Palladium-Catalyzed trans-Hydroalkoxylation: Counterintuitive Use of an Aryl Iodide Additive to Promote C–H Bond Formation

Ashis Das,† Luca Buzzetti,† Mikus Purinš, and Jerome Waser*†

ABSTRACT: We report an enantioselective palladium-catalyzed trans-hydroalkoxylation of propargylic amines with a trifluoroacetaldehyde-derived tether to build chiral oxazolidines. Diastereoselective hydrogenation using a heterogeneous palladium catalyst then gave access to protected benzylc amino alcohols in 45−87% yields and 84−94% ee values. Hydroalkoxylation of the alkynes required a catalytic amount of aryl iodide, highlighting the counterintuitive key role played by a putative Pd(II)/ArI oxidative addition complex to promote oxyarylation product instead of oxypalladation/protodemetalation.

KEYWORDS: enantioselective catalysis, palladium catalysis, hydrogenation, chiral auxiliary, amino alcohols, tethers, dynamic kinetic asymmetric transformation

In order to access this important subclass of amino alcohols, we envisioned a new catalytic process via hydroalkoxylation of the triple bond instead of the arylalkoxylation. For it to be successful, a catalyst will need to be designed to promote C–H bond formation via protodemetalation, which had been observed only as a minor side reaction in our previous studies.

Herein, we report the first enantioselective palladium-catalyzed trans-hydroalkoxylation of propargylic amines via in situ tethering (Scheme 1C). The key for success was the counterintuitive use of a catalytic amount of aryl iodide 7a as additive together with a commercially available chiral diphosphine ligand to promote oxypalladation/protodemetalation instead of oxypalladation/reductive elimination. Diastereoselective hydrogenation under standard heterogeneous conditions then gave access to monoaryl amino alcohol derivatives in high yield and stereoselectivity. Fine-tuning of the structure of aryl iodide 7 was essential to promote the desired transformation.

In our previous work, an interesting result was obtained for the tethered oxyarylation of propargylic amine 1a when DACH-phenyl Trost diphosphine ligand L1 and Pd2(dba)3·CHCl3 as the palladium source were used. The desired oxyarylation product 3a′ was obtained in only 66% yield and 66% ee, but the protodemetalation product 3a was observed in 29% yield and 96% ee (Scheme 2).

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We therefore decided to optimize the trans-hydroalkoxylation process as an alternative to the failed alkoxyarylation of terminal alkynes (Table 1). The first obvious experiment was to remove aryl iodide 7b as it should not be needed for the transformation (entry 1). Surprisingly, no product 3a was formed and we only recovered the starting materials. This result indicated that a Pd−Ar complex may be necessary to promote the hydroalkoxylation step. In fact, when a catalytic amount (20 mol %) of iodobenzene (7c) was added, product 3a was obtained in 23% yield and 94% ee (entry 2). In addition, we also observed the formation of the arylated product in about 20% yield. The role of the aryl iodide is not only to oxidize palladium, as the use of Pd(II) catalysts in its absence did not provide 3a (entry 3). Instead, we recovered only the tethered starting material. When the monophosphine ligand L2,11 which gave the best results in our previous work,3 was used, 3a was obtained only in 13% yield and 38% ee (entry 4). We then investigated the effect of substitution on the arene ring. 2-Iodotoluene (7d) provided product 3a in 27% yield and 86% ee (entry 5). 2-Iodobenzotrifluoride (7e) delivered 3a in 30% yield and 92% ee (entry 6), while 2-iodoanisole (7a) gave 3a in good yield (90%) and enantioselectivity (92%) (entry 7). When the methoxy group was substituted with a fluoro group (7f), 3a was obtained in 90% yield and 86% ee (entry 8), while the large tert-butyldimethylsilyloxy-substituted aryl iodide 7g gave 3a in just 9% yield and 64% ee (entry 9). With a methoxy group in the para position (7h), 3a was formed only in 14% yield with 89% ee (entry 10). From these results, it is apparent that ortho substitution with a small potentially coordinating group is beneficial for the yield but has only a slight influence on the enantioselectivity. The DACH-phenyl Trost ligand L1 was the best ligand. Other ligands (entries 11 and 12), including (R)-SIPHOS-PE (L3) and (R)-MOP (L4), delivered 3a in lower yields (50% and 80%, respectively) as a racemate.

86% ee (entry 5). 2-Iodobenzotrifluoride (7e) delivered 3a in 30% yield and 76% ee (entry 6), while 2-iodoanisole (7a) gave 3a in good yield (90%) and enantioselectivity (92%) (entry 7). When the methoxy group was substituted with a fluoro group (7f), 3a was obtained in 90% yield and 86% ee (entry 8), while the large tert-butyldimethylsilyloxy-substituted aryl iodide 7g gave 3a in just 9% yield and 64% ee (entry 9). With a methoxy group in the para position (7h), 3a was formed only in 14% yield with 89% ee (entry 10). From these results, it is apparent that ortho substitution with a small potentially coordinating group is beneficial for the yield but has only a slight influence on the enantioselectivity. The DACH-phenyl Trost ligand L1 was the best ligand. Other ligands (entries 11 and 12), including (R)-SIPHOS-PE (L3) and (R)-MOP (L4), delivered 3a in lower yields (50% and 80%, respectively) as a racemate.

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**Table 1. Optimization of the Formation of Oxazolidine 3a**

| entry deviation from conditions | yield (%) | ee (%) |
|--------------------------------|----------|-------|
| 1 no 7b                          | <5       |       |
| 2 7c                             | 23       | 94    |
| 3 no 7, PdCl2, Pd(OAc)2, PdI2 or Pd[MeCN]4(BF4)2 | <5       |       |
| 4 7c, L2 instead of L1           | 13       | 38    |
| 5 7d                             | 27       | 86    |
| 6 7e                             | 30       | 76    |
| 7 7a                             | 90       | 92    |
| 8 7f                             | 90       | 86    |
| 9 7g                             | 9        | 64    |
| 10 7h                            | 14       | 89    |
| 11 L3 instead of L1              | 50       | <5    |
| 12 L4 instead of L1              | 80       | <5    |
| 13 toluene instead of DCM        | >95      | 80    |
| 14 ethyl acetate instead of DCM  | 50       | 85    |
| 15 7a, L1, 0.4 mmol scaled       | 83       | 90    |

*Reaction conditions: 0.1 mmol of 1 (1 equiv), 2 (1.4 equiv), ligand (7 mol %), K3PO4 (1.0 equiv), ArI 7 (20 mol %), and Pd catalyst (2.5 mol %) in 0.5 mL of solvent unless specified otherwise.

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0.4 mmol, reducing the catalyst and the ligand loading to 1.25 and 3.5 mol %, respectively, to give a similar yield and stereoselectivity (entry 15).

We then evaluated the scope of the transformation (Scheme 3). Aryl propargylic amines, prepared in a single step from the terminal alkyne (see the Supporting Information), gave access to the corresponding trisubstituted olefins bearing the chiral oxazolidine auxiliary in good yield and stereoselectivity.

On the para position of the aryl ring, both electron-rich and electron-poor substituents were tolerated and the products $3b$−$d$ and $3e$−$l$ were obtained in 72−87% yields and 84−94% ee values. The functional group tolerance included halogens ($3e$−$i$) and even a potentially Pd(0) sensitive bromine ($3g$), an ester ($3j$), a ketone ($3k$), and a cyanide ($3l$). meta-substituted products $3m$−$p$ were obtained in 79−89% yields and 86−90% ee values. The reaction was more sluggish with substituents in an ortho position, and only product $3q$ bearing a small fluoride group could be isolated in 45% yield and 84% ee. The disubstituted product $3r$ was obtained in 77% yield and 86% ee.

The reaction tolerated heterocycles such as thiophene ($3s$), pyridine ($3t$), and quinoline ($3u$) on the alkyne. Propargyl amines with alkyl substituents on the alkyne delivered products $3v$,$w$ in lower yield and enantioselectivity. To evaluate the scalability of this protocol, the reaction on propargyl amine $3a$ was performed on a 3 mmol scale and gave an 82% yield of $3a$ without loss of the optical purity. The absolute configuration of the products was assigned by an X-ray crystallographic analysis of $3a$, confirming the Z geometry of the double bond.

We then examined the stereoselective hydrogenation directed by the installed chiral oxazolidine. We submitted alkene $3a$ to hydrogenation with Pearlman's catalyst. Under these conditions, we could access the reduced and benzyl-deprotected product $4a$ in 85% yield and 90% ee with perfect diastereoselectivity and retention of the enantiopurity (Scheme 4).

Substitution at the para ($4a$−$j$), meta ($4m$,$n$,$r$), and ortho ($4q$) positions of the arene was well tolerated, as were different electronic properties. However, chlorine-, bromine-, and heterocycle-containing olefins did not deliver the hydrogenation products. An ester was well tolerated and gave product $4j$ in 82% yield, while ketone $3k$ and nitrile $3l$ were further reduced to the corresponding alcohol $4k$ and amine $4l$.

The hydrogenation of $3a$ proceeded on a 1 mmol scale without any loss of stereoselectivity. The deprotection of the ...
trifluoroacetate group on 4a could be easily performed with toluenesulfonic acid to give deprotected amino alcohol 8 in 74% yield.

A speculative reaction mechanism based on literature precedents in palladium catalysis is presented in Scheme 5.14

Scheme 5. Speculative Catalytic Cycles

From NMR experiments, we saw a reversible reaction of propargylic amine 1a with ethoxy trifluoroethanol 2 to produce hemiaminal I.1 The catalytic cycle is most probably initiated by oxidative addition of ArI on Pd(0) complex II to give Pd(II) complex III. Reaction with I can then occur either via syn- or anti-palladation,15 both being well established.16 Both pathways would require decoordination of the X ligand (most probably iodide) on palladium, to enable either coordination of the alkyne for anti-palladation (IV to VII) or coordination of the oxygen for syn-palladation (V to VI). As the geometry of product 3a indicates that protodemetalation is occurring from trans-palladation complex VII, an isomerization of cis-palladation complex VI would be required to explain the formation of the product in case of syn-palladation. Although rare, similar isomerizations have been proposed.17 In case of VI, it could be facilitated by the donating effect of the oxygen atom. From VII, protodemetalation then gives product 3a and regenerates Pd(II) complex III. Alternatively, reductive elimination would lead to tetrasubstituted product 3a’. As oxypalladation can be reversible, it is not clear if the dynamic kinetic resolution process of I would occur at this step or only at the stage of isomerization/reductive elimination.

15P(1H) NMR studies first confirmed the formation of a Pd(0)dba diphosphine (L1) complex, as reported in the literature.18 When o-iodoanisole 7a was added to the Pd(0)L1-dba species, an immediate reaction was observed with the appearance of two new signals in the NMR (see section E in the Supporting Information). However, the exact structure of this species remains unclear, as the NMR data does not match the reported spectra of Pd oxidative addition complexes with bidentate phosphine ligands.19 With regard to the promotion of the reaction by the aryl iodide additive, it would be difficult to understand why more electrophilic palladium salts such as PdCl2, Pd(OAc)2, PdI2, and Pd[MeCN]3(BF4)2 would fail in the oxypalladation step. Therefore, the aryl ligand may be important to accelerate the protodemetalation step by increasing the electron density on palladium. The potentially coordinating small ortho substituent in 7a,f may play a role in promoting protodemetalation over reductive elimination. More in-depth mechanism studies are needed to elucidate the reaction mechanism and propose a model for stereinduction and additive effects.

In conclusion, we have developed a palladium-catalyzed hydroalkoxylation of propargylic amines based on in situ tether formation. After diastereoselective hydrogenation directed by the catalytically formed chiral oxazolidine auxiliary, valuable enantioenriched amino alcohol precursors were obtained. The key for success in the hydroalkoxylation reaction was the use of an ortho-substituted aryl iodide as an additive. Currently, this effect is not well understood and mechanistic investigations will be the topic of future work. The discovery of the importance of aryl palladium oxidative addition complexes in promoting alkyne functionalization and protodemetalation has nevertheless already set the basis for the development of new catalytic processes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.2c01809.

Experimental procedures and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest. Raw data for NMR, IR and HPLC is available free of charge from Zenodo.org: https://doi.org/10.5281/zenodo.6634788.
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