allylic hydrogen atom as a "leaving group" not only would obviate the installation of the allylic leaving groups necessary for traditional

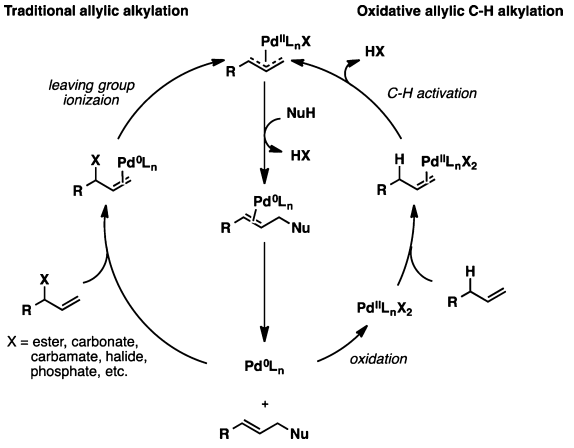

Figure 4. Comparison of oxidative and redox-neutral palladium-catalyzed AAA reactions.

redox-neutral AAA reactions, but also would avert the chemoselectivity issues inherent in having such groups in a synthetic sequence.

In 2008, Shi and co-workers described the first catalytic intramolecular allylic alkylation of both activated and unactivated C−H bonds with β-dicarbonyl derivatives in the presence of $Pd(OAc)_2$, 1,2-bis(benzylsulfinyl) ethane,[18] and benzoquinone.[19] Contemporaneous with that report, White and Young demonstrated a similar intermolecular allylic C−H alkylation of activated C−H bonds with methyl nitroacetate,[20a] and they later extended that work to an analogous intermolecular allylic C−H alkylation using unactivated C−H bonds.[20b] Recently, Sharma and Hartwig reported a one-pot process involving an initial Pd-catalyzed oxidation followed by an in situ Ir-catalyzed allylic alkylation.[21] Our group has also been interested in performing palladium-catalyzed allylic C−H alkylations, specifically of 1,4-dienes and 1,4-enynes.[22] At the time, however, there were no reports of either stoichiometric or catalytic asymmetric allylic alkylation reactions that proceeded via C−H activation. We recently provided a preliminary communication of the first examples of such a method.[23] These reactions construct all-carbon quaternary stereocenters with high levels of enantiocontrol by utilizing prochiral nucleophiles, a class of substrates upon which palladium AAA catalysts often struggle to induce asymmetry.[24] To date, there has been no report wherein the same structural type of chiral ligand can affect both oxidative and nonoxidative Pd-catalyzed AAA reactions. Herein, we provide a full account of the design and development of a new class of non-C_2-symmetric chiral ligands that enabled this advance. Also, we describe the first direct comparison of the performance of the presumed π-allylpalladium intermediate in the AAA reaction via oxidative and redox-neutral reaction manifolds. This new ligand family has provided an excellent approach to the difficult challenge of AAA of 1,3-diketones.

RESULTS AND DISCUSSION

The first report of a nucleophilic addition to a stoichiometrically prepared π-allylpalladium complex was made in 1965 by Tsuji and co-workers, who demonstrated that sodium diethyl malonate could be allylated with $[(\eta^3\text{-}C_3H_5)PdCl]_2$ in the presence of DMSO.[25] In 1973, we developed a sequence wherein an overall allylic alkylation from olefins was achieved by conversion of the olefin to a π-allylpalladium complex, which

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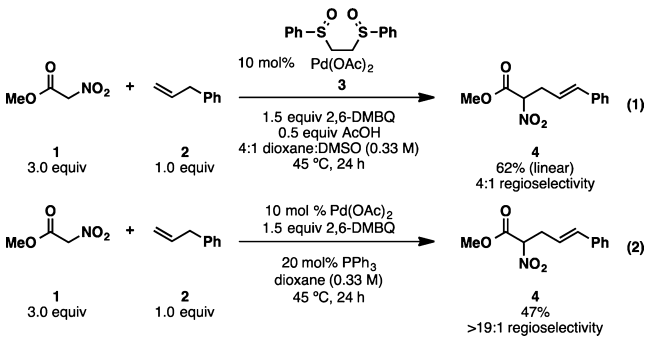
then was subjected to nucleophilic attack in the presence of phosphine ligands.[26] Despite nearly half a century of advances in organometallic chemistry, only recently have there been reports of methods that reduce this two-step procedure to a single-step palladium-catalyzed process, and all have employed sulfoxides as ligands (*vide supra*). In our early work, we found that such conditions failed with more substituted allyl substrates. While studying the alkylation of π-allylpalladium species, our group discovered that phosphorus-based ligands proved advantageous for promoting attack by stabilized nucleophiles on such complexes, a discovery that has provided the basis of Pd-AAA chemistry ever since.

Considering the success this family of ligands continues to demonstrate in achieving chemo-, regio-, and stereocontrol in palladium-catalyzed allylic substitution processes across a wide array of contexts, we hypothesized that if phosphorus-based ligands could be made to promote palladium-catalyzed allylic C−H alkylations then there would be a similarly great opportunity to dramatically expand both the scope and selectivity of AAA reactions. At the outset of our research program, however, there was a report from the White group that plainly claimed that phosphorus ligands are not compatible with the oxidative conditions necessary for C−H activation.[27] These remarks, however, were made in the context of allylic *acetoxylation* reactions (specifically, enantioselective allylic acetoxylations of terminal alkenes using a heterobimetallic catalyst system composed of both palladium(II) and chromium(III) salts), and we immediately questioned whether there might be meaningful differences between that process and an analogous allylic *alkylation* reaction. More precisely, we postulated that either the mechanism of allylic C−O bond formation is dissimilar enough from allylic C−C bond formation or the reaction conditions necessary to achieve such transformations are distinct enough so that such a broad statement is not generally applicable. Indeed, under the White group's optimized conditions, (*E*)-methyl 2-nitro-5-phenylpent-4-enoate (**4**) is obtained in 62% yield as a 4:1 mixture of regioisomers, favoring the linear product from the reaction of methyl 2-nitroacetate (**1**) with allylbenzene (**2**) (eq 1). If 1,2-



bis(phenylsulfinyl)ethane palladium acetate (**3**) is replaced with $Pd(OAc)_2$, 20 mol % PPh_3 is added, and the reaction is conducted without the addition of AcOH or DMSO, then (*E*)-methyl 2-nitro-5-phenylpent-4-enoate (**4**) is formed in 47% yield as a single regioisomer (eq 2).

We hypothesized that methyl 2-nitroacetate (**1**) would not be an ideal nucleophile for our optimization studies partly because we anticipated that distinguishing between the similarly sized ester and nitro substituents of the activated methylene would be challenging for a chiral catalyst and also because we were concerned that any alkylation products might succumb to racemization under the reaction conditions. Accordingly, we began our exploratory work with 2-acetylcyclopentanone as the nucleophile for alkylation with allylbenzene (**2**). The employment of 2,6-dimethylbenzoquinone (2.6-DMBQ) was necessary to observe any desired reactivity, but the 1.5 equiv reported by White and Young could be reduced to 1.0 equiv without any observable decrease in catalytic efficiency. Importantly, benzoquinone itself was not a competent oxidant for this process, an observation that the White group has also made.[28] The reaction temperature could also be reduced from 45 to 35 °C, which in some cases led to a concomitant increase in enantioselectivity (*vide infra*); conducting the alkylation at ambient temperature generally gave only trace amounts of the desired product. Lowering the catalyst loading from 10 mol % $Pd(OAc)_2$ and 20 mol % PPh_3 to 5.0 and 7.5 mol %, respectively, did not result in a diminution in yield, but the addition of 1.0 equiv of bases such as K_2CO_3 or NaOAc or acids such as AcOH was significantly deleterious to the reaction conversion. On the basis of these preliminary results, we turned to the key challenge of our program: the design of a chiral ligand class that would be compatible with the highly oxidizing allylic C−H alkylation reaction conditions.

Palladium catalysts prepared using our DPPBA ligands are not suitable for such a process because they undergo facile oxidation to form stable palladium(II) adducts that are catalytically inactive (Figure 5).[29] A screen of many other

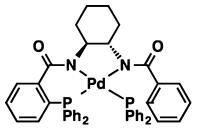


Figure 5. Catalytically inactive DPPBA Pd^{2+} complex.

known ligands for palladium provided no strong leads (for examples, see the Supporting Information). However, at the conception of this research program there was a vigorous and sustained effort in our laboratories to discover new phosphoramidite-based catalysts for palladium-catalyzed trimethylenemethane cycloadditions.[30] Intrigued by the possibility that such ligands might prove useful in this circumstance, we discovered a new class of phosphoramidites that support palladium-catalyzed asymmetric allylic C−H alkylation reactions. These non-C_2-symmetric ligands are modular in design (i.e., each aryl ring and the biaryl backbone can be independently changed) and are readily accessed from pyroglutamic acid (Scheme 1). In a representative synthesis, esterification of l-pyroglutamic acid (**5**) with 1-naphthalene methanol using DCC in the presence of catalytic DMAP followed by carbamate formation with Boc_2O affords pyrrolidine (**6**) in 63% overall yield. Chemoselective semi-reduction of the lactam carbonyl with $LiBHEt_3$ and then treatment with methanol and catalytic *p*-TsOH provides the corresponding aminal (**7**) in 37% yield. Copper(I) bromide mediated addition of phenylmagnesium bromide in the presence of $BF_3{\cdot}OEt_2$ gives the desired trans-substituted pyrrolidine (**8**) in 83% yield.[31] 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 TFA liberates the unprotected pyrrolidine (**9**) in 74% yield, which undergoes base-promoted coupling with a slight excess of chlorophosphite (**10**) to afford representative ligand **L10** in 54% yield.

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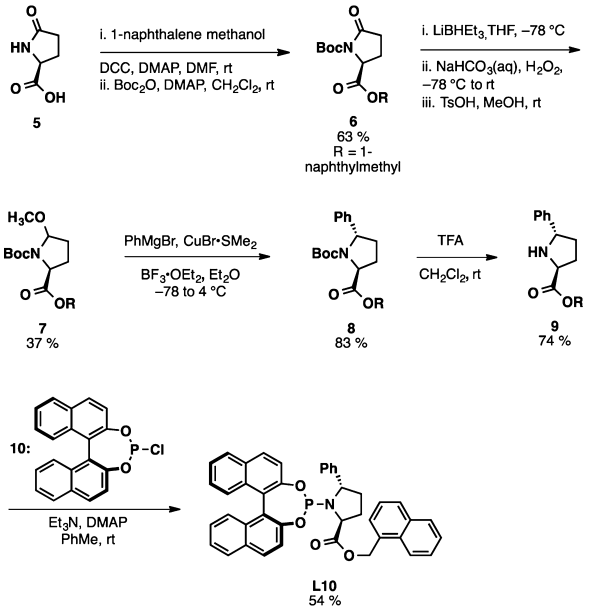
Scheme 1. Synthesis of Chiral Phosphoramidite Ligands Based on Pyroglutamic Acid



Although the enantioselective palladium-catalyzed allylic alkylation of 1,3-diketone nucleophiles has been known since a 1978 report from Kagan and co-workers,[32] highly enantioselective examples of such a transformation are rare.[33] The most notable example of these is a 2003 report from Kuwano, Uchida, and Ito, who demonstrated that a palladium catalyst with BINAP as the chiral ligand is able to perform unsymmetrically the nonoxidative enantioselective allylic alkylations of various 1,3-diketones to give the corresponding products in high yields with enantiomeric excesses that range from 64 to 89%.[34] This paucity is likely due to the steric and electronic similarities of the two carbonyl groups that the reacting center bears, between which many catalysts struggle to discriminate.

Taking this class of nucleophiles as a significant challenge to be met, we decided to evaluate our new set of phosphoramidite ligands in oxidative palladium-catalyzed allylic C−H alkylations, employing 2-acetyl-1-tetralone (**11**) as the nucleophile, allylbenzene (**2**) as an electrophile, 2,6-DMBQ as an oxidant, and Et_3N as base in the presence of $Pd(OAc)_2$ (5.0 mol %) and phosphoramidite ligand (7.5 mol %) in THF at 60 °C for 24 h (Figure 6). When the pyrrolidine subunit is substituted with a phenyl ring (**L11**), allylic C−H alkylation product **12** was obtained in 83% conversion and 72% ee. Substitution on this aromatic ring is generally not well tolerated. A reaction with the corresponding *para*-biphenyl ligand (**L12**) gave **12** in only 14% conversion and 30% ee, and the *meta*-biphenyl analog (**L13**) gave no desired product at all. The corresponding *meta*-terphenyl ligand (**L14**) yielded **12** in 70% ee, but only at 10% conversion. Further increasing the steric bulk of this substituent is deleterious because the reaction with the 3,5-di-*tert*-butylphenyl ligand (**L15**) gave no desired product. Neither the 1-naphthyl (**L16**) nor 2-naphthyl (**L17**) ligand offered improvement in terms of conversion or enantioselectivity, and replacement of the aromatic ring with the saturated cyclohexane (**L18**) provided **12** in only 29% conversion and 25% ee.

The effect of the ester substituent of **L11** on both the reactivity and enantioselectivity of the allylic C−H alkylation

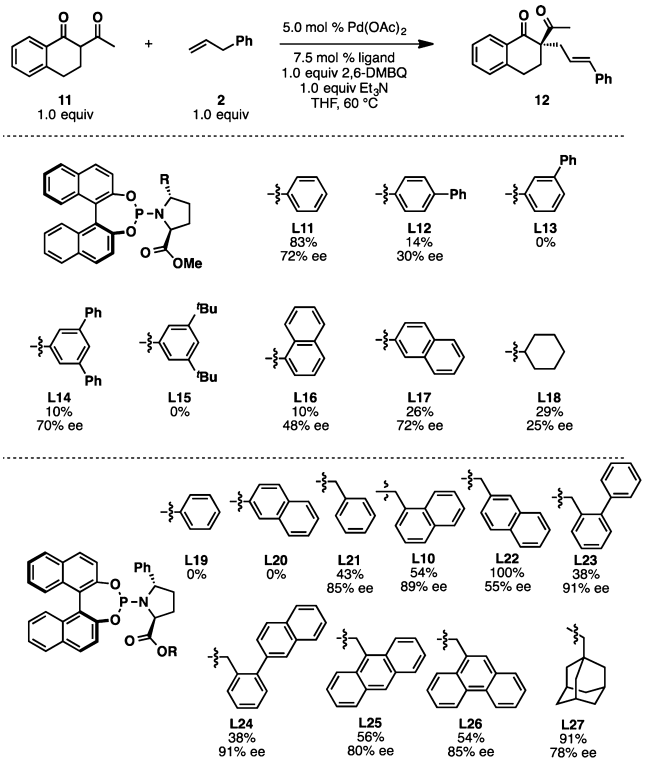


Figure 6. Palladium-catalyzed enantioselective allylic C−H alkylations with selected non-C_2-symmetric phosphoramidite ligands. Reactions were run for 24 h, and conversions to the product are indicated.

was next examined. Replacing the methyl substituent with either a phenyl (**L19**) or a 2-naphthyl (**L20**) group gave inactive catalysts, presumably because these sterically demanding groups inhibit the C−H activation event. However, substitution with a benzyl group (**L21**) yielded **12** in 43% conversion and 85% ee. With a benzylic 1-naphthyl ester (**L10**), the reaction delivered **12** in 54% conversion and 89% ee. The reaction conversion increased to 100% with the corresponding benzylic 2-naphthyl ligand (**L22**), and the desired product was obtained in 55% ee. Increasing the steric bulk of the aryl group, as in **L23**−**L26**, gave no significant improvement. Interestingly, switching the methyl group to an adamantyl enhanced the reactivity significantly and resulted in decent enantioselectivity. Among the ligands we prepared and evaluated, phosphoramidite **L10** gave the best combination of yield and enantioselectivity, and conducting the reaction with 10 mol % ligand enhanced its reproducibility. A solvent screen demonstrated that THF was ideal for conducting the transformation, in terms of both reactivity and enantioselectivity. Varying concentration and stoichiometry did not provide a significant benefit to the transformation. Ultimately, it was found that if 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 3 h, then desired product **12** could be isolated in 89% yield and 85% ee.

We then moved to evaluate the scope of allylarenes that will undergo reaction with 2-acetyl-1-tetralone (**11**) (Figure 7). The *para*-methyl benzoate electrophile (**13**) gave the corresponding product in 83% yield and 69% ee, compared with 89% yield and 85% ee obtained with allylbenzene (**2**). Neither the *para*-methoxy (**14**) nor *para*-nitrile (**15**) substrate reacts to afford any alkylated product. In the former case, the electron-rich

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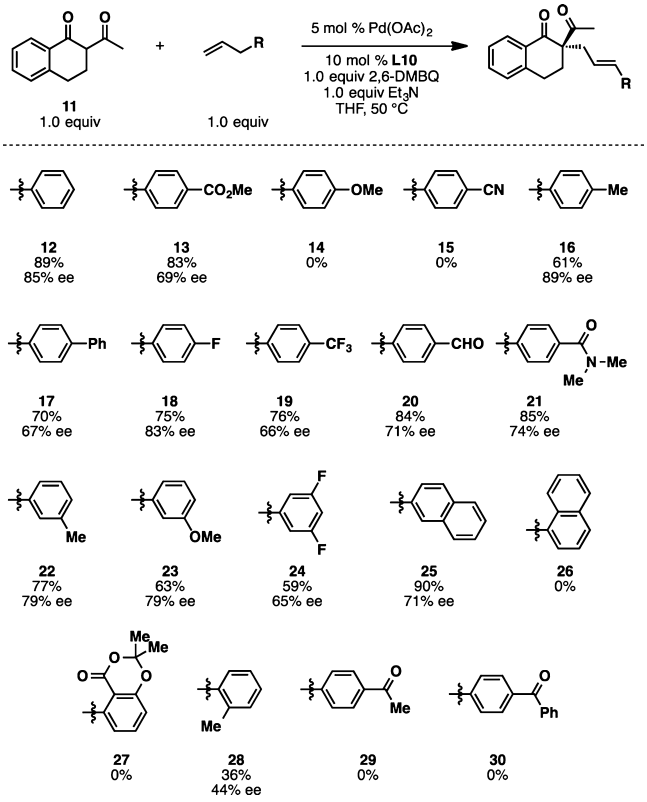
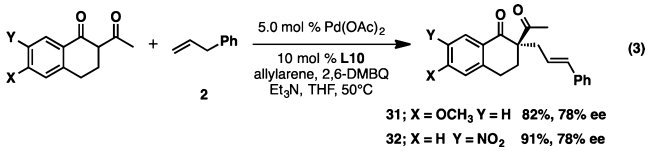


Figure 7. Enantioselective allylic C−H alkylation of 2-acetyl-1-tetralones with various allylarene pro-electrophiles. Reactions were run for 24 h, and isolated yields of the product are indicated.

aromatic ring may sufficiently deactivate the benzylic protons toward C−H cleavage by substantially decreasing their basicity. In the latter case, it is possible that the electron-withdrawing character of the nitrile is not at fault, but rather the ability of its nitrogen lone pairs to coordinate palladium. Such engagement likely disrupts both the reactivity and selectivity of the C−H alkylation process. The *para*-methyl derivative (**16**), however, performs well, giving the corresponding product in 61% yield and 79% ee. This result suggests that a moderately electron-rich aromatic ring is compatible with this allylic C−H alkylation, as long as the electron-rich groups do not approach the donating ability of a methoxy group. The analogous *para*-biphenyl substrate (**17**) also performs well, giving the desired product in 70% yield and 67% ee, indicating that the reaction tolerates a fair amount of steric bulk at the aromatic portion of the electrophile. The *para*-fluoro (**18**) and *para*-trifluoromethyl (**19**) substrates give the corresponding products in 75 and 76% yield and 83 and 66% ee, respectively. Impressively, electrophiles bearing either an aldehyde (**20**) or a dimethyl amide (**21**) are well-tolerated when such substitution is at the para position, giving the products in 84 and 85% yield and 71 and 74% ee, respectively. The successful alkylation of **20** underscores the remarkably mild reaction conditions and chemoselectivity of this allylic C−H alkylation protocol because no competitive nucleophilic addition into the highly electrophilic carbonyl is observed, even after prolonged reaction times.

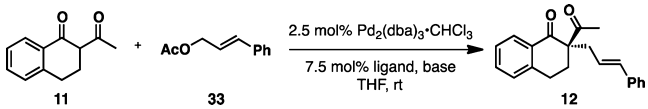
The *meta*-methyl substrate (**22**) reacts well, providing the desired product in 77% yield and 79% ee. Although the *para*-methoxy substrate (**14**) failed to react, the *meta*-methoxy substrate (**23**) gives the alkylated material in 63% yield and 79% ee. Unlike a *para*-methoxy substituent, which is a strong π-donor, a *meta*-methoxy is a predominantly σ-withdrawing group. This result is consistent with the hypothesis that only moderately electron-rich aromatic rings can be activated at the benzylic position, and both neutral and strongly electron-withdrawing aromatic rings are well-tolerated. The 3,5-difluoro substrate (**24**) provided the allylated material in 59% yield and 65% ee, and the 2-naphthyl analog (**25**) performed well to generate the desired product in 90% yield and 71% ee. With this catalyst system, it appears that ortho substitution is not well tolerated for electrophiles such as **26** and **27**. Even when the ortho substituent is only a methyl group (**28**), the desired product was isolated in only 36% yield and the stereoselectivity dropped precipitously. Surprisingly, despite the fact that aldehydes, esters, and amides are well-tolerated, neither the *para*-methyl ketone (**29**) nor a *para*-phenyl ketone (**30**) substrate gave any product. It is noteworthy to mention that in all cases examined, the linear regioisomer was obtained in >19:1 selectivity, demonstrating the remarkable regioselectivity of this allylation process.

Substituted tetralones bearing both an electron-donating group (6-methoxy) and an electron-withdrawing group (7-nitro) were examined and delivered cinnamylated products (**31** and **32**) in comparable yields (82 and 91%, respectively) and comparable enantioselectivities (78% ee) as illustrated in eq 3.



Because ligand **L10** performed so well in the oxidative Pd-AAA, we were interested in seeing if this particular ligand is also applicable in the traditional Pd-AAA and whether these two approaches differ in selectivity—in other words, how identical are the reactivities of the π-allylpalladium complexes generated by these two different paradigms? To evaluate the phosphoramidite−palladium catalyst for the optimization of traditional Pd-AAA of 1,3-diketones, 2-acetyl-1-tetralone (**11**) and cinnamyl acetate (**33**) were chosen as model substrates. Traditional Pd-AAA bidentate ligands **L6**−**L9** (Table 1), which have enjoyed incontestable success in the field, delivered product **12** in high yield but with varying levels of enantioselectivity (Table 1, entries 1−4). Using non-C_2-symmetric phosphoramidate ligand **L10** gave dialkyl-1,3-

Table 1. Ligand Screen for Palladium-Catalyzed AAA of 11[a]



entry	ligand	base	yield (%)[b]	ee (%)[c]
1	(*S*,*S*)-**L6**	Et_3N	89	41
2	(*S*,*S*)-**L7**	Et_3N	84	61
3	(*S*,*S*)-**L8**	Et_3N	92	73
4	(*S*,*S*)-**L9**	Et_3N	94	68
5	**L10**	Et_3N	87	83
6[d]	**L10**	Et_3N	76	88

[a]All reactions were conducted at 0.2 M using 1.0 equiv of **11** and **33** in 0.2 mmol scale. [b]Isolated yield. [c]Enantiomeric excess determined by chiral HPLC. [d]Reaction run at 50 °C.

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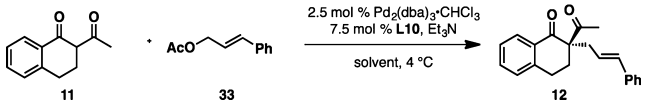
diketone **12** in 86% yield and 83% ee after 12 h (Table 1, entry 5). Surprisingly, the enantiomeric excess showed a slight inverse temperature effect. No formation of a regioisomeric product was observed. An extensive screening of solvents showed DME to be superior both in terms of reactivity and enantioselectivity (Table 2). Furthermore, the choice of base had a significant

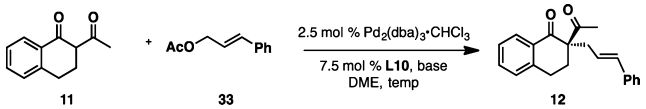
Table 2. Solvent Screen for Palladium-Catalyzed AAA of 11[a]



entry	solvent	yield (%)[b]	ee (%)[c]
1	THF	94	83
2	dioxane	73	81
3	DME	91	86
4	toluene	78	80
5	DCE	82	78

[a]All reactions were conducted at 0.2 M using 1.0 equiv of **11** and **33** in 0.2 mmol scale. [b]Isolated yield. [c]Enantiomeric excess determined by chiral HPLC.

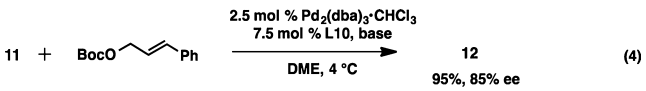
Table 3. Base Screen for Palladium-Catalyzed AAA of 11[a]



entry	base		yield (%)[b]	ee (%)[c]
1	Et_3N	50 °C	91	86
2	Et_3N	room temperature	90	86
3	Et_3N	4 °C	90	89
4	Et_3N	−20 °C	89	89
5	DBU	4 °C	77	78
6	Hunig's base	4 °C	75	8
7	Cs_2CO_3	4 °C	90	81
8	Na_2CO_3	4 °C	82	90
9	Li_2CO_3	4 °C	90	92

[a]All reactions were conducted at 0.2 M using 1.0 equiv of **11** and **33** in 0.2 mmol scale. [b]Isolated yield. [c]Enantiomeric excess determined by chiral HPLC.

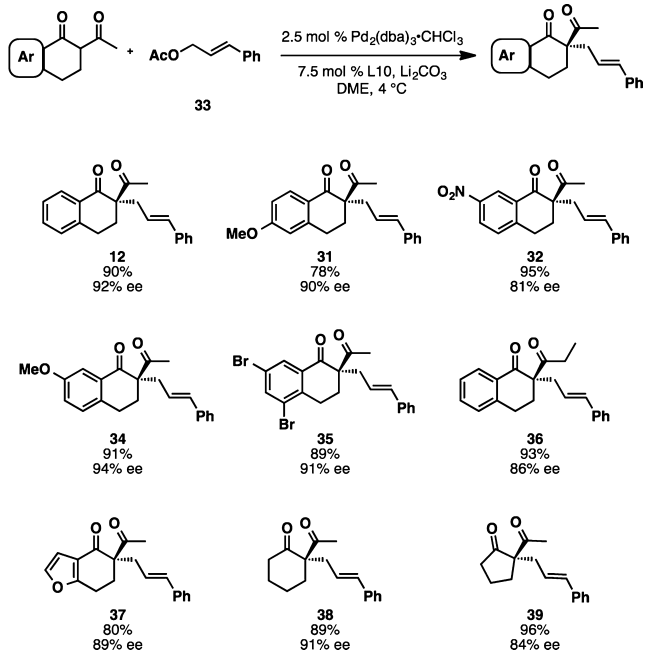
impact on the enantiomeric excess (Table 3). In particular, employing Li_2CO_3 as the base proved optimal and delivered desired product **12** in 90% yield and 92% ee; the advantageous nature of Li^+ is further noted by the use of cinnamyl t-butylcarbonate as the substrate, as illustrated in eq 4. In this



case, the leaving group serves as the base in which the only counterion is the Pd. In the absence of a counterion other than the Pd, the enantiomeric excess turns out to be slightly lower than that obtained when triethylamine was used as base.

With the optimized reaction conditions in hand (Table 3, entry 9), a variety of 1,3-diketones were subjected to Pd-AAA (Table 4). In general, good to excellent yields and enantioselectivity were obtained. Acetyl-6-methoxy-1-tetralone gave compound **31** in 78% yield and 90% ee, and 2-acetyl-7-

Table 4. Nucleophile Scope of Palladium-Catalyzed Enantio-Selective Allylic Alkylations[a]

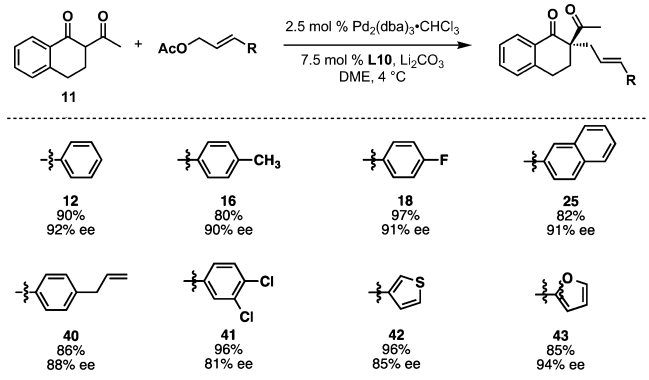


[a]All reactions were conducted using 1.0 equiv of nucleophile and 1.0 equiv of electrophile in 0.1 mmol scale at 0.2 M in DME using 1 eq. of Li_2CO_3, 2.5 mol % $Pd_2(dba)_2(CHCl_3)$ and 7.5 mol % **L10**.

nitro-1-tetralone analogously provided compound **32** in 95% yield and 81% ee. Electron-donating nucleophiles gave decent to excellent yields of products **34** and **35** (89 to 91%) with comparable enantioselectivity (94 and 91%, respectively). The reaction of a 2-propionyl substrate proceeded with slightly lower enantioselectivity than that with the 2-acetyl substrate, delivering product **36**. We were pleased to observe similar enantiodiscrimination for furanyl-fused product **37** and 2-acetyl cyclohexanone product **38**. A five-membered ring system underwent alkylation with cinnamyl acetate as well, delivering **39** in 96% yield and 84% ee.

Different electrophiles were also investigated to emphasize the extension of the asymmetric allylation of unsymmetric 1,3-diketones (Table 5). To test the scope of allyl electrophiles

Table 5. Electrophile Scope of Palladium-Catalyzed Enantioselective Allylic Alkylations[a]



[a]All reactions were conducted using 1.0 equiv of nucleophile and 1.0 equiv of electrophile in 0.1 mmol scale at 0.1 M in DME.

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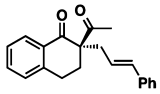
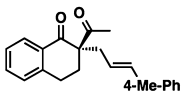
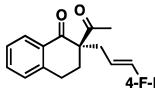
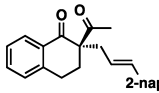
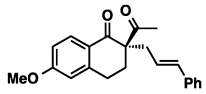
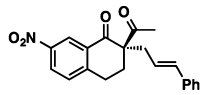
under the optimized conditions, we synthesized a variety of cinnamyl acetate derivatives via the Horner−Wadsworth−Emmons reaction as a key step in a three-step−one-purification protocol. Electron-donating substituents on the aromatic ring of the cinnamyl group gave excellent yields (85−97%) with high enantioselectivity in the range of 90%. Moderately electron-rich substrates are tolerated because compound **16** was isolated in 80% yield and 90% ee and compound **25** was obtained with 82% yield and 91% ee. Diverse electron-rich aromatic systems such as thiophene (**42**) or furan (**43**) derivatives are also tolerated.

Oxidative and traditional Pd-AAA could be utilized in this transformation to afford the alkylated products in decent yields and enantiopurity. In general, Pd-AAA via C−X activation gave both a higher reactivity and a higher enantioselectivity (Table 6). The most significant exception is the alkylation with a 2-

Table 6. Comparison of Reactivity and Enantioselectivity between Oxidative and Traditional Pd-AAA

entry	product	compound	C-H activation[a] %yield	C-H activation[a] %ee	traditional Pd-AAA[b] %yield	traditional Pd-AAA[b] %ee
1		**12**	89	85	90	92
2		**16**	61	79	80	90
3		**18**	75	83	97	91
4		**25**	90	71	82 80[c]	91 87[c]
5		**31**	82	78	78 96[c]	90 84[c]
6		**32**	91	78	95	81

[a]Performed under conditions illustrated in Figure 6. [b]Performed under conditions illustrated in Table 4. [c]Performed under conditions illustrated in Figure 6, except using 2.5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, no quinone and the appropriate cinnamyl acetate derivative.

napthalene substituent (Table 6, entry 6). A yield of 92% and 71% ee are observed with oxidative Pd-AAA, whereas a yield of 82% and an enantioselectivity of 91% were obtained with traditional Pd-AAA. To some extent, the differences may stem from a cation effect because an ion pair is the actual nucleophile.

Support for such a conjecture derives from our studies on β-ketoesters where the choice of cation had a large effect on enantiomeric excess under otherwise identical conditions.[35] To examine this question, we studied traditional Pd-AAA under the conditions of the oxidative process. Interestingly, the results came midway between the optimized conditions for each. A possible cause for the lowering of the enantiomeric excess for the oxidative reaction could be the effect of the quinone as an achiral ligand under the oxidative process that competes with the chiral phosphine ligand. The idea that quinones can serve as ligands for Pd is well documented.[36] We do note that for traditional AAA we utilized a dba complex for our Pd(0) source. Because dba can serve as a ligand during alkylation, we performed the reaction described in Table 6 entry 5 under the conditions described in Table 6 footnote [c], but we replaced $Pd_2(dba)_3{\cdot}CHCl_3$ with CpPd(allyl), which has only the phosphine as a ligand. The enantiomeric excess under these revised conditions was the same, demonstrating that dba is not involved in the catalytic cycle. Thus, the current results support both a role for the cation associated with the nucleophilic anion and the quinone being responsible for the differences in enantiomeric excess between the oxidative and nonoxidative processes involving the same π-allylpalladium core. An attempt to see if the cation effect impacts the enantiomeric excess under oxidative conditions failed because addition of lithium salts to such reactions gave mainly decomposition and very low conversion to allylated products.

CONCLUSIONS

The stability of the phosphorus toward the oxidant in these reactions is curious. That quinones can oxidize trivalent phosphorus compounds has been noted by Mukaiyama, who employed them as the oxidant in a Mitsunobu reaction.[35] Phosphoramidites, particularly, would be thought to be susceptible to such oxidants. Presumably, the success of these reactions derives from the coordination of the quinones as ligands to the palladium. Such coordination is well-documented and is the reason that quinones are particularly effective at oxidizing low-valent Pd to higher-valent Pd.[37] Further evidence for such coordination does occur is illustrated by a control experiment. When we performed the nonoxidative AAA in the presence of the quinone, reaction stopped at 13% conversion. This observation is consistent with the quinone coordinating the Pd making it effectively a Pd(+2) complex which is not catalytically active for the traditional AAA process.

The design of a novel class of non-C_2-symmetric pyroglutamic acid-derived phosphoramidite ligands has led us to the development of the first examples of enantioselective allyl C−H activation as well as the report of a traditional Pd-AAA of 1,3-diketones, a most challenging pro-chiral nucleophile. To our delight, the reaction, typically, provided chiral 2,2-dialkyl-1,3-diketones in high yields (25 examples) in 65−89% ee for the oxidative process and 81−94% ee for the nonoxidative process. The broad substrate scope and mild conditions make this procedure a valuable reaction for the synthesis of unsymmetric 1,3-diketones. The enantioselectivity of our nonoxidative are somewhat higher than the range of 64−89% ee reported by Kuwano et al. Furthermore, they required −60 °C; whereas, we operate at 4 °C. Remarkably, our oxidative process exhibits a range similar to that of Kuwano et al. even though our reaction temperature is 50 °C and theirs is −60 °C. This study is the first to compare directly the effect of method of generation of the π-allylpalladium intermediate on ee. As Table 6 illustrates, higher enantiomeric excess is typically obtained via the nonoxidative method compared to the oxidative method. The source of this difference appears, most likely, to derive from the change in the counterion for the nucleophile (Table 3) combined with the quinone serving as an achiral ligand that modifies the chiral environment around the Pd. This striking difference suggests that the C−H activation in the oxidative process is the rate-determining step. Further

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studies to improve the selectivity and scope of the reaction as well as the broader applicability of this new ligand type are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

General remarks, experimental procedures, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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