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Palladium-Catalyzed Dynamic Kinetic Asymmetric Transformation of Racemic Biaryls: Axial-to-Central Chirality Transfer

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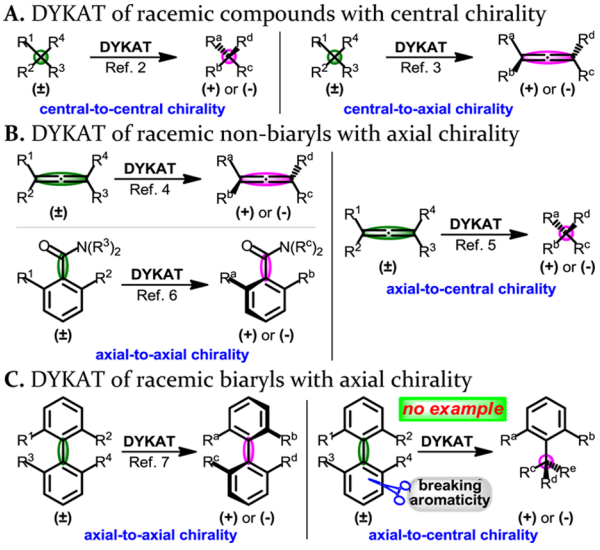
Supporting Information

ABSTRACT: The first dynamic kinetic asymmetric transformation of racemic biaryl substrates on the basis of axial-to-central chirality transfer has been realized. Chiral Pd-NHC complexes were found to catalyze the dynamic kinetic asymmetric spiroannulation of 4-(2-bromoaryl)-naphthalen-1-ols (or 2′-bromo-[1,1′-biphenyl]-4-ols) with internal alkynes, affording a series of enantioenriched spirocyclic products bearing an all-carbon quaternary stereocenter in good yields (up to 95%) with excellent enantioselectivities (up to 97% ee).

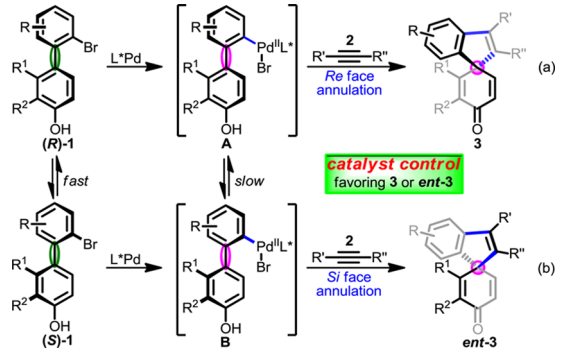
Dynamic kinetic asymmetric transformation (DYKAT) represents one of the most powerful and economical strategies for the synthesis of enantioenriched compounds in the field of asymmetric synthesis.[1] The key feature of DYKAT is the ability to convert both enantiomers of the racemic starting material into a single, optically pure product with a theoretical yield of 100%. To date, great advances have been achieved in this area. Remarkably, a number of excellent catalytic and enzymatic DYKATs with racemic compounds bearing sp^3 stereocenters have been successfully realized (Scheme 1A).[2,3] Meanwhile, some fascinating transformations featuring the same concept have been implemented by using racemic allenes or amides (Scheme 1B).[4−6] Recently, the pursuit of more challenging DYKATs with dynamic mixtures of rapidly racemizing biaryls has seen significant progress. Several elegant examples were reported for accessing optically enriched biaryls via this strategy (Scheme 1C, left).[7] However, DYKAT of an atropisomeric biaryl, with concomitant creation of a new sp^3 stereocenter, by breaking the aromaticity of one aryl ring remains a daunting challenge (Scheme 1C, right). Notably, asymmetric synthesis of compounds with central chirality from enantiopure biaryls on the basis of dearomatizing axial-to-central chirality transfer has been dramatically limited,[8] in part due to the need for high-cost chiral biaryls. In contrast, DYKAT, allowing the direct use of readily available racemic biaryls, would become a more economical and desirable solution to this novel axial-to-central stereochemical transformation.

In this context, we embarked to develop a catalytic DYKAT of racemic biaryls to access a new type of enantioenriched compounds bearing a sp^3 stereocenter. This DYKAT proposal originated from our recent studies on transition-metal-catalyzed dearomatization of 2-naphthol derivatives with alkynes.[9] The synthetic value of these racemic reactions has been reflected by the capacity of transferring one biaryl scaffold into another spirocyclic framework bearing an all-carbon quaternary stereocenter, which offers a potential opportunity for enabling the DYKAT of biaryls via axial-to-central chirality transfer. Along these lines, we speculated that the phenolic derivative **1**, which interconverts rapidly between (***R***)-**1** and (***S***)-**1**, would be an ideal candidate for the anticipated DYKAT (Scheme 2). Presumably, a

Scheme 1. Previous Work on DYKAT



Scheme 2. Design of a DYKAT of Configurationally Labile Biaryls via Axial-to-Central Chirality Transfer



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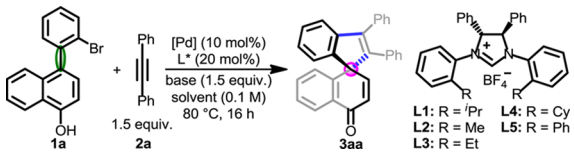
chiral catalyst might be able to discriminate the enantiotopic faces of the phenolic ring in **1**, and further differentiate the formation rates of **3** and ***ent*-3**. However, catalyst-controlled asymmetric dearomatization of phenolic derivatives being restricted from a single enantioface is very challenging, and to date, only a handful of leading examples have been disclosed.[10] Herein, we describe the successful execution of our design for a Pd(0)-catalyzed DYKAT of racemic **1**. To the best of our knowledge, this work represents the first example of DYKAT of racemic biaryls on the basis of axial-to-central chirality transfer.

To test the feasibility of our hypotheses, atropisomeric **1a**[11] and alkyne **2a** were selected as the model substrates. The study commenced with a search for chiral Pd catalysts that can promote the anticipated DYKAT of **1a** with **2a** in an enantioselective manner. Much to our delight, a key breakthrough was ultimately achieved by identifying chiral N-heterocyclic carbenes (NHCs) **L1**−**L5** as the effective ligands. These readily available C_2-symmetric NHCs were pioneered by Grubbs and have proven to be excellent promoters for Ru-catalyzed asymmetric ring-closing metathesis,[12,13] while their use in Pd-catalyzed asymmetric transformations remains underdeveloped.[14] As shown in Table 1,

Table 1. Optimization of the Reaction Conditions



entry	[Pd]	L*	base	solvent	yield (%)[a]	ee (%)[b]
1	$Pd_2(dba)_3$	**L1**	NaO^{t}Bu	toluene	18	62
2	$Pd_2(dba)_3$	**L1**	NaO^{t}Bu	DCE	22	55
3	$Pd_2(dba)_3$	**L1**	NaO^{t}Bu	DME	8	73
4	$Pd_2(dba)_3$	**L1**	NaO^{t}Bu	THF	45	40
5	$Pd_2(dba)_3$	**L1**	NaO^{t}Bu	1,4-dioxane	12	90
6	$[Pd(allyl)Cl]_2$	**L1**	NaO^{t}Bu	1,4-dioxane	51	64
7	$PdCl_2$	**L1**	NaO^{t}Bu	1,4-dioxane	<5	−
8	$Pd(O_2CCF_3)_2$	**L1**	NaO^{t}Bu	1,4-dioxane	42	70
9	***Pd(OAc)$_2$***	***L1***	***NaO^{t}Bu***	***1,4-dioxane***	***53***	***91***
10	$Pd(OAc)_2$	**L1**	LiO^{t}Bu	1,4-dioxane	19	35
11	$Pd(OAc)_2$	**L1**	KO^{t}Bu	1,4-dioxane	<5	−
12	$Pd(OAc)_2$	**L2**	NaO^{t}Bu	1,4-dioxane	17	60
13	$Pd(OAc)_2$	**L3**	NaO^{t}Bu	1,4-dioxane	26	75
14	$Pd(OAc)_2$	**L4**	NaO^{t}Bu	1,4-dioxane	37	81
15	$Pd(OAc)_2$	**L5**	NaO^{t}Bu	1,4-dioxane	<5	−
16[c]	$Pd(OAc)_2$	**L1**	NaO^{t}Bu	1,4-dioxane	89	29

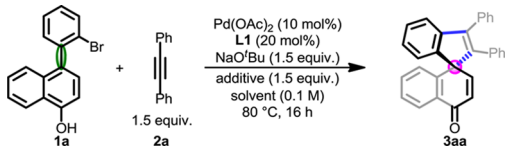
[a]Isolated yield. [b]Determined by chiral HPLC. [c]**1a** was replaced by **1a**′.

the initial finding showed that the desired reaction proceeded in the presence of $Pd_2(dba)_3$ (10 mol %), **L1** (20 mol %), and NaO^{t}Bu (1.5 equiv) in toluene at 80 °C, affording the spirocyclic product **3aa** in 18% yield with 62% ee (entry 1).

Encouraged by this primary observation, we attempted to improve the reaction performance by screening a variety of solvents, which revealed a significant impact on not only the catalytic activity of the Pd catalyst but also the stereocontrol of the spiroannulation of **1a** with **2a** (entries 2−5). In coordinating solvents THF and 1,4-dioxane, the reaction led to higher chemical yield (45%) and better enantioselectivity (90% ee) for **3aa**, respectively. Taking 1,4-dioxane as the reaction solvent, several Pd sources were investigated (entries 6−9), and $Pd(OAc)_2$ turned out to be the optimal catalyst precursor in terms of reactivity and enantioselectivity (53% yield, 91% ee). The reaction was then examined by using other bases such as LiO^{t}Bu and KO^{t}Bu (entries 10 and 11), but none of them could give comparable result as the run with NaO^{t}Bu. Subsequently, a series of NHC ligands, which incorporate a methyl, ethyl, cyclohexyl, or phenyl group on the *ortho*-position of the aryl side chains, were assayed for the DYKAT of **1a** (entries 12−15). The experimental results indicated that the alkyl-substituted NHCs (**L2**−**L4**) were generally effective, with the bulkier ligand showing the better catalytic outcome. However, **L5** that bears an *ortho*-phenyl substituent was totally inactive toward the desired spiroannulation. Additionally, achiral NHC ligands such as SIPr and SIMes were also tested, but they could not enable the formation of **3aa** at all. This observation illustrated that devising mono-*ortho*-alkyl-substituted aryl side chains in **L1**−**L4** were crucial for the title transformation. Up to this point, the superior conditions for **1a** could provide product **3aa** in 53% yield with 91% ee (entry 9). Notably, the related attempt with the iodo counterpart of **1a** (**1a**′) showed higher reactivity (89% yield), but the enantioselectivity dropped dramatically (29% ee) (entry 16).

We posited that the modest chemical conversion for **1a** after the above optimization might be the result of alkyne **2a**'s binding toward the Pd center of intermediate **A** (or **B**) was inhibited by the ligated bromide. So TBA-halide salts were first studied as the additive for the model reaction (Table 2, entries 1−3), and TBAI

Table 2. Evaluation of the Additive Effects



entry	additive	solvent	yield (%)[a]	ee (%)[b]
1	TBACl	1,4-dioxane	25	3
2	TBABr	1,4-dioxane	48	84
3	TBAI	1,4-dioxane	73	85
4	TBAOAc	1,4-dioxane	10	0
5	NaI	1,4-dioxane	71	86
6	KI	1,4-dioxane	78	87
7	TBAI	THF	74	93
8	NaI	THF	72	96
9	***KI***	***THF***	***91***	***93***

[a]Isolated yield. [b]Determined by chiral HPLC.

was indeed able to improve the reaction conversion, albeit with slight drop of enantioselectivity. Combining with the control run by using TBAOAc (entry 4), the experimental data indicated that the halides could influence the reaction greatly. Moreover, NaI and KI were observed to show similar effects as TBAI (entries 5 and 6). Eventually, it was very lucky to find that the reaction performance could be dramatically enhanced by switching the solvent to THF (entries 7−9). TBAI, NaI and KI affected the reaction very differently. For example, the run with NaI allowed producing **3aa** in 72% yield with 96% ee, while the parallel reaction with KI could give **3aa** in 91% yield with 93% ee. Despite the outstanding enantioselectivity with NaI as the additive, studies of additional starting material combinations illustrated that yields were often poor to modest. Therefore, KI was chosen as the additive for further studies, although its role was unclear at the current stage.

To explore the generality of this DYKAT method, the reaction scope was first examined by employing an important number of

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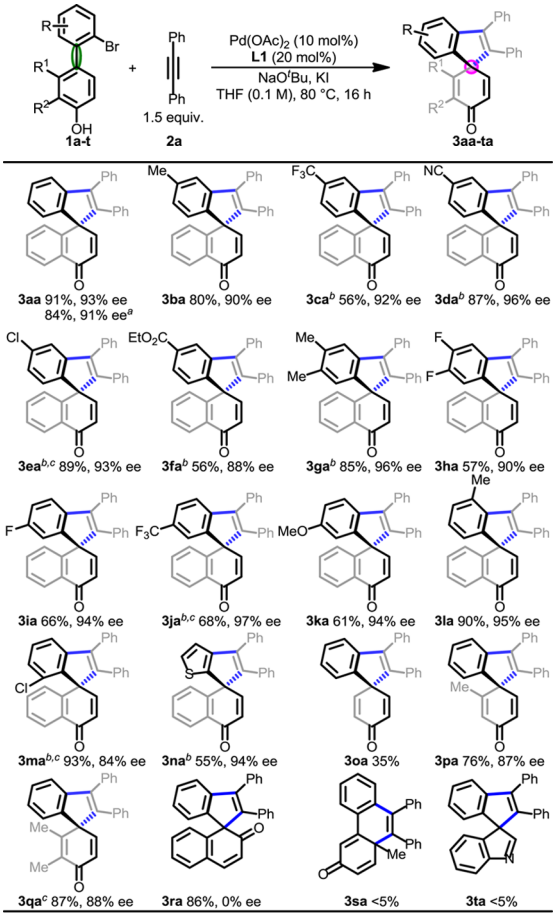
4-(2-bromoaryl)naphthalen-1-ols (**1a**–**n**) to react with **2a**, and the results are summarized in Table 3. Overall, a variety of

Table 3. Survey the Scope of Biaryls

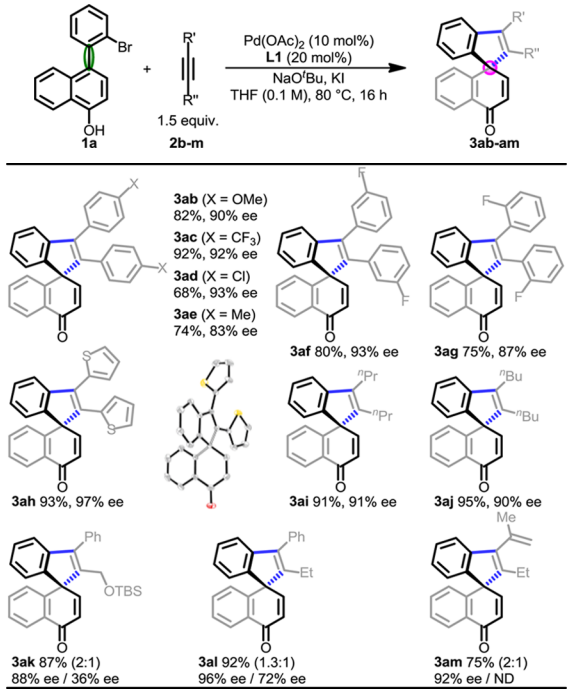


[a]1.0 mmol reaction scale. [b]c = 0.2 M. [c]**L4** was used in place of **L1**.

enantioenriched spiro[indene-1,1′-naphthalen]-4′-ones were successfully prepared in 55–93% yield with 84–97% ee. Satisfactorily, the 1-naphthol coupling partner could be diversely substituted on the 4- or 5-position of the phenyl ring, including electron-neutral or electron-donating groups such as methyl (**1b**,**g**) and methoxy (**1k**) groups, and electron-withdrawing groups such as trifluoromethyl (**1c**,**j**), cyano (**1d**), chloro (**1e**), ester (**1f**), and fluoro (**1h**,**i**) groups. For substrates **1c**, **1d**, **1f**, and **1g**, higher concentration (0.2 M) was used to provide appreciable yields for their corresponding products. For substrates **1e** and **1j**, **L4** was proven to be the better ligand. Remarkably, a sterically congested substrate **1l** was tolerable, affording spirocyclic **3la** in 90% yield with 95% ee via two challenging C–C bond-forming steps. Moreover, substrate **1m** that contains two *ortho*-halide groups (Cl and Br) was able to undergo the title DYKAT to produce **3ma** in 93% yield with 84% ee, implying that the two enantiomers of **1m** could interconvert rapidly under the reaction conditions.[15] Notably, heterocyclic **1n** was also effective for this process. More importantly, the phenol derivatives were found to be suitable for this transformation. Symmetrical **1o** was first investigated, and the achiral **3oa** was collected in 35% yield. Next, unsymmetrical phenolic **1p** and **1q** were then tested, and enantioenriched **3pa** and **3qa** were obtained in good yields. Finally, we have to mention that substrate **1r**, the asymmetric transformation of which was actually attempted previously,[9c] could be converted into the desired product **3ra** in 86% yield, but no stereocontrol was realized. This outcome indicated that configurationally labile biaryls were required for enabling this novel DYKAT method. In addition, no encouraging results were achieved for substrates **1s** and **1t** under the current reaction conditions.

We next turned our attention to study on the spiroannulation of various alkynes with **1a** (Table 4). Regarding the symmetrical

Table 4. Survey the Scope of Alkynes



alkynes containing aromatic rings, a broad range of substituents were tolerated on the *para*- (**2b**–**e**), *meta*- (**2f**), or *ortho*-position (**2g**), and products **3ab**–**ag** were obtained in 68–92% yield with 83–93% ee. To our delight, the alkyne **2h** bearing heterocyclic groups such as 2-thienyl could undergo the annulation with **1a** efficiently, leading to **3ah** in 93% yield with 97% ee. The absolute configuration of **3ah** was assigned to be (*S*) by X-ray. Moreover, dialkylacetylenes (**2i**,**j**) were also adaptable in this process. Specifically, the runs with unsymmetrical **2k**–**m** proceeded smoothly to give products **3ak**–**am** in 75–92% yield with 88–96% ee (for major regioisomers), and the alkene and silyl functionalities remained untouched. With respect to the regioselectivities (1.3:1 to 2:1), the alkynes **2k**–**m** were preferentially installed in such a manner that the alkyl group is close to the spirocyclic carbon center, which is opposite to the related examples.[9a,c]

To demonstrate the potential utility of this method, two transformations of product **3aa** were performed (Scheme 3). The results indicated that the enone functionality could be manipulated properly under mild reaction conditions.

In conclusion, we have developed an unprecedented Pd-catalyzed enantioselective annulation of phenolic derivatives with alkynes, leading to a new class of spirocyclic molecules bearing an all-carbon quaternary stereogenic center with excellent enantioselectivities (up to 97% ee). This process, to the best of our knowledge, is the first successful example of transferring one class of racemic atropisomeric biaryls into

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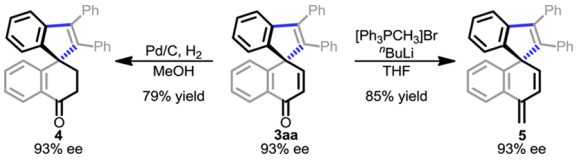
Scheme 3. Synthetic Transformations of 3aa



another type of optically enriched compounds with central chirality relying on the DYKAT strategy.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) Unconsumed **1m** was always recovered as a racemic mixture when the reaction between **1m** and **2a** was conducted at 30−80 °C.

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