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Palladium-catalyzed asymmetric annulation between aryl iodides and racemic epoxides using a chiral norbornene cocatalyst†

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Abstract

Herein, we describe our initial development of an asymmetric Pd-catalyzed annulation between aryl iodides and racemic epoxides for synthesis of 2,3-dihydrobenzofurans using a chiral norbornene cocatalyst. A series of enantiopure ester-, amide- and imide-substituted norbornenes have been prepared with a reliable synthetic route. Promising enantioselectivity (42–45% ee) has been observed using the isopropyl ester-substituted norbornene (**N1***) and the amide-substituted norbornene (**N7***).

The 2,3-dihydrobenzofuran (DHBf) moiety is frequently found in pharmaceuticals and agrochemicals that are commonly prepared in their enantiopure form (Fig. 1).¹ While a number of approaches have been developed for DHBfs, asymmetric synthesis of this structural motif is rare.^{2,3} Recently, we reported a direct annulation between simple aryl iodides and terminal epoxides for synthesis of DHBfs *via* palladium/norbornene (Pd/NBE) cooperative catalysis, also known as Catellani-type reactions (Scheme 1a).^{4–6} The reaction shows a reasonably broad substrate scope with high yields and excellent functional group tolerance; however, the DHBf products generated in this reaction are racemic. While using an enantiopure epoxide as a coupling partner can lead to enantiomerically enriched products,⁴ prior chiral resolution or asymmetric synthesis of epoxides would be needed.⁷ Given the wide availability of racemic epoxides from both commercial and preparative prospects, it would be attractive if one enantiomer of racemic epoxides could selectively react *during* their annulative coupling with aryl iodides.⁸ Herein, we describe our preliminary results on a palladium-catalyzed asymmetric DHBf synthesis between aryl iodides and racemic epoxides using an enantiopure NBE cocatalyst (Scheme 1b). To the best of our knowledge, this should represent the first chiral NBE scaffold-promoted asymmetric reaction *via* aryl halide-mediated Pd/NBE catalysis.^{9–11}

†Electronic supplementary information (ESI) available. CCDC 1859743 and 1859744. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8qo00808f

Conflicts of interest

There are no conflicts to declare.

The optimal NBE cocatalyst found in this annulation reaction was the isopropyl ester-derived NBE (**N1**), and the proposed catalytic cycle is depicted in Fig. 2.¹² Given that the scaffold of **N1** is chiral, we were motivated to examine the feasibility of realizing a kinetic resolution in the coupling with racemic epoxides using enantiopure **N1**. We hypothesized that, during the reaction of the key **ANP** intermediate, the chirality of NBE **N1** would create a chiral pocket around the palladium, which could consequently promote one enantiomer of the epoxide to react faster than the other one.

To test the hypothesis, a reliable route was first developed to prepare enantiopure **N1*** (Scheme 2). Using 2,10-camphorsultam as a chiral auxiliary, the diastereomeric amide-derived NBEs (**A** and **B**) were separated through silica gel chromatography, and each could be isolated in good yields. The structures of NBEs **A** and **B** have also been characterized through X-ray crystallography (Fig. 3).¹⁵ Subsequent hydrolysis and esterification afforded the desired enantiomerically enriched **N1*** in 42% yield (98% ee).

To our delight, the preliminary result shows that, when 20 mol% **N1*** was employed as the ligand, promising enantioselectivity (42% ee) could be obtained (Table 1, entry 1). It is worthy to mention that direct use of sulfonamide NBE **A** could also give the desired product with moderate enantioselectivity (Table 1, entry 2). To further optimize the enantioselectivity, different reaction conditions were applied (Table 1). First, using different reaction temperatures (entries 3–5), adding more **N1*** (entry 6), running the reaction with a mixed solvent (entry 7) or changing the reaction time (entries 8–9) nearly had no influence on the enantioselectivity. In addition, employing a metal–salen complex as a chiral Lewis acid cocatalyst (entries 10–12) completely shut down the reaction. Decreasing the amount of epoxide **2a** from 4.0 equiv. to 0.5 equiv. (entries 13–15) gave lower yield and lower enantioselectivity, though the exact reason is unclear.

On the other hand, a series of chiral NBEs (**N1***–**N13***) with ester or amide substituents have been prepared in their enantiopure forms *via* a similar fashion as **N1***. Their reactivity and enantioselectivity have been examined in the annulation reaction (Table 2). Some interesting trends have been observed. For various ester-substituted NBEs (**N1***–**N6***), the isopropyl ester-derived **N1*** still gave the highest ee. Increasing or decreasing steric hindrance around the ester led to lower enantioselectivity. It is worth noting that **N3*** with a *t*-butyl ester moiety showed low reactivity. Amide and imide-substituted NBEs were also investigated. Encouragingly, the pyrrolidine amide-derived **N7*** gave the highest enantioselectivity (–45% ee or 72.5 : 27.5 er) albeit in a low yield. Evans auxiliary-type NBEs based on chiral oxazolidinone (**N9***–**N13***) have also been synthesized.¹³ While the simple oxazolidinone-derived **N9*** gave a good yield and promising ee, the bulkier **N10***–**N13*** cocatalysts with additional stereocenters on auxiliaries unfortunately showed no reactivity under the current conditions.

Considering the sharp reactivity difference between **N9*** and **N10–13***, we postulated that the steric interaction between the bulky RuPhos ligand and the additional substituent on oxazolidinone might be the reason for the low reactivity. Hence, other Buchwald phosphine ligands¹⁴ were explored using **N12*** as the cocatalyst (Table 3). Interestingly, when XPhos and CPhos were employed as the ligands, the reaction with **N12*** could then provide the

desired product **3aa*** in –25% ee and –31% ee, respectively (entries 1 and 2). Other Buchwald ligands still showed no reactivity similar to the case with Ruphos (entries 3–5).

Considering that XPhos ligand was the most effective ligand when using the bulky **N12*** cocatalyst, other oxazolidi-none-derived **N10***, **N11*** and **N13*** were also examined under the XPhos conditions (Scheme 3). While **N10*** and **N11*** indeed showed good reactivity, the enantioselectivity remained moderate. Surprisingly, **N13***, a diastereomer of **N12***, only gave a trace amount of product, suggesting that the reaction is very sensitive to the steric environment around the palladium catalyst.

Then the substrate scope was briefly examined using **N1*** as the cocatalyst (Scheme 4). Substituted aryl iodides and more functionalized racemic epoxides were all competent substrates. The highest ee (42%) was still obtained from simple 2-iodotoluene with 1,2-epoxyhexane. Ester substitution at the *para* position of the aryl iodide decreased both the yield and the ee (**3ba***). In addition, glycidyl ether-type epoxides gave a high yield but moderate enantioselectivity (**3ac*** and **3ab***).

Finally, to understand the “matched/mismatched” situation regarding the stereochemistry of chiral NBEs and epoxides, enantiopure epoxide (*S*)-**2b** reacted with aryl iodide **1a** in the presence of two enantiomers of **N1***, namely (+)**N1*** and (–)**N1***, as cocatalysts (Fig. 4). Kinetic monitoring clearly suggests that the stereochemistry of (–)**N1*** matches epoxide (*S*)-**2b**, which gave 88% of the desired product within an hour. In contrast, the other enantiomer (+)**N1*** only gave 19% yield during the same reaction period, which indicates the mismatched case.

Conclusions

In summary, we describe our initial efforts on developing an asymmetric annulation reaction between aryl iodides and racemic epoxides *via* Pd/NBE cooperative catalysis. A series of enantiopure NBEs have been prepared with a reliable synthetic route. In particular, the isopropyl ester-substituted NBE (**N1***) could afford the DHBF product in good yields and promising enantioselectivity. While the ee at this stage is still moderate, the availability of such a family of chiral/enantiopure NBE cocatalysts should now open the door for developing various asymmetric Catellani-type reactions. Efforts on better understanding of the chiral induction step through DFT calculation and further improving the enantioselectivity *via* a better catalyst design are underway in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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15. CCDC 1859743 (**NBE A**) and 1859744 (**NBE B**)[†] contain the supplementary crystallographic data for this paper.

Fig. 1.
Bioactive compounds containing chiral 2,3-dihydrobenzofurans.

Fig. 2.
Proposed catalytic cycle.

Fig. 3.
X-ray crystal structures of chiral NBEs **A** and **B**.

Fig. 4.
Control experiments regarding the matched/mismatched situation.

a. direct annulation between aryl iodides and epoxides (our prior work) **b. this work** **Scheme 1.**

Annulation between aryl iodides and racemic epoxides.

Scheme 2.

Preparation of enantiomerically enriched **N1***.

Scheme 3.

Examination of **N10***, **N11*** and **N13*** cocatalysts with the XPhos ligand.

Scheme 4.

Substrate scope with enantiomerically enriched **N1***. ^a 5 mol% of **RuPhos-Pd-G4** was used.

Table 1

Optimization study based on **N1***^a

Entry	Change from the standard condition	Yield ^c [%]	ee ^d [%]
1	None	68	42
2 ^b	A instead of N1*	45	33
3	100 °C	67	41
4	80 °C	31	43
5	60 °C	19	44
6	40 mol% N1*	31	41
7	DMF/dioxane = 4 : 1	80	40
8	5 h	37	41
9	10 h	60	41
10	Adding 5 mol% Co (salen)	Trace	—
11	Adding 5 mol% Cr (salen)	Trace	—
12	Adding 5 mol% Mn (salen)	Trace	—
13	2.0 equiv. 2a	66	31
14	1.0 equiv. 2a	53	28
15	0.5 equiv. 2a	32	33

^aThe reaction was run with 0.2 mmol **1a** and 0.8 mmol **2a** in 2 mL DMF for 24 h.^b150 mol% of **A** was used.^cYields are determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard.^dThe ee was determined using chiral HPLC.

Table 2

Testing different substituted chiral NBEs^a

^a The reaction was run with 0.2 mmol **1a** and 0.8 mmol **2a** in 2 mL DMF for 24 h. Yields were determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. The ee was determined using chiral HPLC based on isolated pure products.

Table 3

Reactions with **N12*** using different Buchwald ligands^a

Entry	Ligand	Yield [%]	ee [%]
1	XPhos	57	–25
2	CPhos	24	–31
3	BrettPhos	Trace	—
4	DavePhos	Trace	—
5	SPhos	Trace	—

<p>XPhos</p>	<p>R = NMe₂ CPhos R = H DavePhos</p>	<p>BrettPhos</p>	<p>SPhos</p>
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^aThe reaction was run with 0.2 mmol **1a** and 0.8 mmol **2a** in 2 mL DMF for 24 h. Yields are determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. The ee was determined using chiral HPLC based on isolated pure products.