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**Palladium-Catalyzed Asymmetric α-Arylation of Alkynitriles**

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Supporting Information Placeholder

**ABSTRACT:** Asymmetric arylation of alkynitriles forms quaternary stereocenters in good enantiocontrol for the first time. A lithium heterodimer consisting of an alkynitrile anion and a disilylamine ion is the actual species responsible for the stereodetermining transmetalation in the catalytic cycle.

In the past two decades, significant progress has been gained in the transition metal-catalyzed asymmetric couplings of carbonyl compounds.1,4 Intermolecular coupling processes offered α-arylation and vinylation products in good enantiocontrol excess (ee) and efficiently formed quaternary stereocenters α to carbonyl groups such as cyclic ketones, oxindoles, and lactones (eq 1 in Fig 1). The enantioselective C-C coupling has also been extended to intramolecular arylation and vinylation of aldehydes and amides, and ketones.4 Asymmetric intermolecular coupling of acyclic enolates is more challenging to achieve, due to the need of E/Z control of the enolates. To this end, we5 and other groups6 have reported metal-catalyzed asymmetric arylation using geometrically defined soft enolates of esters (eq 2), cyclic ketones and lactones, which produced base-sensitive tertiary α-stereocenters.

Alkynitriles are present in drugs such as a verapamil (antiarrhythmic) and anastrozole (advanced breast cancer). Moreover, the nitriles are readily transformed to many useful groups in organic synthesis, for example, after hydrolysis,6 hydrogenation,7 addition of hydride and organometallic reagents,8,9 dipolar cycloaddition,10 and other processes.12 Previously, Hartwig13 and others14 disclosed Pd-catalyzed procedures for non-stereoselective arylation, which led to achiral or racemic products via in situ deprotonation of alkynitriles or decarbonylation processes.15 Most of the conditions employed strongly donating monophosphines as ancillary ligands to achieve good catalytic activity. However, a catalytic enantioselective arylation of alkynitriles remained elusive. The challenge is associated with the difficulty in catalyst differentiation of three groups on the α carbon.

At present, catalytic C-C bond forming processes to prepare enantiomERICALLY RICH α-arylated alkynitriles remain underdeveloped,16 examples including nickel-catalyzed coupling of α-bromonitriles and diaryl zinc reagents (eq 3),17 and reductive coupling of α-chloronitriles and heteroaryl iodides (eq 4).18 In both cases, the nitriles were introduced as electrophiles to produce new tertiary stereocenters, and the structures of products that afforded good ee values remained quite restricted. Moreover, in 2016, Stahl and Liu et al. also reported a copper-catalyzed asymmetric cyanation of benzylic C-H bonds to form new tertiary stereocenters.19

![Figure 1. Examples of asymmetric arylation of enolates and arylation of α-halonitriles and benzylnitriles](image-url)

Herein, we report the first example of Pd-catalyzed asymmetric coupling of aryl halides and alkynitriles that generated quaternary centers in good ee (eq 5). In a test case of α-isopropyl benzonitrile and 2-naphthyl bromide, a combination of a palladium complex and a phosphoramidite ligand L delivered the desired product in 70% yield and 90% ee. The absolute configuration of the coupling product was determined to be 2R, based on single-crystal X-ray diffraction analysis. A strong base, lithium hexamethyldisilazide (LiHMDS) was used for in situ deprotonation of the alkynitrile. The reaction also produced a byproduct, naphthalene via β hydrogen elimination from α-cyanoalkyl group on Pd, which accounted for material balance.

During our catalyst optimization of the model reaction, we initially detected only <10% ee, in the presence of chelating bisphosphines such as binap, difluorphos and segphos. The result was consistent with previous observations of others on the alkynitrile coupling. After many trials, we were gratified to discover that a Feringa’s ligand20 delivered a significant level of stereinduction, 84% ee (Scheme 1). We also tested a diastereomeric form of Feringa’s ligand and it led to the same enantiomeric product as the major one (87% ee). Thus, the binaphthyl back-
bone is the main determinant in setting the absolute configuration of the product, while the amine fragment had little influence.

To further improve the stereoselectivity of the coupling reaction, we tested phosphoramidite (5a,S,S)-L on a partially hydrogenated binaphthyl skeleton.²² To our satisfaction, it led to the coupling product in 90% ee. Furthermore, other modification of aryl rings of the amine fragment didn’t lead to further enhancement of the ee, while a small dimethyamine fragment in the phosphorus ligand resulted in a much less active and less selective Pd catalyst (19% ee). We observed that Qi-Lin Zhou’s phosphoramidite on a spiro-diindany1 scaffold afforded a very low level of stereoinduction (9% ee).²³

![Scheme 1. The influence of phosphoramidite ligands in a model arylation reaction](image)

During condition optimization of the model reaction, an interesting effect of additives emerged (Scheme 2). In the presence of tetramethylethylene-1,2-diamine (TMEDA), the ee value of the product increased from 60% to 90%. In comparison, adding (-)-sparteine to the reaction resulted in 75% ee, while the additives of \(N,N\)-dimethylpropyleneurea (DMPU) or hexamethylphosphoric triamide (HMFA) provided slightly < 90% ee. The presence of a crown ether completely inhibited the catalytic transformation, indicating the lithium ion is intimately involved in the catalysis, maybe in the transmetallation step; the only detectable byproduct was naphthalene (42%) with the rest of material recovered.

![Scheme 2. Additive effect on the model arylation reaction](image)

The combination of palladium source and \((S,S,S,)-L\) was successfully applied to asymmetric coupling of other aryl bromides with the model benzyl nitrile (Scheme 3). Not only electron-deficient but also electron-rich aryl halides reacted smoothly. Two indolyl bromides were also coupled in good ee values. However, other bromides such as 3-bromobenzothiophene and 3-bromoindole, 2-bromothiophene led to low yields of the products. The reactions of aryl iodides led to low yields. The strong base also caused fast hydrolysis of most aryl trillates.

![Scheme 3. Examples of aryl bromides in asymmetric coupling with \(\alpha\)-isopropylbenzyl nitrile](image)

We also examined the scope of alkynitriles in couplings with aryl bromides (Scheme 4). The examples of aryl bromides were chosen for easy separation of enantiomers in chiral HPLC analysis. Both electron-donating and withdrawing groups were tolerated on \(\alpha\)-aryl rings of nitriles. Furthermore, the nitriles can have linear alkyl chains contain-
ing both benzylether and aniline groups, and enantioemic ratio of products was generally >9:1. Notably, the last two cases in the presence of TMEDA gave low yields (<40%) of the coupling products and in <80% ee’s. The main side reactions were identified to be the reduction of the C-Br bonds to PhNMMe (35-55%) and bimolecular condensation of alkynylithanes to another molecule of the nitrile (around 10% for 4 dia stereomers of β-ketoalkynilithanes). When TMEDA was replaced by HMPA,22 the two reactions gave reasonable yields of desired products (>50%) along with PhNMMe byproduct (25-35%), while the condensation of alkynylithanes was prevented. Unfortunately though, benzynitriles bearing other α groups (eg., methyl, ethyl and cyclohexyl) led to low yields (<20%).

Figure 2. Mechanistic study

The ee value of catalytic enantioselective processes is diagnostic of the species directly involved in the formation of new stereogenic centers. Therefore, to probe the transmetalation species, we prepared a dimeric complex [{Ph(t-Pr)C=CNiLi(TMEDA)}]: A containing a core of Li₂N₅, using a Boche’s procedure (eq 6 in Fig 2).24 The iminyl carbon has distinct ¹³C signals at 154.7 ppm for C2 and 50.4 ppm for C3, indicative of significant negative charge localizing on C3 and a Li-bound nitrile group at the nitrogen instead of C3.25

When complex A was used in the model catalytic reaction of 2-naphthyl bromide, it only gave 75% ee surprisingly (eq 7, entry 1). The value is significantly lower than 90% ee observed under in situ deprotonation conditions (eq 5). Next, we added LiHMDS to the coupling conditions, but the ee remained almost unchanged (entry 2). Interestingly, we found that when both LiHMDS and TMEDA were added, the ee was enhanced to 89% (entry 3). It is almost identical to the value from in situ deprotonation (90% ee). Additionally, TMEDA, LiBr or HN(SiMe₃)₂ alone had little effect on the streoselectivity of the model reaction (entries 4-6).

Carlier and Collum et al. reported that heterodimer B existed in equilibrium with homodimer A in solution, in the presence of LiHMDS and TMEDA.26 Thus, we allowed complex A and LiHMDS and TMEDA in an equimolar ratio (per Li) to stand in d₆-toluene overnight, which gave a clean sample of complex B (eq 8). The isopropyl methine has a distinct heptet at 2.79 ppm, which is shifted upfield from 2.83 ppm of A. When the solution of B was used in the catalytic reaction, it indeed gave the product in 89% ee (31% yield). Therefore, we concluded that the active transmetalating species is heterodimer B instead of homodimer A in the model catalytic reaction.

Recently, Gschwind et al. revealed that cis-(L)_2PdCl₃ complexes of Feringa-type phosphoramidite are stabilized by extensive CH-π and π-π interactions between two ligands of L, when compared with the trans isomer.27 Putting all the information together, we conclude that the transmetalation of B to cis-(L)_2Pd(aryl)Br sets the configuration in the coupling product (eq 9). Two cis-ligands L formed a C₂-symmetrical pocket around the palladium center. After the transmetalation, the chiral α-cyanoalkyl ligand in complex C undergoes very slow epimerization and C-C reductive elimination is relatively fast.

The coupling of aryl triflates isn’t synthetically useful, due to fast hydrolysis in the presence of the strong base. Notwithstanding, the result of 2-naphthyl triflate provides additional support for the stereo-determining nature of the transmetalation process. The reaction afforded 64% ee in the absence of LiBr (eq 10). We suggest that the disilylamide occupies the fourth coordination site on the palladium center. In comparison, the ee increased to 82% in the presence of LiBr (1 equiv). This is probably due to partial conversion of the disilylamide complex to a bromide complex, the latter being more stereoselective towards transmetalation with B.

The nitrile groups in the arylation products are readily converted to other functionalities (Scheme 5), for example, an amide after basic hydrolysis, a ketone via Grignard addition, an alcohol via DIBAL-H reduction, an N-acetyl protected amine after hydride reduction. In two cases (b and c), we noticed the ee value slightly increased after flash chromatography, probably due to accidental separation of dimers or oligomers on silica.28 All of the enantoieriched compounds bear quaternary centers and they are tedious to make otherwise.

Scheme 5. Transformation of nitrile groups

In conclusion, we report the first examples of enantioselective arylation of benzynitriles that produced quaternary stereocenters in good ee values. To our surprise, heterodimer B consisting of a ketenemide anion and a disilylamide anion is responsible for the stereoselective transmetalation.

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, spectra for new compounds (PDF)

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**Notes**
The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank Singapore Ministry of Education Academic Research Fund (MOE2013-T2-2-007 and MOE2014-T1-001-021) for financial support. ZJ contributed most experiments in this work.

REFERENCES

Pd catalysts
LiHMDS
TMEDA

good ee
>30 examples

not responsible for stereo-determining transmetalation