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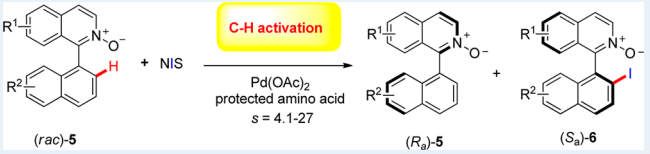
Pd(II)-Catalyzed Intermolecular Direct C−H Bond Iodination: An Efficient Approach toward the Synthesis of Axially Chiral Compounds via Kinetic Resolution

De-Wei Gao, Qing Gu,* and Shu-Li You*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

Supporting Information

ABSTRACT: An efficient protocol to synthesize axially chiral compounds via kinetic resolution by Pd(II)-catalyzed direct C−H iodination was realized (up to s = 27). The iodide product could be easily transformed to aryl-substituted pyridine N-oxides via the Suzuki−Miyaura coupling, which proved to be a suitable catalyst in asymmetric allylation of benzaldehyde with allyltrichlorosilane.



KEYWORDS: *axial chirality, iodination, kinetic resolution, N-oxide, Pd(II)-catalyzed*

Axially chiral molecules are prevalent in biologically active natural products[1] as well as ligands[2] or catalysts[3] in asymmetric catalysis. These compounds have attracted broad attention due to their unique biological profiles and wide applications in catalytic enantioselective processes, even in industrial scale (Figure 1).[4] Accordingly, it is not surprising that

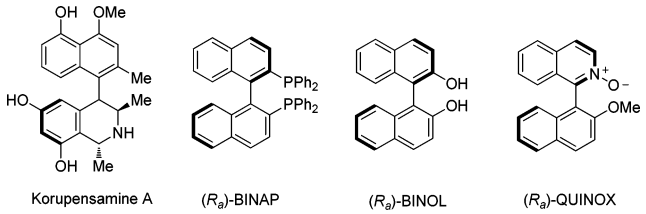


Figure 1. Selected axially chiral biaryl natural product, ligands, and catalysts.

diverse strategies have been developed to construct these axially chiral scaffolds. Generally, the methods employed extensively involved desymmetrization of prochiral biaryls,[5a,d,f] dynamic kinetic resolution of biaryl atropisomers,[5b,c,e] asymmetric oxidative homocouplings,[6] catalytic asymmetric cross couplings[7] and transition-metal-catalyzed enantioselective [2 + 2 + 2] cycloaddition.[8] Despite the recent progress in construction of chiral biaryl skeletons, the catalytic asymmetric synthesis of axially chiral compounds via C−H bond functionalization remains to be rare but highly desirable.[9]

Over the past decade, the development of C−H bond functionalization process has been undoubtedly one of the hottest topics, and great progress has been witnessed in this field.[10] Nevertheless, the enantioselective synthesis of chiral compounds, especially sterically encumbered biaryls via C−H bond activation, remains a difficult task.[9a−c,11] In 2008, a breakthrough on Pd(II)-catalyzed asymmetric C−H alkylation using mono N-protected amino acid (MPAA) as a ligand has been made by Yu and co-workers.[12] Cramer, Kündig, and other groups have devoted much effort to Pd(0)-catalyzed asymmetric C−H functionalization reactions.[13] We also realized the enantioselective synthesis of planar-chiral ferrocenes[14] through Pd-catalyzed asymmetric C−H arylation[14a,c] and annulation reactions.[14b] In addition to these enantioselective C−C bond formations described above, very recently, the groups of Wang[15a] and Yu[15b] reported outstanding examples of asymmetric C−O and C−I bond-forming reactions, respectively. As part of our continuous interest in developing asymmetric C−H functionlization reactions, we decided to explore the synthesis of axially chiral biaryl compounds considering their importance in both academia and industry. Herein we report an efficient approach toward the synthesis of axially chiral compounds via kinetic resolution by Pd(II)-catalyzed C−H bond iodination.

We initiated our studies on the kinetic resolution of (*rac*)-**5a** through asymmetric C−H iodination using MPAA as chiral ligands. In the presence of 10 mol % $Pd(OAc)_2$, 20 mol % HCO-L-Phe-OH, and 1.5 equiv of NIS in CH_3CN at 80 °C, the asymmetric C−H iodination/kinetic resolution afforded product **6a** in 21% yield but without enantioselective control (entry 1, Table 1). We then screened different mono N-protected amino acids. The results are summarized in Table 1. The utilization of Ac-L-Phe-OH or Boc-L-Phe-OH could improve the ee of the product, albeit in low conversion (entries 2−3, Table 1). No enantioselective control was obtained by using Piv-L-Phe-OH (entry 4, Table 1). Gratifyingly, the reaction with Bz-L-Phe-OH could afford **6a** in 42%

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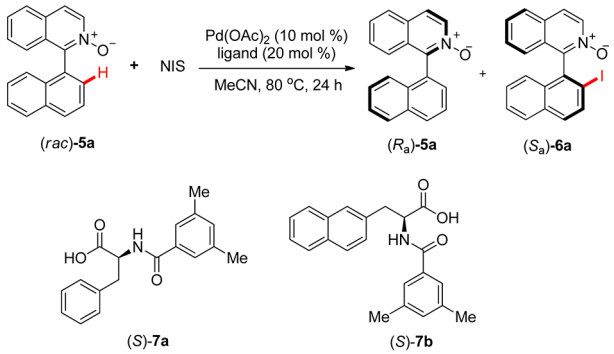
Table 1. Optimization of C−H Iodination[a]



		yield (%)[b]		ee (%)[c]			
entry	ligand	(R_a)-5a	(S_a)-6a	(R_a)-5a	(S_a)-6a	conversion (%)[d]	s[e]
1	HCO-L-Phe-OH	72	21	0	0	nd	nd
2	Ac-L-Phe-OH	50	17	18	81	nd	nd
3	Boc-L-Phe-OH	nd	14	nd	13	nd	nd
4	Piv-L-Phe-OH	70	9	0	0	nd	nd
5	Bz-L-Phe-OH	48	42	54	75	45	8.3
6	Bz-L-Nva-OH	43	32	35	77	54	2.5
7	Bz-L-Leu-OH	41	30	35	75	56	2.4
8	(*S*)-**7a**	32	44	66	70	48	11.8
9	(*S*)-**7b**	39	39	60	76	55	5.2
10[f]	(*S*)-**7a**	49	31	42	88	41	6.0
11[g]	(*S*)-**7a**	45	39	60	76	42	20
12[h]	(*S*)-**7a**	29	61	39	18	63	2.2
13[i]	(*S*)-**7a**	26	42	32	47	68	1.8
14[j]	(*S*)-**7a**	nd	trace	nd	nd	nd	nd

[a]Reaction conditions: (*rac*)-**5a** (0.2 mmol), NIS (0.3 mmol), $Pd(OAc)_2$ (10 mol %), ligand (20 mol %) in CH_3CN at 80 °C unless noted otherwise. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. [d]Determined by ^1H NMR with CH_2Br_2 as an internal standard. [e]Selectivity factor, $s = k_{rel}(fast/slow) = \ln[(1 - C)(1 - ee)]/\ln[(1- C)(1 + ee)]$, where ee is the percent enantiomeric excess of **5a** and C is the conversion. [f]At 60 °C. [g]At 70 °C. [h]In THF. [i]In $CHCl_3$. [j]In EtOH.

yield with 75% ee, corresponding to the selectivity factor (s) of 8.3 (entry 5, Table 1). After further examination of different ligands, we found that (*S*)-**7a** was the most effective one (s = 11.8, entry 8, Table 1). When the temperature was lowered from 80 to 70 °C, the s value was further increased to 20 (entries 8, 10, and 11; Table 1). Finally, the solvent effect was investigated, and CH_3CN remained the optimal one (entries 12−14, Table 1). Notably the recovered enantioenriched (R_a)-**5a** did not undergo racemization at 80 °C for 24 h but racemized completely at 120 °C for 4 h. The product (S_a)-6a did not undergo notable racemization even at 160 °C for 4 h.

With the optimized conditions in hand, we started to explore the substrate scope of the reaction. The results are summarized in Table 2. Substrate bearing a methyl group (4′-Me) on the naphthalene ring was well tolerated (s = 27, **5b**). The introduction of a more electron-donating group (4′-MeO) led to a moderate selectivity factor (s = 6.0, **5c**). For the substrate bearing a fluorine atom, higher catalyst loading at increased temperature was needed (**5d**, s = 9.0, 15 mol % $Pd(OAc)_2$, 30 mol % (*S*)-**7a** at 80 °C). Substrates bearing an electron-donating group on the isoquinoline core (6-MeO, 6-Me, 3-Me) all led to their corresponding iodination products with s values ranging from 11 to 20 (**5f**, **5g**, and **5h**). The reaction conditions were compatible with Cl substituent (s = 4.1, **5e**), which provides the possibility of further functionalization. Substrates bearing substituents with varied electronic property on the naphthalene and isoquinoline ring could be well tolerated (s = 9.0−18, **5i**, **5j** and **5k**). Furthermore, 5, 6, 7, 8-tetrahydro-1-(naphthalen-1-yl)isoquinoline-*N*-oxide (**5l**) is well suited to the reaction conditions. The absolute configuration of the products was then determined as S_a by an X-ray crystallographic analysis of a single crystal of enantiopure **6a** (see the Supporting Information for details).

Chiral pyridine *N*-oxides have emerged as a kind of efficient organocatalysts in asymmetric catalysis, such as allylation of aromatic aldehydes, aldol reaction, cyanosilylation of aldehydes and aldimines, and so forth.[16] However, their preparation mainly relied on cobalt-catalyzed asymmetric [2 + 2 + 2] cyclotrimerization,[17] resolution, or chiral HPLC separation.[18] In order to demonstrate the practicality of the newly developed methodology, the obtained chiral pyridine *N*-oxide was tested in asymmetric allylation of aromatic aldehydes with allyltrichlorosilanes. The phenyl substituent was readily introduced via the Suzuki−Miyaura coupling (note: 92% ee of **6a** was obtained by crystallization from the corresponding sample of 76% ee), providing compound **8** without any erosion on enantioselectivity (eq 1). The asymmetric allylation in the presence of 10 mol % chiral pyridine *N*-oxide **8** (91% ee) could proceed to give the product (**9**) in 58% ee, albeit in a low yield (eq 2).

A plausible catalytic cycle was depicted in Scheme 1 on the basis of literature precedent.[15] With the aid of MPAA, the asymmetric C−H bond cleavage may occur via concerted-metathesis deprotonation (CMD) to generate Pd(II) intermediate **A**, accompanied by retaining (R_a)-**5a**. Then **A** is oxidized by NIS to deliver highly reactive Pd(IV) intermediate

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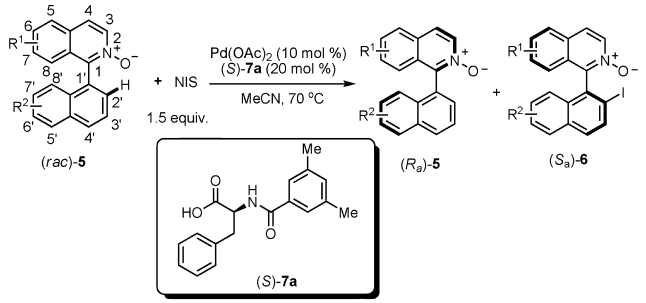
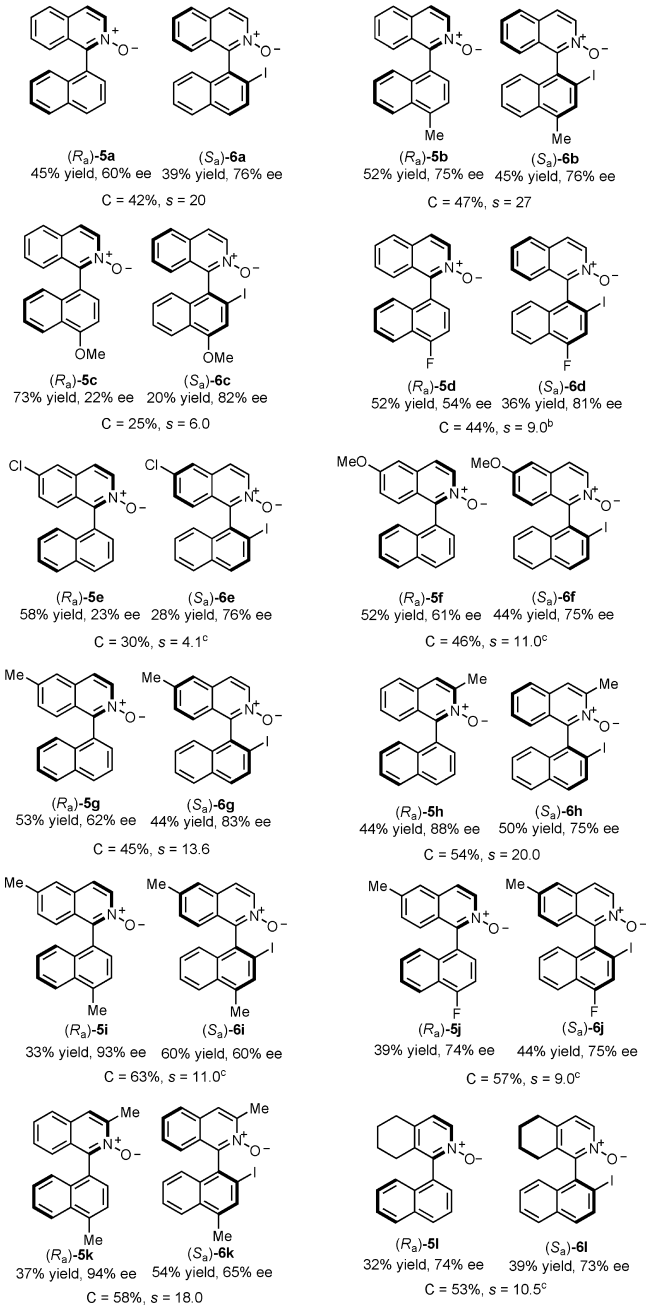
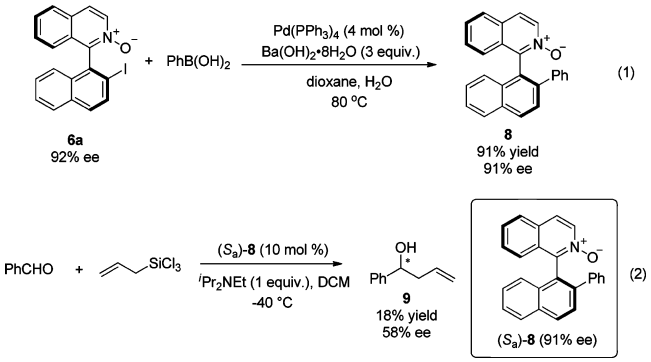
Table 2. Pd(II)-Catalyzed Enantioselective Synthesis of Axially Chiral Compounds[a]

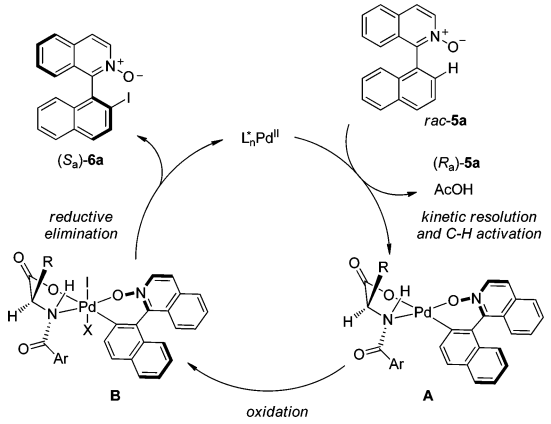




[a]Reaction conditions: (*rac*)-**5** (0.3 mmol), NIS (0.45 mmol), $Pd(OAc)_2$ (10 mol %), (*S*)-**7a** (20 mol %) in CH_3CN at 70 °C. [b]With $Pd(OAc)_2$ (15 mol %), (*S*)-**7a** (30 mol %) in CH_3CN at 80 °C. [c]With $Pd(OAc)_2$ (10 mol %), (*S*)-**7a** (20 mol %) in CH_3CN at 80 °C.



Scheme 1. Plausible Catalytic Cycle



B, and finally reductive elimination of **B** produces the desired product (S_a)-**6a** with the regeneration of the Pd(II) species to finish the catalytic cycle.

In summary, we have developed an efficient protocol to synthesize axially chiral compounds via kinetic resolution by Pd(II)-catalyzed direct C−H iodination. To our knowledge, this strategy provides the first example to access axially chiral biaryl skeletons via enantioselective direct C−H functionalization based on a Pd(II)/Pd(IV) catalytic cycle. Moreover the iodide product could be easily transformed to aryl substituted pyridine *N*-oxides via the Suzuki−Miyaura coupling, which proved to be a suitable catalyst in asymmetric allylation of benzaldehyde with allyltrichlorosilane. Application of these chiral *N*-oxides and development of more efficient asymmetric C−H functionalization process are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analysis data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: qinggu@sioc.ac.cn.
*E-mail: slyou@sioc.ac.cn.

Notes

The authors declare no competing financial interest.

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