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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 disilylamide 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.^{1,2} Intermolecular coupling processes offered α -arylation and vinylation products in good enantiometric excess (ee) and efficiently formed quaternary stereocenters α to carbonyl groups such as cyclic ketones, oxindoles, and lactones (eq 1 in Fig 1).³ 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 an verapamil (anti-arrhythmic) and anastrozole (advanced breast cancer).⁷ Moreover, the nitriles are readily transformed to many useful groups in organic synthesis, for example, after hydrolysis,⁸ hydrogenation,⁹ addition of hydride and organometallic reagents,¹⁰ dipolar cycloaddition,¹¹ 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 decarboxylation 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 enantioenriched α -arylated alkynitriles remain under-developed,¹⁶ examples including nickel-catalyzed coupling of α -bromonitriles and diarylzinc 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

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 benzylnitrile 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 diffractonal analysis. A strong base, lithium hexamethyldisilylamide (LiHMDS) was used for in situ deprotonation of the alkynitrile. The reaction also produced a by-product, 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, difluorophos 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 stereoinduction, 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 (*S_aS_sS*)-**L** on a partially hydrogenated binaphthyl skeleton.²¹ 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 dimethylamine 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-diindanyl scaffold afforded a very low level of stereoinduction (9% ee).²²

Scheme 1. The influence of phosphoramidite ligands in a model arylation reaction

During condition optimization of the model reaction, an interesting effect of additives emerged (Scheme 2). In the presence of tetramethylethylenediamine (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 (HMPA) 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 transmetalation step; the only detectable byproduct was naphthalene (42%) with the rest of material recovered.

Entry	Additives	Product (%)	Ee (%)
1	No additive	52	60
2	TMEDA	70	90
3	(-)-sparteine	70	75
4	DMPU	66	89
5	HMPA	71	86
6	15-Crown-5	0	---

Scheme 2. Additive effect on the model arylation reaction

The combination of palladium source and (*S_aS_sS*)-**L** was successfully applied to asymmetric coupling of other aryl bromides with the model benzylnitrile (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 triflates.

Scheme 3. Examples of aryl bromides in asymmetric coupling with α -isopropylbenzylnitrile

Scheme 4. Examples of alkylnitriles in asymmetric couplings of aryl bromides

We also examined the scope of alkylnitriles 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 α -aryl rings of nitriles. Furthermore, the nitriles can have linear alkyl chains contain-

ing both benzylether and aniline groups, and enantiomeric 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 PhNMe₂ (35-55%) and bimolecular condensation of alkynitrile anions to another molecule of the nitrile (around 10% for 4 diastereomers of β -ketoalkynitriles). When TMEDA was replaced by HMPA,²³ the two reactions gave reasonable yields of desired products (>50%) along with PhNMe₂ byproduct (25-35%), while the condensation of alkynitriles was prevented. Unfortunately though, benzylnitriles bearing other α groups (e.g., 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 transmetalating species, we prepared a dimeric complex [Ph(*i*-Pr)C=C=NLi(TMEDA)]₂ **A** containing a core of Li₂N₂ 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 α carbon.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 stereoselectivity 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 *ds*-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)₂PdCl₂ 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 enantioenriched 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 benzylnitriles that produced quaternary stereocenters in good ee values. To our surprise, heterodimer **B** consisting of a keteneimide 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 all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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chiral ligand

not responsible for stereo-determining transmetalation