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Atroposelective Synthesis of Axially Chiral Biaryls by Palladium-Catalyzed Asymmetric C–H Olefination Enabled by a Transient Chiral Auxiliary

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Dedicated to Professor Biao Yu on the occasion of his 50th birthday

Abstract: *Atroposelective synthesis of axially chiral biaryls by palladium-catalyzed C–H olefination, using tert-leucine as an inexpensive, catalytic, and transient chiral auxiliary, has been realized. This strategy provides a highly efficient and straightforward access to a broad range of enantioenriched biaryls in good yields (up to 98%) with excellent enantioselectivities (95 to >99% ee). Kinetic resolution of trisubstituted biaryls bearing sterically more demanding substituents is also operative, thus furnishing the optically active olefinated products with excellent selectivity (95 to >99% ee, s-factor up to 600).*

Axially chiral biaryl scaffolds are commonly occurring structural motifs in natural products and advanced materials, and they play an important role in synthetic chemistry as privileged chiral ligands and catalysts.[1] Accordingly, great efforts have been devoted to the efficient synthesis of these chiral frameworks,[2] including asymmetric coupling of two arenes by oxidative dimerization or cross-coupling,[3] atroposelective aryl formation by cycloaddition,[4] asymmetric ring-opening of bridged biaryls,[5] asymmetric transfer hydrogenation,[6] stereoselective functionalization of prochiral or racemic biaryls,[7,8] and others.[9] In particular, the atroposelective C–H functionalization through dynamic kinetic resolution (DKR) of biaryls has become one of the most economical and powerful strategies to access these axially chiral biaryls.[8,10] Compared to the others, this strategy enables the conversion of both enantiomers of the racemic biaryls into axially chiral biaryls in a theoretically quantitative yield without the prefuctionalization of starting materials.[8] In 2000, Murai and co-workers reported the rhodium(I)-catalyzed atroposelective C–H alkylation of biaryls with olefins, using a chiral ferrocenyl phosphine ligand, with moderate stereoinduction (up to 49% *ee*).[8a] In 2010, Miller and co-workers reported the atroposelective electrophilic bromination of 3′-hydroxy-[1,1′-biphenyl]-2-carboxylic acid in the presence of a tripeptide.[8b] The major breakthrough in this area was made independently by Zheng and You,[8c] and Wencel-Delord, Colobert, and co-workers[8f] in 2014. The group of You elegantly demonstrated the rhodium(III)-catalyzed C–H olefination/DKR reaction of 1-(naphthalene-1-yl)isoquinolines, using a C_2-symmetric chiral Cp ligand, with moderate to good enantioselective control (58–86% *ee*).[8c] They further improved the enantioselectivity by the design and application of a chiral spiro Cp ligand.[8g] Meanwhile, Wencel-Delord, Colobert and co-workers reported a seminal work on the palladium-catalyzed diastereoselective C–H functionalization of a range of *S*-stereogenic biarylsulfoxides by a DKR strategy.[8f,h] Although these achievements are significant, some of them are still limited to narrow substrate scope, low efficiency, and/or moderate stereocontrol. Therefore, the development of novel strategies to access valuable axially chiral biaryls using readily available starting materials and chiral ligands is highly desirable and challenging. Herein, we report the synthesis of axially chiral biaryls by a palladium-catalyzed C–H olefination/DKR reaction. This strategy employs commercially available *tert*-leucine as an inexpensive, catalytic, and transient chiral auxiliary, thus enabling the efficient synthesis of enantioenriched biaryls in good yields (up to 98%) with excellent enantioselectivities (95 to >99% *ee*).

Recently, transition metal catalyzed C–H functionalization employing catalytic, transient directing groups (DGs) has been realized as a promising strategy since it obviates extra steps to install and remove the external DGs.[11] Yu and co-workers have achieved the creation of central chirality using this elegant strategy.[11d] Motivated by these reports, we envisioned that judicious choice of a transient chiral auxiliary would enable the construction of axial chirality, an approach which has not been realized so far. As shown in Figure 1, we rationalized that a chiral amino acid would reversibly react with *rac*-**1** to form the imines **IM-A** and **IM-B**. C–H cleavage of one diastereomer (**IM-B**) occurred preferentially because of the steric interaction, thus affording an axially stereoenriched biaryl palladacycle intermediate (**C**), which undergoes a typical Heck-type reaction with olefin **2** to give **D**. In situ hydrolysis of the intermediate **D** and reoxidation of Pd^0 to Pd^{II} would afford chiral biaryls (*Ra*)-**3** and close the catalytic cycle.

To test the feasibility of this hypothesis, we initiated our research on identification of a proper chiral amino acid which

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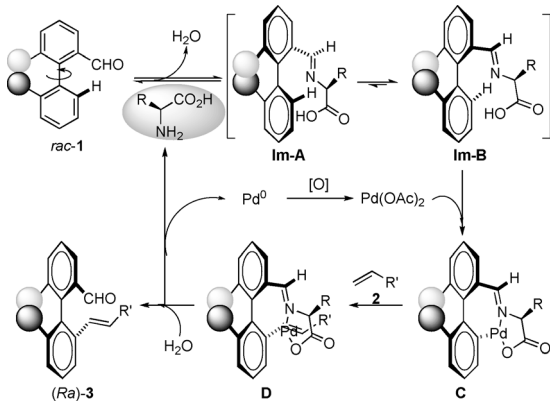
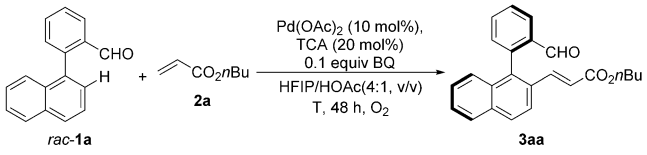


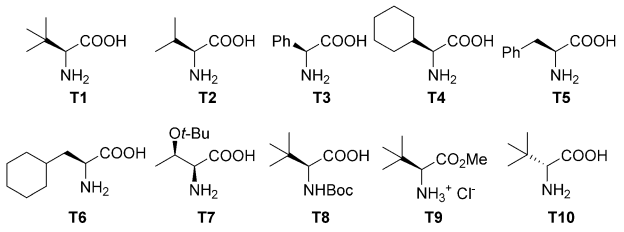
Figure 1. Working hypothesis on atroposelective synthesis of chiral biaryls through C–H olefination/DKR enabled by a transient chiral auxiliary.

can act as an efficient transient chiral auxiliary to promote the palladium-catalyzed C–H olefination/DKR reaction of *rac*-**1a** with butyl acrylate (**2a**; Table 1). To our delight, the reaction proceeded smoothly to afford the desired axially chiral biaryl **3aa** in good yield and moderate enantioselectivity in the presence of 20 mol% L-*tert*-leucine (**T1**) at 90 °C in HFIP/HOAc (entry 1).[8h,12] Encouraged by this, further optimization was first done with a survey of the reaction temperature. We found that the best result was obtained at 60 °C (entry 4). Given that the reaction temperature can dramatically affect the enantioselectivity, we wondered if **3aa** could be easily racemized around 90 °C. To verify the stability of **3aa**, the enantiopure **3aa** was treated either in toluene or under the reaction conditions at 90 °C, and no erosion of the *ee* value was observed, thus clearly indicating that **3aa** was configurationally stable at 90 °C. Given that **3aa** is configurationally stable under 90 °C under the reaction conditions, we assume that the decrease of enantioselectivity might be due to

Table 1: Optimization of reaction conditions.[a]

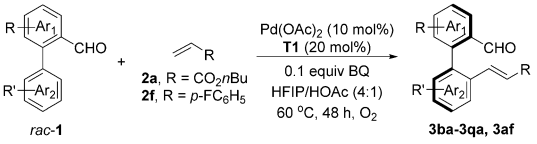


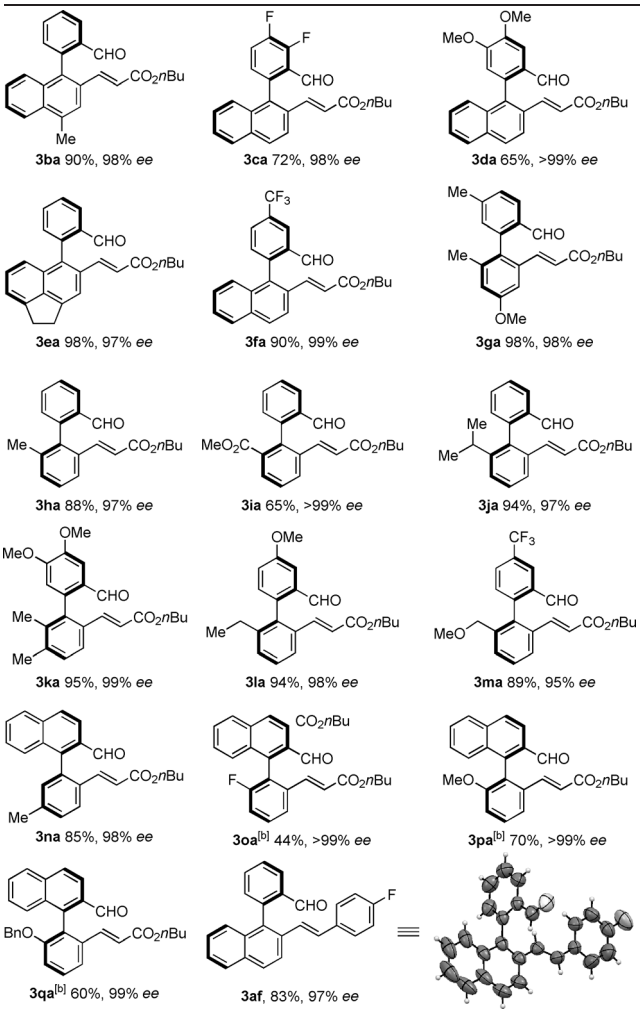
Entry	TCA	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**T1**	90	83	63
2	**T1**	80	86	89
3	**T1**	70	90	92
4	**T1**	60	92 (90)[d]	99
5	**T2**	60	81	63
6	**T3**	60	30	32
7	**T4**	60	70	11
8	**T5**	60	63	67
9	**T6**	60	68	40
10	**T7**	60	58	29
11	–	60	0	–
12	**T8**	60	trace	–
13	**T9**	60	0	–
14	**T10**	60	94 (93)[d]	−99



[a] Reaction conditions: *rac*-**1a** (0.1 mmol), **2a** (3.0 equiv), $Pd(OAc)_2$ (0.1 equiv), TCA (0.2 equiv), BQ (0.1 equiv) in HFIP/HOAc (4:1, v/v, 1 mL) under O_2 for 48 h. [b] Determined by ^1H NMR spectroscopy using dibromomethane as the internal standard. [c] The *ee* value was determined by HPLC. [d] Yield of isolated product is within parentheses. HFIP = hexafluoroisopropyl alcohol, TCA = transient chiral auxiliary.

Table 2: Substrate scope for palladium-catalyzed C–H olefination/DKR of biaryls.[a]





[a] Reaction conditions: *rac*-**1** (0.1 mmol), **2a** (3.0 equiv), $Pd(OAc)_2$ (0.1 equiv), **T1** (0.2 equiv), BQ (0.1 equiv) in HFIP/HOAc (4:1, v/v, 1 mL) under O_2 for 48 h. [b] 96 h.

the isomerization of a certain intermediate generated somewhere along the reaction course.[13]

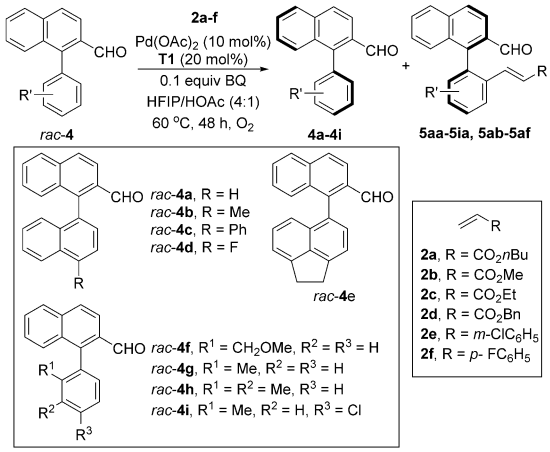
Next, a detailed screening of a range of chiral amino acids (**T1**–**T7**) revealed that L-*tert*-leucine (**T1**) was optimal (Table 1, entries 4–10). Control experiments were also conducted to verify the role of a free amino acid as a transient DG (entries 11–14). No desired product was observed either in the absence of free amino acid (entry 11) or for the use of N- or C-terminus-protected *tert*-leucines (entries 12 and 13). These results strongly support the fact that the amino acid serves as a transient chiral auxiliary to promote the C–H activation, and thus rules out possibility of the aldehyde acting as a weakly coordinating DG and the chiral amino acid serving as a simple chiral ligand.[11d,g,h] When D-*tert*-leucine (**T10**) was used, the other atropisomer was obtained in excellent yield and enantioselectivity (entry 14).

With the optimal reaction conditions in hand, we set out to explore the substrate generality of the atroposelective palladium-catalyzed C–H olefination (Table 2). In general, biaryls bearing substituents at either the 6- or 2′-positions (**1a**–**n**) or sterically less hindered substituents at both the 6- and 2′-positions (**1o**–**q**) proceeded through a DKR pathway to give the desired chiral biaryls in good to excellent yields and with excellent enantioselectivities (**3ba**–**qa**, 95 to >99% *ee*). For C–H olefination of biaryls bearing sterically more demanding substituents at both the 6- and 2′-positions (**4a**–**i**), the reaction through a kinetic resolution (KR) pathway with excellent selectivities (Table 3).

As shown in Table 2, a broad range of racemic biaryl-2-aldehydes (*rac*-**1**) with different substitution patterns were compatible with the strategy. We found that the electronic properties of the substituents on the Ar_1 moiety had a very limited effect on the reaction. Both of biaryls bearing electron-withdrawing (**1c**, **1f,** and **1m**) and electron-donating (**1d**, **1g**, **1k**, and **1l**) groups at the different positions gave the olefinated products in good yields with excellent enantioselectivities. While the electronic properties of the substituents on the Ar_2 moiety can dramatically affect the reactivity, they have no effect on the enantioselectivity, as the reactions of biaryls bearing electron-withdrawing groups (**1i** and **1o**) gave the desired products in low yields (65% and 44% respectively) and those bearing electron-donating groups (**1e, 1g, 1h, 1j**–**n**) proceeded in good yields (85–98%). Notably, trisubstituted biaryls bearing less bulky substituents, such as fluoro (**1o**) and alkoxy, (**1p** and **1q**) were also compatible with a DKR pathway. Although C–H olefination of a 2′-fluorobiaryl led to **3oa** in only 44% yield, the unreacted **1o** was completely racemic, thus ruling out the KR pathway for this substrate. The absolute configuration of the product **3af** was unambiguously determined by the X-ray analysis,[14] and those of other biaryl products were assigned by analogy.[15]

As expected, biaryls bearing sterically more demanding substituents at both the 6- and 2′-positions were configurationally stable. For example, upon measurement of the racemization rate of a representative binaphthyl substrate (**4a**), we found that **4a** displays a remarkably high barrier to rotation and long racemization half-life, even at 150 °C ($t_{1/2}^{rac}$ =228 h; see the Supporting Information for a detailed study), just rendering it a suitable substrate for KR reaction. Then, the scope and efficiency of the palladium-catalyzed C–H olefination/KR of biaryls was investigated under the standard reaction conditions. As illustrated in Table 3, a range of biaryls bearing sterically more demanding substituents at both 6- and 2′-positions were resolved to furnish the optically active olefinated products **5** in 30–47% yield with 95 to greater than 99% *ee*, and the starting materials were recovered in 43–63% yield with 60–97% *ee* (entries 1–9; *s*-factor = 72–600). Various other acrylates were compatible with this reaction (entries 10 and 12). Styrenes with electron-withdrawing substituents, such as chloro and fluoro, were also found to be efficient coupling partners, thus giving good yields and selectivities (entries 13 and 14). Unfortunately, electron-rich styrenes failed to give the desired products under the reaction conditions. One of the advantages of kinetic resolution is that the enantioselectivity of either the substrate or the product could be improved by simply adjusting the

Table 3: Substrate scope for palladium-catalyzed C–H olefination/KR of biaryls.

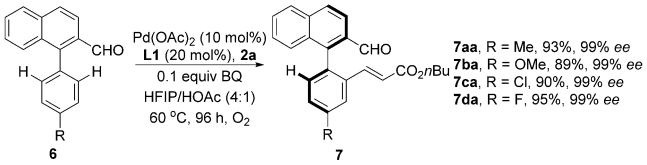


Entry	*rac*-**4**	**5**	**4** Yield [%][a]	*ee* [%][b]	**5** Yield [%][a]	*ee* [%][b]	*s*[c]
1	**4a**	**5aa**	51	79	42	>99	483
2	**4b**	**5ba**	56	73	44	99	438
3	**4c**	**5ca**	54	89	46	>99	600
4	**4d**	**5da**	43	87	41	95	111
5	**4e**	**5ea**	46	97	46	97	278
6	**4f**	**5fa**	55	76	45	98	227
7[d]	**4g**	**5ga**	63 (50)	60 (87)	37 (43)	95 (98)	72 (283)
8	**4h**	**5ha**	45	69	30	95	81
9	**4i**	**5ia**	60	70	40	99	419
10	**4a**	**5ab**	55	69	45	99	413
11	**4a**	**5ac**	47	95	47	95	146
12	**4a**	**5ad**	60	69	37	>99	413
13[d]	**4a**	**5ae**	57 (49)	61 (96)	40 (49)	98 (98)	185 (392)
14[d]	**4a**	**5af**	57 (48)	67 (87)	40 (41)	95 (>99)	79 (570)

[a] Yield of isolated product. [b] The *ee* value was determined by HPLC. [c] $s = \ln[(1-C)(1-ee_4)]/\ln[(1-C)(1+ee_4)]$, $C = ee_4/(ee_4+ee_5)$. [d] Data within parentheses is for reaction run for 96 h.

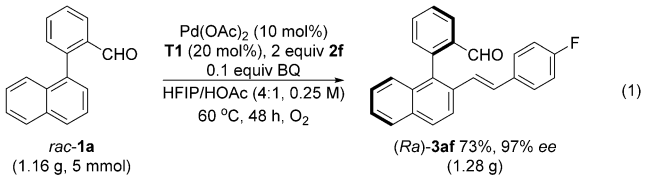
conversion. Therefore, we prolonged the reaction time of several reactions with relatively low conversion and selectivity, and as expected, both the *ee* value of the starting materials and the selectivity were significantly improved (entries 7, 13, and 14, results within parentheses).

Finally, we found that atroposelective desymmetrization of the proaxially biaryls **6** was also operative (Scheme 1). The desired axially chiral biaryls were obtained in excellent yields and enantioselectivities by simply extending the reaction time to 96 hours.

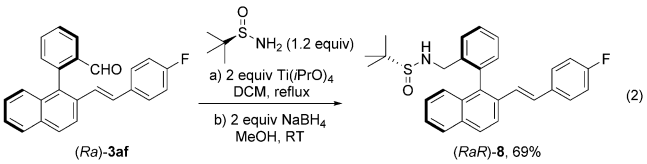


Scheme 1. Palladium-catalyzed C–H olefination/desymmetrization of proaxially biaryls.

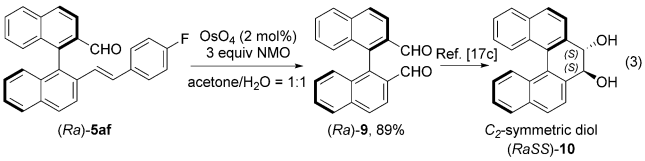
To showcase the practicality of the strategy, a gram-scale C–H olefination/DKR reaction was carried out. The olefination of *rac*-**1a** with **2f** on a 5 mmol scale gave the desired product (*Ra*)-**3af** without notable change in either the yield (1.28 g, 73%) or enantioselectivity (97% *ee*) [Eq. (1)].



To further demonstrate the potential utility of this method, further transformations of the products were performed. A promising sulfur-olefin ligand, (*RaR*)-**8**, was generated in 69% yield by the reductive amination of (*Ra*)-**3af** [Eq. (2); DCM = dichloromethane].[16] *Trans*-9,10-dihydrophenanthrene-9,10-diols are privileged structures in natural products (e.g., FD-594 and pradimicin A)[17a,b] and a class of promising chiral ligands with potential utility in asymmetric catalysis.[15c] Oxidative cleavage of the double bond in (*Ra*)-**5af** gave the enantiopure diarylaldehyde (*Ra*)-**9** in 89% yield, and it could be readily transformed into the novel C_2-symmetric diol (*RaSS*)-**10** by pinacol cyclization [Eq. (3)].[17c]



In summary, we have developed a highly efficient and practical strategy for the synthesis of axially chiral biaryls by palladium-catalyzed atroposelective C–H olefination. This strategy employs commercially available *tert*-leucine as an inexpensive, catalytic, and transient chiral auxiliary, thus enabling the efficient synthesis of enantioenriched biaryls in good yields (up to 98%) with excellent enantioselectivities (95 to >99% *ee*). Further synthetic applications of the axially chiral biaryls in the total synthesis of natural products and asymmetric reactions is underway.



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Conflict of interest

The authors declare no conflict of interest.

Keywords: atropisomerism · biaryls · olefination · kinetic resolution · palladium

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[14] CCDC 1533316 (**3af**) contains 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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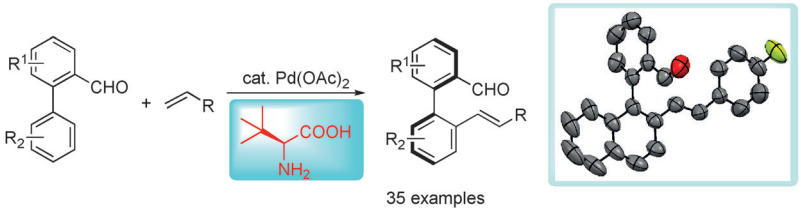
Communications

Kinetic Resolution

Q.-J. Yao, S. Zhang, B.-B. Zhan, B.-F. Shi* ——————— ■■■■–■■■■

Atroposelective Synthesis of Axially Chiral Biaryls by Palladium-Catalyzed Asymmetric C–H Olefination Enabled by a Transient Chiral Auxiliary



No attachements: The title reaction employs *tert*-leucine as a transient chiral auxiliary and provides efficient access to enantioenriched biaryls in good yields (up to 98%) with excellent enantioselectivities (up to >99% *ee*). Kinetic resolution of trisubstituted biaryls bearing sterically more demanding substituents is also operative, thus furnishing the optically active olefinated products with excellent selectivity (up to >99% *ee*, *s*-factor up to 600).