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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 azapalladation 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 allenenes.^[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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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*-xyl.

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 Difluorpos 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-dihydropyran, 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 = toluene-sulfonyl.

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 7 m.^[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.

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