

Asymmetric Wacker-Type Oxyallenylation and Azaallenylation of Cyclic Alkenes

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Abstract: Palladium-catalyzed three-component carboetherification of cyclic alkenes proceeded to give *trans* adducts exclusively with excellent enantioselectivity through a Wacker-type pathway. The reaction is also applicable to other oxygen nucleophiles, such as water, phenols, and carboxylic acids, as well as some electron-poor aryl amines.

Catalytic carboetherification and carboamination of alkenes allows the construction of a new C@C bond and a new C@O/N bond in a single reaction.^[1] The three-component reaction is particularly attractive in terms of convergence and the possibility to establish two new stereocenters. Many existing three-component examples involve carbon-radical addition to alkenes as the key step.^[2] The development of such an asymmetric radical reaction still remains a challenge. Until now, most examples of asymmetric carboetherification and carboamination have been limited to two-component reactions initiated by intramolecular heteropalladation^[3] or heterocupration^[4] (Figure 1 a). In a similar strategy, Mazet and co-workers strategically placed hydroxy and sulfonamide groups at *ortho* positions of aryl palladium species, which set the stage for intramolecular *syn* attack at a bound cycloalkene, 2,3-dihydrofuran.^[5] In an oxy-Heck-Matsuda reaction developed by Correia et al.,^[6] aryl insertion produced an η^3 -benzyl complex, which, in turn, was intercepted by a pendant phenol to produce dihydrobenzofurans. The tethering strategy was also utilized by Wolfe and co-workers for asymmetric *anti* attack of external amines on an allylphenyl Pd species to form 2-amidoindanes.^[7] Furthermore, Liu and co-workers recently disclosed a truly three-component copper-catalyzed asymmetric arylsulfonamidation of styrene, which proceeded by amino-radical addition to styrene and subsequent formation of a new stereocenter at the benzylic position.^[8]

Herein, we report the first three-component example of asymmetric oxyallenylation,^[9] using propargylic acetates and oxygen nucleophiles, such as alcohols, phenol, carboxylic

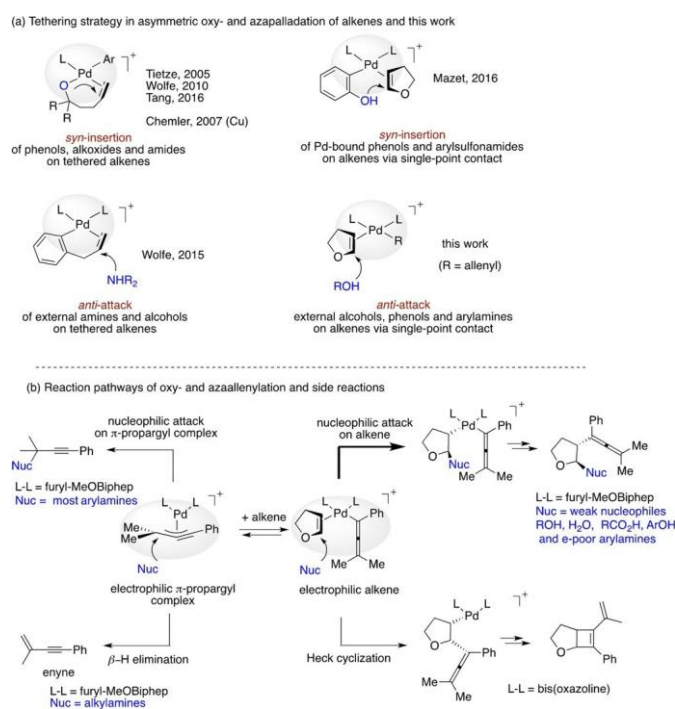


Figure 1. a) Use of tethering for asymmetric induction in the oxy- or azaallenylation of alkenes. b) Plausible pathways of oxy- and azaallenylation and side reactions.

acids, and water (Figure 1 b). The reactivity can also be extended to electron-deficient aryl amines. The reaction led to exclusive *trans* heteroallenylation in excellent enantioselectivity. Allenes are important intermediates in organic synthesis, especially so with the advent of many metal-catalyzed stereoselective and/or regioselective reactions to prepare substituted allenes.^[10]

To produce the Wacker-type adducts, several side reactions must be prevented (Figure 1 b): 1) The *s*-allenyl complex of palladium must undergo fast Wacker-type *anti* heteropalladation of alkenes instead of *syn* insertion^[11] or Heck *syn* carbopalladation, the latter leading to fused cyclobutenes, which we reported previously.^[12] 2) The allenyl complex may exist in equilibrium with the *p*-propargyl complex, which can eliminate a β -hydrogen atom to give an enyne. 3) The *p*-propargyl complex is electrophilic and can undergo propargylic substitution if nucleophilic amines are used.

Tethering of alkenes to the inserting heteroatoms or metal-bound aryl rings is a commonly employed strategy to facilitate asymmetric insertion (see Figure 1 a).^[13] For simple alkenes that bind to catalysts through a single point of

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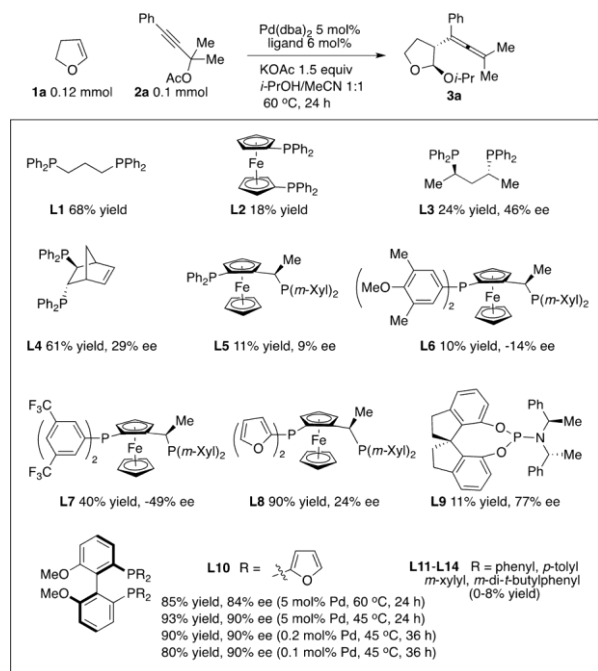
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contact, stereocontrol by catalysts still remains a challenge. Therefore, there has been no asymmetric example of the archetypical Wacker *anti* attack on simple monoolefins.

In our recent study of a model Heck annulation of 3-phenylpropargyl acetate **2a** and 2,3-dihydrofuran (Scheme 1), a new product of alkoxyallenylation **3a** was obtained in 68 % yield through the reaction of the cosolvent, isopropanol in the presence of Pd(dba)₂ and dppp. A small amount of the enyne by-product was also detected.



Scheme 1. Effect of bisphosphines on a model alkoxyallenylation of 2,3-dihydrofuran (yields and *ee* values of **3a** are indicated). dba = dibenzylideneacetone, Xyl = *m*-xylyl.

Encouraged by this finding, we then screened chiral bisphosphines to develop an enantioselective variant. In most cases, β -elimination to the enyne was the main side reaction, whereas Heck annulation was rarely seen, except with the ligand Norphos **L4** (23 % yield). For example, biaryl diphosphines, such as BINAP, Segphos and Difluorphos gave the desired product **3a** in less than 5% yield. Notably, the trifluoromethylated Josiphos ligand **L7** provided **3a** in 40 % yield with 49 % *ee* (and 28 % elimination). Josiphos ligand **L8** bearing electron-withdrawing 2-furyl groups afforded **3a** in 90 % yield with 24 % *ee*, and notably without any elimination. Gratifyingly, a palladium catalyst with furyl-MeOBIPHEP **L10** afforded **3a** in 85 % yield with 84 % *ee* at 60 °C. Moreover, 90 % *ee* and 80 % yield were observed at 45 °C in the presence of 0.1 mol % Pd catalyst. Importantly, no enyne was detected. In comparison, catalysts formed by other MeOBIPHEP ligands **L11**–**L14** containing parent *P*-phenyl and electron-donating *P*-aryl substituents had almost no activity, and elimination was the main side reaction. As compared to triphenylphosphine, 2-furylphosphines are much weaker σ -donors to transition metals and better π -acceptors.^[14] They form an electronically deficient allenyl palladium center,

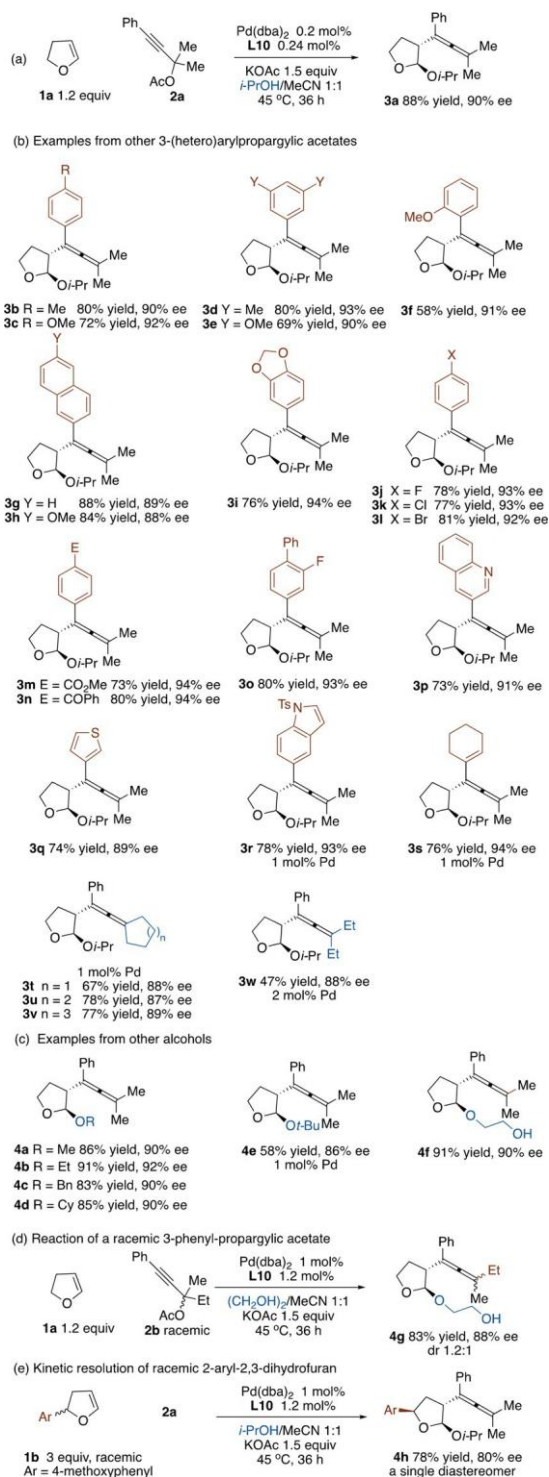
which activates the bound alkene for Wacker attack by nucleophiles. This trend is consistent with the higher Wacker reactivity observed with electron-deficient Josiphos **L7** and **L8** as compared to **L6**. Notably, both MeOBIPHEP and Josiphos form quite large bite angles of 948 and 978, respectively, at palladium(II) centers,^[15] which may also help to prevent elimination. The corresponding monoxide of bisphosphine **L10** was also prepared and tested, but it only led to **3a** in low yield with less than 10 % *ee*.^[16]

The palladium catalyst (0.2 mol %) of **L10** was then applied to reactions of 2,3-dihydrofuran with other propargylic acetates bearing both electron-rich and electron-deficient aryl rings in the 3-position (Scheme 2 b). Esters, ketones, acetals, aryl bromides, fluorides, and chlorides were well tolerated. Furthermore, the reaction tolerated quinoline, thiophene, and indole (products **3 p**–**r**). When 3-aryl propargylic acetates containing 1,1-diethyl and cycloalkyl substituents were used, 1–2 mol % of the Pd catalyst was enough to give full conversion (products **3 t**–**w**). Unfortunately, 3-alkyl propargylic acetates only afforded the adducts in low yields. Other alcohols, including benzyl alcohol, cyclohexanol, *tert*-butyl alcohol, and ethylene glycol also reacted smoothly (Scheme 2 c, products **4 a**–**f**). The reaction of racemic propargylic acetate **2b** led to a mixture of two allenyl isomers **4 g**, both with 88 % *ee* (Scheme 2 d). However, primary and secondary propargylic acetates did not react at all. The racemic 2,3-dihydrofuran **1b** substituted with a *p*-methoxyphenyl ring afforded the single diastereomer **4h** with 80 % *ee*. The observed enantiofacial selectivity translates to an *s* value of 9 (Scheme 2 e). Unfortunately, in the reaction of 2,3-dihydrofuran, only simple addition of isopropanol to the alkene group was detected.

N-*tert*-butoxycarbonyl-2,3-dihydropyrrole (**1 c**) was another reactive alkene in this transformation (Scheme 3), whereby different aryl rings at the 3-position of the propargylic acetate were tolerated (products **5 b**–**f**), and both primary and secondary alcohols coupled in good yields (products **5 i**–**m**). Notably, simple addition of alcohols to the double bond was also detected, accounting for the rest of the material. Reactions of cyclopentene afforded only a small amount of the desired products, however.

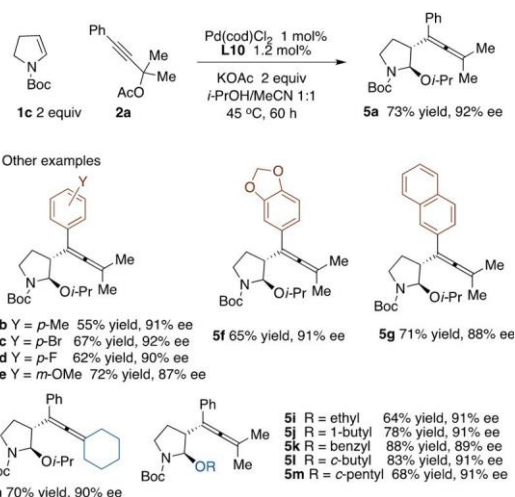
When **1a** was treated with acetic acid and phenol in acetonitrile, the *trans* adducts **6a** and **6b** were also generated exclusively (Scheme 4 a,b). The reaction with water generated **6c** as both *trans* and *cis* isomers in a ratio of 4:1 (Scheme 4 c), whereas a similar reaction of *N*-Boc-substituted dihydropyrrole **1c** afforded exclusively *trans* isomer **6d** (Scheme 4 d). The minor *cis*-lactol **6c** was probably formed through reversible ring opening of the initially formed *trans* lactol. Notably, adduct **6a** was also detected in small amounts in reaction mixtures of alkoxyallenylation in Scheme 2, but purified **6a** remained unreactive when subjected to the conditions of catalytic alkoxyallenylation. Thus, **6a** was chemically incompetent as an intermediate for the alkoxyallenylation process.

We also attempted to replace alcohols with amine nucleophiles in acetonitrile. When aniline and indoline were used, propargylic amination of **2a** was the main side reaction (see Figure 1 b). Moreover, aliphatic amines, such as diethyl-

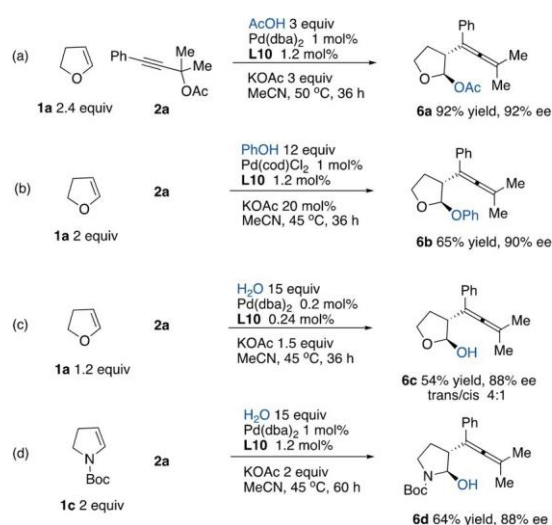


Scheme 2. Alkoxyallenylation of 2,3-dihydrofuran.

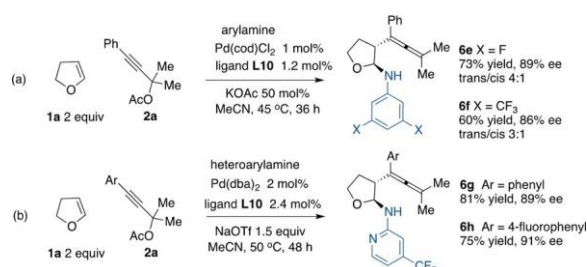
amine and pyrroline, led to elimination of 2a to give the enyne. However, fluorinated aryl amines and pyridyl amines of attenuated nucleophilicity reacted smoothly to provide azaallenylation adducts (Scheme 5 a,b). The initially formed *trans* *N,O*-acetals 6 e,f probably underwent reversible ring opening to generate the minor *cis* isomers. NaOTf accelerated the addition of pyridyl amines to give products 6 g,h



Scheme 3. Alkoxyallenylation of *N*-Boc-2,3-dihydropyrrole.



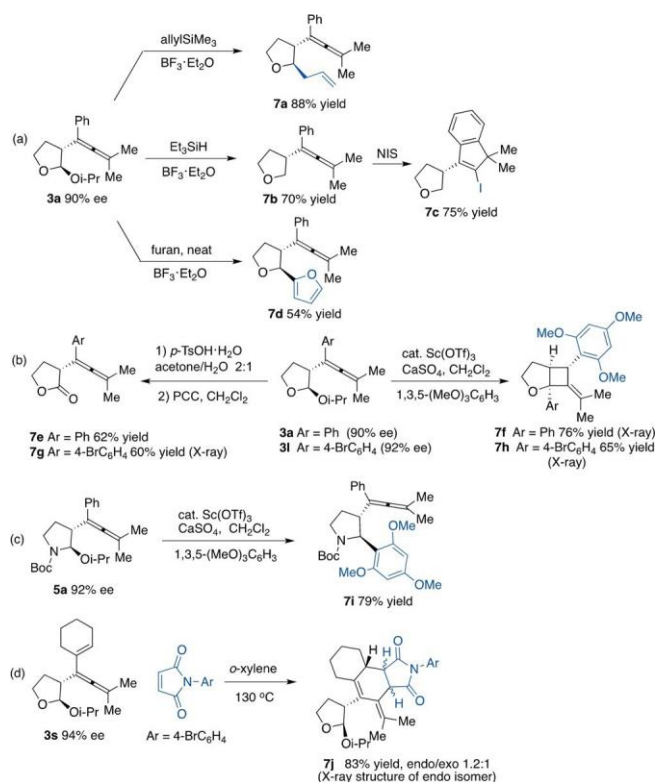
Scheme 4. Wacker-type oxyallenylation using acetic acid, phenol, and water.



Scheme 5. Wacker-type azaallenylation triggered by the attack of an aryl amine. Tf = trifluoromethanesulfonyl.

(Scheme 5 b); without this additive, no conversion was detected.

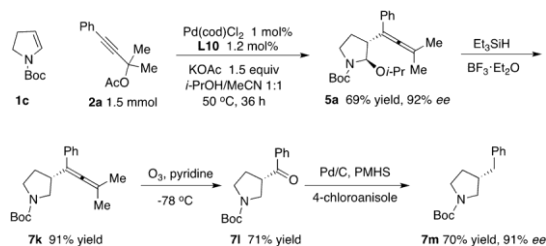
To demonstrate the synthetic utility of the transformation, we subjected adduct 3a to Friedel-Crafts allylation and heteroarylation with an allylsilane^[17] and furan (Scheme 6 a). Acetal 3a was also reduced to 7b by triethylsilane, and then underwent facile iodocyclization to 7c upon treatment with



Scheme 6. Transformations of alkoxyallenylation adducts. Ts = toluenesulfonyl.

N-iodosuccinimide (NIS).^[18] Acidic hydrolysis of **3a** and PCC oxidation furnished butyrolactone **7e** (Scheme 6b). In all cases, no erosion of enantiopurity was observed. Next, we attempted arylation of the oxonium species derived from **3a** under Friedel–Crafts conditions. Surprisingly, scandium triflate efficiently catalyzed the addition of 1,3,5-trimethoxybenzene to **3a** but giving a highly strained, fused cyclobutane **7f** through an unprecedented sequence of cationic reactions (Scheme 6b). A bromophenylated acetal **3l** was also readily converted into **7h**, whose configuration was established by X-ray diffraction analysis (Scheme 6b).^[19] However, the analogous Friedel–Crafts reaction of **5a** resulted in simple arylation (Scheme 6c). A thermal Diels–Alder reaction of **3s** with an *N*-aryl maleimide produced a mixture of two isomers of **7j** (Scheme 6d).

Adduct **5a** was also subjected to silane reduction and selective ozonolysis to give ketone **7l** (Scheme 7).^[20] Subsequent palladium-catalyzed reduction with polymethylhydro-



Scheme 7. Synthesis of chiral 3-benzoyl- and 3-benzylpyrrolidine. cod = 1,5-cyclooctadiene.

siloxane (PMHS) afforded *N*-(*tert*-butoxycarbonyl)benzylpyrrolidine **7m**.^[21] Chiral 3-benzylpyrrolidines are one type of heterocyclic amines used in drug discovery,^[22] but few efficient stereoselective methods for their synthesis exist to date.^[23]

In summary, we have reported an asymmetric Wacker-type coupling of propargylic acetates, cyclic alkenes, and external nucleophiles, such as alcohols, phenols, carboxylic acids, water, and electron-deficient aryl amines. For the first time, asymmetric Wacker-type attack of truly external nucleophiles on monoolefins proceeded without any aid of directing groups. Notably, the use of electron-deficient furyl-MeOBIPHEP proved crucial to both the reactivity and stereoselectivity of the asymmetric Wacker-type process.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: allenens · asymmetric catalysis · carboetherification · palladium catalysis · Wacker reaction

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