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Asymmetric Three-Component Heck/Amination of Nonconjugated Cyclodienes

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Abstract: Asymmetric Heck/amination of nonconjugated cyclodienes proceeds to give substituted cyclohexylamines in good enantioselectivity and exclusive trans configurations. Substituted chiral cyclohexylamines are lead-like compounds and they are becoming increasingly important in drug discovery. Primary and secondary anilines, indoline and benzylamines are suitable amines in this reaction. A weakly-donating diphosphine, Kelliphite forms a deep unsymmetrical pocket, which is essential for stereoselective anti-attack of external amines.

In the early 1990s, Larock et al. reported that Heck amination of nonconjugated dienes produced a rac-allyl Pd species, which was finally trapped by external amines and malonates (Fig 1a).[1] The reaction involved a key step of palladium migration via sequential C-H hydrogen elimination and reinsertion.[2-3] For many years, an asymmetric variant with nonconjugated dienes has remained elusive. In comparison, asymmetric Heck insertion of conjugated dienes followed by palladium migration via allylic Pd species has met much success.[4] For example, in 1993 Shibasaki et al. reported intramolecular cyclization of alkynyl triflates on a pendant conjugated diene (cyclopentadiene), which was quenched by nucleophilic attack by acetate or benzylamine in 80% ee.[4a] Only in 2019, Wu et al. disclosed asymmetric Heck cyclization onto a tethered 1,4-cyclohexadiene, which was successfully trapped by malonates, phenols and a special aniline (Fig 1b).[5] In this reaction, alkene insertion was the stereodetermining step. Moreover, tethering of two reaction partners made asymmetric alkene insertion much easier to achieve than intermolecular cases.

Herein, we report the first asymmetric examples of 3-component Heck/amination of nonconjugated cyclic dienes (Fig 1c). This domino reaction combines two major classes of organometallic reactions, alkene insertion and allylic substitution, and use easily available reagents to add an aryl ring and an amine on cyclic dienes with excellent stereocontrol of two new stereogenic centers. Thus, this reaction is ideally suited for the preparation of chiral arylated cyclohexylamines.

Substituted cyclohexylamines are becoming increasingly important as core motifs in drug candidates. The amine functionalities not only help to assemble fragments of drugs, but also provide hydrogen bonding sites with target receptors. Saturated azacycles, including those carrying stereogenic centers, help to reduce promiscuous binding and also confer unique three-dimensional shape, thus increasing the chance of success through clinical trials.[6] Examples of drugs containing cyclohexylamine fragments include carbapane for the treatment of bipolar depression (see Fig 2) and glimepiride which stimulates insulin secretion.[7] Some drug candidates carrying 3-substituted cyclohexylamines are also shown in Fig 2, along with the diseases that they target,[8] but efficient stereoselective methods for these chiral amines are still lacking.[9]

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Fig 1. Examples of asymmetric Heck/amination of nonconjugated dienes.

Fig 2. Examples of drugs and candidates containing cyclohexylamines.
Several obstacles were foreseen in developing such an asymmetric transformation as in Fig 1c: a) a weakly donating ligand is needed to activate the π-allylic complex for external nucleophilic attack, but it may be easily displaced by alkylamines in the reaction mixture. b) Asymmetric amination on substituted π-cycloallylic complexes of Pd is nontrivial, and only a limited number of examples of this kind have been reported today.\(^{(10\text{c})}\) The last step of amine attack may be reversible,\(^{(11)}\) especially in alcoholic solvents, which can racemize the products. We did encounter ee erosion over time in glycol, for example, using Et\textsubscript{3}N and i-Pr\textsubscript{2}NEt as bases instead of proton sponge.

![Scheme 1](image)

**Scheme 1.** The effect of ancillary ligands on model arylation/amination (yields and ees of 3a are indicated).

We initially attempted to use aryl triflates in a model Heck/amination, but they underwent partial hydrolysis and reduction under basic conditions. Later, we switched to aryl iodides and used ethylene glycol solvent. The alcohol was known to promote reversible ionization of arylpalladium halides in Heck reactions.\(^{(12)}\) The ionization creates a vacant site, crucial for subsequent alkene insertion, palladium migration and formation of cationic π-cycloallyl species (see Fig 1c).

In a model reaction with phenyl iodide, 1,4-cyclohexadiene and indoline, we screened an extensive list of chiral ligands (Scheme 1 and for details, see the Supporting Information). For example, BINAP and Difluorphos delivered desired adduct 3a in good yields, but the ee value was zero, unfortunately. Other chiral phosphines formed catalysts with very low activity, including Josiphos ligands, DIPAMP, Norphos, PHOX and QUINAP. The Pd catalysts of two chiral phosphoramidites only showed moderate activity and gave less than 20% ee. Trost ligands on a backbone of trans-1,2-diaminocyclohexane are usually considered to be the first choice of chiral ligands for Pd-catalyzed asymmetric amination of cycloallylic electrophiles,\(^{(13)}\) but they only provided around 50% ee in our model reaction. Luckily, we finally identified that Kelliphite afforded excellent results, providing adduct 3a in good yield, exclusive trans-selectivity and 94% ee. This electron-deficient diphosphate was previously invented for rhodium-catalyzed asymmetric olefin hydrosilylation.\(^{(16)}\)

With the optimal catalyst in hand, we examined the scope of aryl iodides in reactions with indoline (Scheme 2). It is worth pointing out that aryl fluorides, chlorides and bromides were well preserved in the Pd catalysis (3b–f). The ester, ketone, aldehyde and nitroarene were also tolerated (3h–k). Electron-rich aryl iodides, including \(p\)-tolyl and \(p\)-anisyl, provided adducts with indoline in the range of 70–80% ee (3l–o), but greater than 90% ee was obtained in similar reactions using \(o\)-bromoaniline (3r–u). These brominated adducts can be readily converted to useful tetrahydrocarbazoles via Heck cyclization (see Scheme 5b). Moreover, adduct 3y was subjected to single-crystal X-ray diffraction, which set its configuration to be (3R,SS).\(^{(15)}\) Both thiophene and indole were well tolerated in this reaction (3p–q), while 3-pyridyl iodide was fully consumed, but did not afford any desired product.

![Scheme 2](image)

**Scheme 2.** Scope of aryl iodides in asymmetric arylation/amination.

Next, we examined the scope of amines (Scheme 3). Typical primary amines provided the adducts in the range of 80% ee. Both electron-donating and withdrawing groups can be present on anilines (4b–d). Notably, anilines carrying \(o\)-substituents produced adducts with greater than 90% ee (4e–i). Aryl fluorides, bromides and chlorides were well tolerated, as well as an unprotected \(N\)-H indole (4k). Furthermore, nearly perfect ee was received in reactions of bulky \(o\)-,\(\alpha\)-alkylated anilines (4l–m). This trend can be explained on the ground of steric factor that the disfavored transition state is further destabilized by larger anilines.
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(see Fig 3). Single-crystal crystallographic analysis of compound 4j ascertained its absolute configuration. Secondary anilines were also suitable substrates which delivered products in around 90% ee (4n-p). Furthermore, dibenzylation, tetrahydroisoquinoline and a methoxyamine reacted to give adducts in moderate ee values (4q-s). Unfortunately, smaller amines such as diethylamine and pyrrolidine can bind to cationic palladium species which inhibited the catalytic process. For the same reason, heteroaryl amines of pyridine, pyrimidine and benzoxazole did not afford any desired adducts.

\[
\text{Ph-1} \quad \text{H}_2\text{N} \stackrel{3 \text{ equiv}}{\text{Ph}} \quad \text{Ph} \quad \text{PdCl}_2 \quad 5 \text{ mol\%} \\
\text{H}_2\text{N} \stackrel{2 \text{ equiv}}{\text{Ph}} \quad \text{Ph} \quad \text{proton sponge 2 equiv} \\
\text{ethylene glycol 45 °C, 3 d} \\
\text{Ph} \quad \text{PdCl}_2 \quad 5 \text{ mol\%} \\
\text{H}_2\text{N} \quad \text{ee 96%, yield, 82% ee}
\]

**Scheme 3. Scope of arylamines and an alkoxyamine in asymmetric arylation/amination.**

Unfortunately, reactions of other substituted 1,4-cyclohexadienes catalyzed by Pd/Kelliphite afforded several isomers in low stereoselectivity. It should be pointed out that the diene-insertion step became stereo-determining in these reactions. After switching to a Trost ligand, DACH-Naph, we found that 1-methyl-1,4-cyclohexadiene gave two isomers in a ratio of ~3:1, the major isomer 5a in 72% ee, while the minor 5b as racemic (eq 1).

Lucky, we later discovered that the Heck/amination of 1,5-cyclooctadiene also afforded adducts 6 in excellent ees (Scheme 5). Both primary and secondary anilines reacted smoothly and the reaction tolerated steric elements next to the nitrogen atom of anilines (6b-d). Simple Heck byproducts accounted for the rest of the material.

**Scheme 4. Asymmetric arylation/amination of 1,5-octadiene**

To demonstrate synthetic usefulness of the Heck/amination, adduct 7b was hydrogenated to afford trans-isomer 7c, which was patented for the treatment of diabetes (Scheme 5a). In another example, brominated adduct 4g readily underwent Pd/dppf-catalyzed Heck cyclization to provide all-syn tetrahydrocarbazole 7d (Scheme 5b). Partially hydrogenated carbazoles are core motifs in many drug candidates targeting diseases such as cancers and neurodegenerative diseases, but only racemic samples were used in biological testing. There are only a few enantioselective methods to prepare them.

**Scheme 5. Application in synthesis of medicinally active compounds.**

To understand the origin of enantioselectivity in the model reaction (Fig 3), we performed DFT calculation of the reaction pathway at the W97X-D-31G(d)/SDD level. First, the central biphenyl ring of (R,R)-Kelliphite was found to be flexible. Based on calculation, its complex of PdCl2 formed by the (S)-conformer of the central biphenyl is much more stable than (R)-form, which is also consistent with observation made with rhodium complexes. In the key step of indoline attack at π-allyl palladium species, two dominant transition states leading to enantionic products 3a were 3.1 kcalmol\(^{-1}\) apart in energy, in good agreement with observed 94% ee at 60 °C. Close examination of the chiral pocket of the 7,8-cyclohexenyl complex formed by (R,S,R)-Kelliphite reveals that two peripheral xylyl rings of Kelliphite form deep crevice, which partially buries the π-cyclohexenyl fragment. Moreover, the left xylyl ring is relatively open to accommodate the incoming indoline leading to the major enantiomer. In contrast, the right peripheral xylyl ring forms a rigid steep wall, which obstracts the alternative approach of indoline that forms the minor enantiomer.
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Fig 3. Favored and disfavored transitions states (left and right) for indoline attack on \( \eta^1 \)-5-phenyl-2-cyclohexenyl complex of (R,S)-Kelliphite. The Kelliphite-Pd fragment is shown in space-filling representation, while indoline (in green) and \( \eta^1 \)-phenylcyclohexyl (in black) in ball-and-stick.

In summary, we report a three-component arylation/amination of nonconjugated cyclic dienes in complete trans-selectivity and excellent enantioselectivity. Afteraryl insertion, palladium migration leads to formation of electrophilic \( \eta^2 \)-allyl complexes. They were activated by a weakly donating Kelliphite for external attack of amines. Kelliphite also forms a deep chiral pocket that allows enantioselective attack of the \( \eta^2 \)-allyl fragment by external amines from the opposite side of palladium.

References


Asymmetric Three-Component Heck/Amination of Nonconjugated Cyclodienes

Heck arylation of nonconjugated dienes produces a π-allyl complex, which is trapped by various amines in excellent enantioselectivity and exclusive trans configuration.