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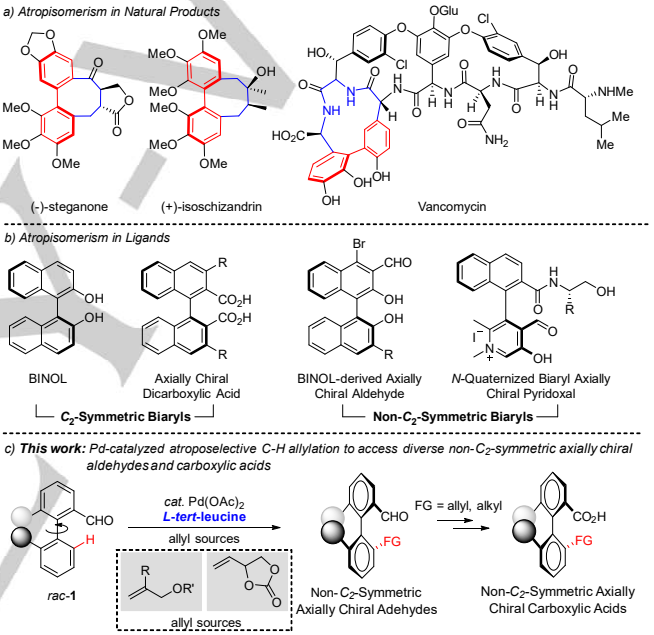
Pd-Catalyzed Atroposelective C−H Allylation via *β*-O Elimination: Diverse Synthesis of Axially Chiral Biaryls

Gang Liao,[a] Bing Li,[a] Hao-Ming Chen,[c] Qi-Jun Yao,[a] Yu-Nong Xia,[a] Jun Luo[a] , and Bing-Feng Shi*[a,b]

Abstract: Biaryl atropisomers are of significant importance in natural products, pharmaceuticals and asymmteric synthesis. The efficient synthesis of these chiral scaffords with full enantiocontrol and high diversity remains challenging. Reported herein is a Pd-catalyzed atroposelective C–H allylation with *tert*-leucine as an efficient, catalytic chiral transient auxiliary. A wide range of enantioenriched biaryl aldehydes were prepared in synthetically useful yields with excellent enantioselectivities (up to >99% ee) via *β*-O elimination. The reaction could be carried out in gram scale without the erosion of ee value. A variety of axially chiral carboxylic acids could be obtained in high enantiopurity. The resulting axially chiral biaryl aldehydes and carboxylic acids might be used in asymmetric synthesis as chiral ligands and/or organocatalysts.

Axially chiral biaryls are common structural motifs in a broad range of synthetically challenging and medicinally important agents, such as natural products and pharmaceuticals (Scheme 1 a).[1] Moreover, axially chiral biaryl compounds, such as 1,1'-bi-2-naphthols (BINOLs) and their derivatives (eg. chiral phosphoric acids, phosphoramidites, etc) have also been widely used as privileged ligands in asymmetric synthesis (Scheme 1 b).[2,3] In 2004, Akiyama[4] and Terada[5] pioneeringly reported the use of BINOL-derived phosphoric acids as a new family of chiral Brønsted acid catalysts. Since then, chiral Brønsted acid catalysts has received considerable attentions for asymmetric synthesis. Numerous variations, mostly derived from BINOLs have been developed. Surprisingly, the corresponding axially chiral carboxylic acids, an important class of moderate Brønsted acids, has rarely been employed, probably due to the lack of efficient strategies to access these ligands with high enantiopurity and structural diversity. A breakthrough in this field was made by Maruoka and coworkers, who developed a series of axially chiral dicarboxylic acids possessing a binaphthyl backbone.[6] These axially chiral dicarboxylic acids have been widely used in a series of enantioselective reactions.[6]

More recently, there has been a growing interest in developing new asymmetric reactions using axially chiral aldehydes as ligands.[7-9] In 2014, Guo and coworkers reported the first enantioselective *α*-alkylation of 2-aminomalonates with 3-indolylmethanols using axially chiral aldehyde.[8a] They also demonstrated the catalytic asymmetric activation of glycine esters using a novel chiral aldehyde catalyst modified from chiral BINOL. [8b] Zhao and co-workers recently designed a novel *N*-quaternized biaryl axially chiral pyridoxal catalyst for biomimetic asymmetric Mannich reaction.[9] In this regard, the discovery and identification of novel types of axially chiral aldehydes and/or carboxylic acids as ligands/catalysts might strongly depend on the developing of new synthetic methodologies.



Scheme 1. The importance of axially chiral biaryls and our synthetic strategy.

Therefore, substantial efforts have been devoted to the synthesis of these axially chiral biaryl backbones.[10] Among these elegant methods, the atroposelective C–H functionalization provides an efficient and straightforward strategy to access these axially chiral structures.[11] Seminal works by Murai,[12] Millller,[13] You,[14] Wencel-Delord and Colobert,[15] Antonchick and Waldmann,[16] and Cramer,[17] have proved the power of this strategy. Despite of these advances, the construction of these important scaffolds with full stereocontrol remains particularly challenging, likely as a result of the difficulty in finding proper ligands for enantioselective synthesis.

In 2016, a pioneering work of Pd-catalyzed enantioselective C(sp^3)–H arylation to create a point chirality using a chiral amino acid as a transient directing group was demonstrated by Yu and coworkers.[18] More recently, the same group has further achieved the Pd(II)-catalyzed enantioselective fluorination of C(sp^3)−H bond via a Pd(II)/Pd(IV).[19] Inspired by these advances, coupled with the goal of synthesizing new types of non-C_2-symmetric axially chiral ligands as asymmetric catalysts and our long-

[a] G. Liao, B. Li, Q.-J. Yao, Y.-N. Xia, J. Luo, Prof. Dr. B.-F. Shi
Department of Chemistry, Zhejiang University
Hangzhou 310027 (China)
E-mail: bfshi@zju.edu.cn.
Homepage: http://mypage.zju.edu.cn/en/bfshi/.
[b] Prof. Dr. B.-F. Shi
State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin 300071 (China)
[c] H.-M. Chen
School of Chemical & Environmental Engineering, Wuyi University, Jiangmen 529020 (China)

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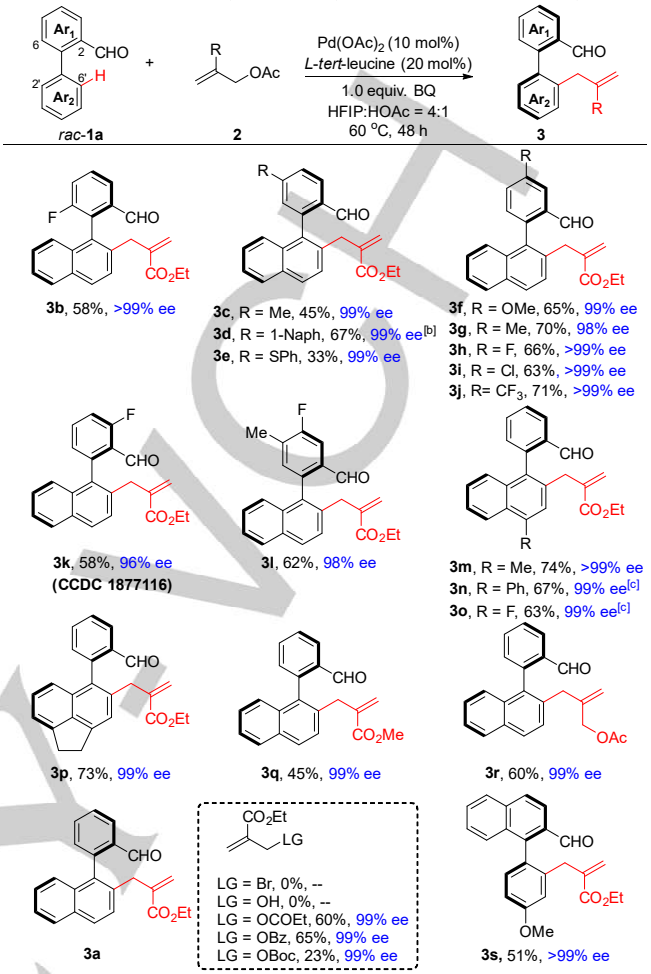
standing interests in enantioselective C–H functionalization,[20] we sought to develop a general and efficient strategy to prepare these axially chiral biaryl motifs with high levels of enantiocontrol and high diversity. Asymmetric allylic alkylation (AAA) reaction with Morita–Baylis–Hillman (MBH) carbonates or acetates has been demonstrated to be an effective method to create a new stereogenic center. In addition, the resulting allylic moiety is also a versatile handle for further transformations.[21] As all reported asymmetric allylation reactions are limited to the preparation of centrally chiral compounds, there is still no report on the creation of axial chirality by the introduction of allylic surrogates into the biaryl atropisomers. Here we report a highly atropo-enantioselective route to these biaryl compounds by Pd-catalyzed C–H allylation with different allylic reagents via *β*-O elimination. This strategy provides an efficient access to a wide range of enantioenriched biaryls (up to >99% ee). The realization of this strategy also establishes a platform for rapid access of non-C_2-symmetric axially chiral aldehydes and carboxylic acids, offering an opportunity for developing new types of axially biaryl chiral ligands/catalysts for asymmetric reactions.

We initiated our research by conducting the reaction of biaryl *rac*-**1a** with **2a** at 60 °C in the presence of 10 mol% $Pd(OAc)_2$ (Table S1). After screening several solvents, we were delighted to find that the reaction proceeded smoothly at 60 °C in HFIP and gave the allylation product **3a** in 16% yield with excellent enantioselectivity using *L-tert*-leucine as a transient chial auxilary, (Table S1, entry 5, 99% ee). Detailed optimization of solvent revealed that HFIP/HOAc was the optimal (entry 7, 26%, 99% ee). Other solvents totally inhibited the reaction, which suggests the acidity of catalytic system was crucial for the occuring of the reaction (entries 1-4). Intriguingly, the desired product **3a** was obtained in 59% yield with 99% ee when the reaction was conducted in O_2 atmosphere. This result indicated the efficiency of the reaction was significantly affected by oxidant. We then turned our attention to explore the effects of oxidants. BQ turned out to significantly improve the yield with maintained enantioselectivity (entry 12, 77%, 99% ee). Other amino acids, however, suffered from lower reactivity and poor stereoselectivity (entries 13-15 and Table S4).

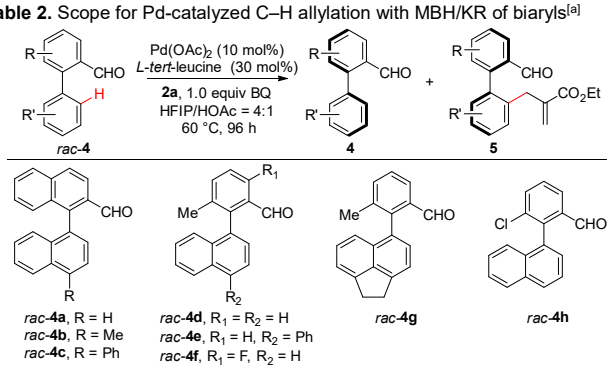
With the optimal conditions in hand, we sought to demonstrate the generality of this protocol. A broad range of biaryls containing substituents at either the 6- or 2' positions underwent a dynamic kinetic resolution (DKR) pathway (Table 1, **1a-1o**, **1r**). Various substituted phenylnaphthalenes underwent the desired allylation smoothly, indicating that the electronic properties of the substituents on phenyl and naphthalene motiety did not affect the reactivity and enantioselectivity (**3a-3o**, 33 to 74% yields, 96 to >99% ee). The reaction is compatible with different halogens, such as fluoro and chloro. In addition to **2a**, other allylation reagents were also compatible with this strategy (**3p** and **3q**). Furthermore, we became interested in whether **3a** could be obtained wtih other allylic surrogates bearing with different leaving groups. The outcomes showed that the leaving groups had a great influence on the reactivity. No reaction happened when -Br severed as the leaving group, indicating that β-bromo elimination is difficult. Hydroxy is also an ineffective leaving group and allylic reagents containing other leaving groups, such as -OCOEt, -OBz, -OBoc show lower efficiency than **2a**. It is also noteworthy that the reaction can be applied to proaxially biaryl **3s** via a desymmetrization process to give **3r** in 51% yield and >99% ee.

Table 1. Scope for Pd-catalyzed C–H allylation with MBH/DKR of biaryls[a]



[a] Reaction conditions: *rac*-**1** (0.1 mmol), **2** (0.3 mmol), $Pd(OAc)_2$ (0.01 mmol), *L-tert*-leucine (0.02 mmol), BQ (0.1 mmol) HFIP/HOAc = 4:1 (1 mL), 60 °C, air, 48 h. [b] *L-tert*-leucine (0.03 mmol). [c] *L-tert*-leucine (0.03 mmol), 70 °C, air, 72 h.

Table 2. Scope for Pd-catalyzed C–H allylation with MBH/KR of biaryls[a]



entry	4	5	4		5		s[c]
			yield (%)	ee (%)[b]	yield (%)	ee (%)[b]	
1	**4a**	**5a**	51	68	41	94	54
2	**4b**	**5b**	44	85	34	98	270
3	**4c**	**5c**	59	49	36	99	324
4	**4d**	**5d**	51	86	33	98	276
5	**4e**	**5e**	53	75	35	98	236
6	**4f**	**5f**	43	78	36	98	88
7	**4g**	**5g**	45	94	36	94	115
8	**4h**	**5h**	39	79	25	98	240

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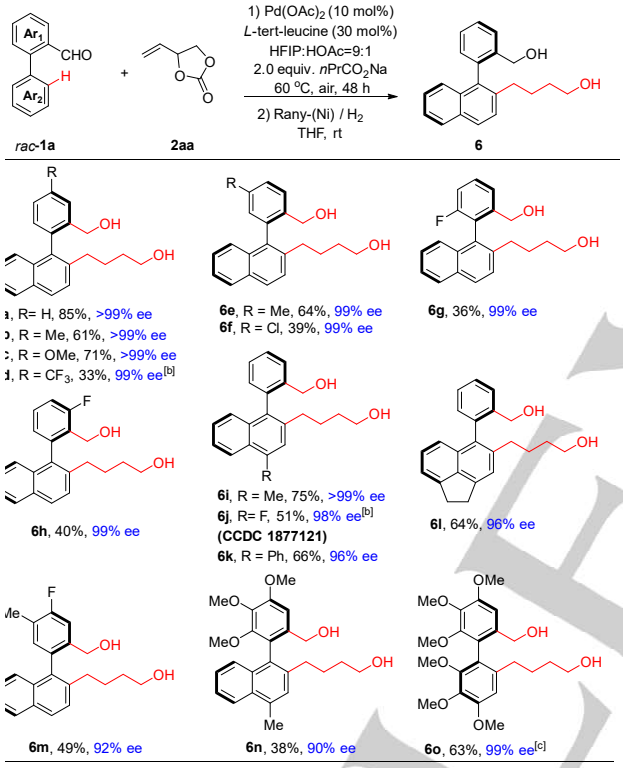
[a] Reaction conditions: *rac*-**4** (0.1 mmol), **2** (0.3 mmol), $Pd(OAc)_2$ (0.01 mmol), *L-tert*-leucine (0.03 mmol), BQ (0.1 mmol), HFIP/HOAc = 4:1 (1 mL), 60 °C, air, 96 h. Isolated yield. [b] The ee value was determined by HPLC. [c] s = ln[(1-C)(1-ee_4)]/ln[(1-C)(1+ee_4)], C = ee_4/(ee_4+ee_5).

Next, we examined whether the asymmetric C–H allylation of biarys could be applicable to kinetic resolution (KR) of biaryls bearing sterically more bulky substituents at both the 6- and 2' positions. To our delight, excellent selectivities were observed under slightly modified conditions as shown in Table 2. The allylated products **5** were obtained in 25%-41% yield with 94 to 99% ee, and the starting materials were recovered in 39%-59% yield with 49 to 94% ee (entries 1-7, *s*-factor = 54-324). It should be noted that 3-chloro-biaryl **4h** was found to be compatible with this reaction affording excellent selectivity (entry 8, *s*-factor = 240).

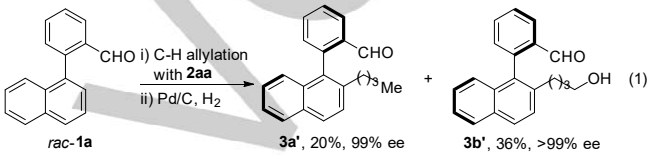
Table 3. Pd-catalyzed C–H Allylation with 4-Vinyl-1,3-dioxolan-2-one /reduction with Raney-Ni[a]



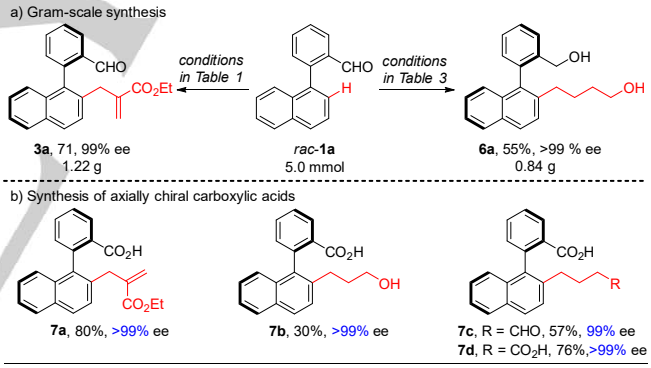
[a] Reaction conditions: 1) *rac*-**1** (0.1 mmol), **2aa** (0.4 mmol), $Pd(OAc)_2$ (0.01 mmol), *L-tert*-leucine (0.03 mmol), ^{n}PrCO$_2$Na (0.2 mmol), HFIP/HOAc = 9:1 (1 mL), 60 °C, air, 48 h; 2) Rany-Ni/H_2. [b] $Pd(OAc)_2$ (0.015 mmol). [c] 70 °C, 96 h.

These results prompted us to explore whether the mode of *β*-O elimination could be applied to the use of other allylic surrogates, which could enabled the synthesis of other type of non-C_2-symmetric biaryls. We chose 4-vinyl-1,3-dioxolan-2-one **2aa** as a versatile coupling partner due to that it exhibits high activity on *β*-O elimination with the evolution of CO_2 as a driving force.[22] We carried out the reaction of *rac*-**1a** with **2aa** under our established reaction conditions. Fortunately, we found that **2aa** was amenable to this transformation, albeit with a mixture of *E/Z* isomers. Further optimizations revealed that the reaction proceeded most efficiently with 4.0 equiv of **2a** in the presence of 10 mol% $Pd(OAc)_2$, 30 mol% *L-tert*-leucine and 2.0 equiv of nPrCO$_2$Na in HFIP/HOAc (9:1) at 60 °C for 48 h. To avoid the isolation of *Z/E* isomers, the reaction mixture after C–H allylation was subjected to the reduction with Raney-Ni to afforded the alkylated biaryl **6a** in 85% yield and >99% ee in a two-step sequence (see Supporting Information for details).

The scope of biaryls were also examined with **2aa** as the reaction partner (Table 3). Although the yield was significant affected by the electronic properties of the substituents, the enantiocontrol remained remarkely high (**6a-o**, 96 to >99% ee). Generally, the electron-donating aromatic substrates delivered products more efficiently (**6a-c**, **6e**, **6i**, **6k-l**), while those with electron-deficient groups tended to afford products in a lower yield (**6d**, **6f-h**, **6j**). However, biaryl bearing trimethoxy on Ar_1 gave the desired product **6n** in 38% yield with slightly decreased enantioselectivity (90% ee). In comparison, with additional methoxy substituents on Ar_2, the corresponding product **6o** was isolated in 63% yield and 99% ee. The absolute configuration of products **3k** and **6j** was unambiguously determined by X-ray analysis and those of other biaryls were assigned by analogy.[23]



In the interest of accessing more structurally diverse axially chiral aldehydes, we explored the reduction of the allylated product with other reducing agents. When Pd/C was used as the catalyst, biaryl aldehydes **3a'** and **3b'** were obtained in excellent enantioselectivities with 20% and 36% yield, respectively (eq 1).



Scheme 2.Gram-scale synthesis and synthesis of axially chiral carboxylic acids.

Gram-scale synthesis and synthetic transformations to various axially chiral carboxylic acids were also conducted (Scheme 2). Firstly, a 5 mmol-scale reaction of *rac*-**1a** and **2a** was performed, delivering **3a** in 71% yield and 99% ee. Then the gram-scale reaction of *rac*-**1a** with **2aa** was conducted, the resulting product could be easily reduced to **6a** in 55% yield with maintained enantioselectivity (>99% ee). Secondly, the oxidation of the resulting chiral aldehydes all proceeded smoothly, affording the desired axially chiral acids in satisfactory yields without erosion of ee value (up to >99% ee, see supporting information for details).

In conclusion, a Pd-catalyzed atroposelective C–H allylation via β-O elimination using a transient auxiliary strategy was developed. This protocol expands the asymmetric allylic alkylation (AAA) reaction from central chirality to axial chirality. *tert*-Leucine served as an efficient and catalytic transient chiral auxiliary. A broad range of enantioenriched biaryls were obtained in synthetically useful yields with excellent enantioselectivities (up to > 99% ee). The axially chiral biaryl aldehydes could be further converted into enantiomerically pure axially chiral carboxylic acids. Further

applications of these axially chiral biaryl aldehydes and carboxylic acids in asymetric synthesis are currently ongoing.

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Keywords: atroposelective • C–H allylation • biaryls • palladium • ligands

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[23] Suitable crystals were selected for measurement on an Oxford Diffraction Gemini A Ultra diffractometer with $Cu_{K\alpha}$ radiation (λ = 1.54178 Å). CCDC 1877116 (**3k**) and 1877121 (**6j**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Pd-Catalyzed Atroposelective C−H Allylation via β-O Elimination: Diverse Synthesis of Axially Chiral Biaryls

A Pd-catalyzed atroposelective C–H allylation with two kinds of allylic surrogates were reported. *tert*-Leucine was identified as an efficient, catalytic transient chiral auxiliary. A wide range of enantioenriched biaryls were prepared in synthetically useful yields with excellent enantioselectivities (up to >99% ee) via *β*-O elimination. The reaction could be easily scaled up and the allylated axially chiral biary aldehydes could be further converted to enantiomerically pure axially chiral carboxylic acids.