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Combined Dynamic Kinetic Resolution and C–H Functionalization for Facile Synthesis of Non-Biaryl-Atropisomer-Type Axially Chiral Organosilanes

Zhao Li[+],[a] Xu Wang[+],[a] Yu-Ming Cui,*[a] Jun-Han Ma,[a] Li-Lei Fang,[a] Lu-Lu Han,[a] Qin Yang,[a] Zheng Xu,[a] and Li-Wen Xu*[a, b]

Dedicated to Prof. Albert S. C. Chan on the occasion of his 70th birthday

Abstract: Although asymmetric C–H functionalization has been available for the synthesis of structurally diverse molecules, catalytic dynamic kinetic resolution (DKR) approaches to change racemic stereogenic axes remain synthetic challenges in this field. Here, a concise palladium-catalyzed DKR was combined with C–H functionalization involving olefination and alkynylation for the highly efficient synthesis of non-biaryl-atropisomer-type (NBA) axially chiral oragnosilanes. The chemistry proceeded through two different and distinct DKR: first, an atroposelective C–H olefination or alkynylation produced axially chiral vinylsilanes or alkynylsilanes as a new family of non-biaryl atropisomers (NBA), and second, the extension of this DKR strategy to twofold *o,o'*-C–H functionalization led to the multifunctional axially chiral organosilicon compounds with up to >99% *ee*.

Axially chiral compounds are widespread in natural products[1] and biologically active molecules[2] and found in numerous applications, especially in asymmetric synthesis[3] serving as chiral auxiliaries, ligands, and organocatalysts. Therefore, the catalytic synthesis of such compounds has been a research topic of great interest. Among the many elegant methods[4] for their synthesis, the direct asymmetric functionalization of the inert C–H bond has attracted growing attention in terms of its atom economy and step economy.[5,6] In contrast to the intensively investigated directing group-assisted mono *ortho* C–H bond activation of substituted arenes (Figure 1a), the asymmetric functionalization of two or more arene C–H bonds to access to axially chiral products is much less explored. In this regard, Wang and co-workers reported the first chiral spiro-Cp/Rh-catalyzed enantioselective *o*- and *m*-C–H dual activation to synthesize C–N axially chiral *N*-aryloxindoles.[7] Compared with general *o*- and *m*-C–H dual activation, achieving the site- and enantioselective activation of both *ortho* C–H bonds is more challenging likely due to the racemic axially chirality[8]: 1) the stereoselective functionalization reactions through *o*- and *m*-C–H activation are not suitable for the construction of axially chiral biaryl atropisomers, especially through twofold C–H functionalization on both *ortho* C–H bonds of an aryl ring; 2) although a

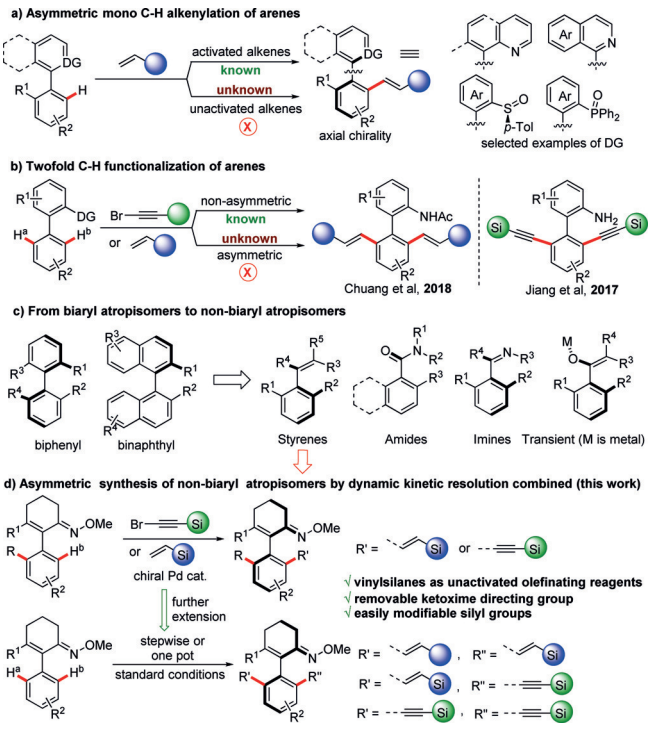

Figure 1. Catalytic asymmetric synthesis of axially chiral molecules through transition-metal-catalyzed C–H functionalization: from classic biaryl atropisomers to non-biaryl atropisomers (this work).

[a] Z. Li,[+] X. Wang,[+] Y.-M. Cui, J.-H. Ma, L.-L. Fang, L.-L. Han, Q. Yang, Dr. Z. Xu, Prof. Dr. L.-W. Xu
Key Laboratory of Organosilicon Chemistry and Material Technology of Ministry of Education, and Key Laboratory of Organosilicon Material Technology of Zhejiang Province
Hangzhou Normal University
No. 2318, Yuhangtang Road, Hangzhou 311121 (P. R. China)
E-mail: ym_cui@hznu.edu.cn
liwenxu@hznu.edu.cn

[b] Prof. Dr. L.-W. Xu
State Key Laboratory for Oxo Synthesis and Selective Oxidation
Suzhou Research Institute and Lanzhou Institute of Chemical Physics
Chinese Academy of Sciences
Hangzhou 311121 (P. R. China)

[+] These authors contributed equally to this work.

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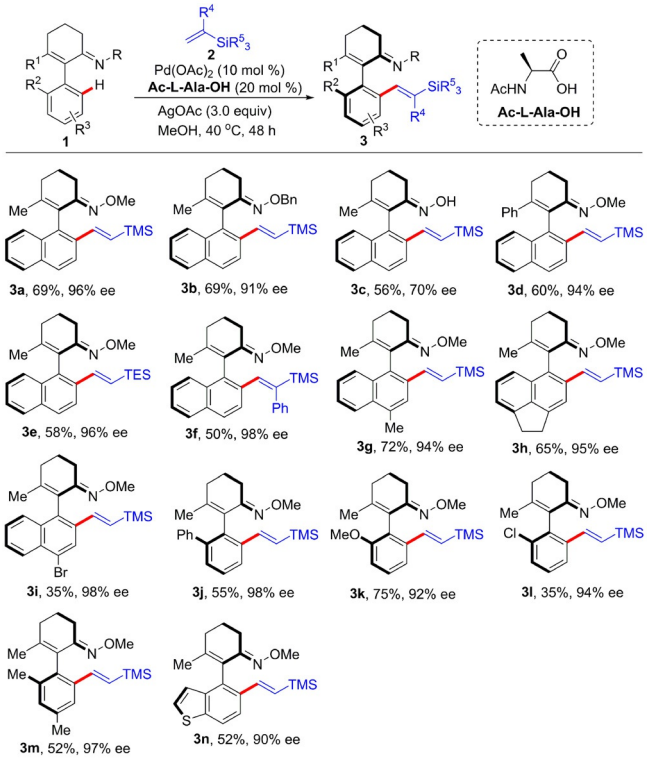
chiral axis can be constructed by introducing two substituents through *o*- and *m*-C–H activation whether they are the same or not, it is limited from the kinetic resolution process of racemic atropisomers through *o*- and *o*′-C–H activation.

To date, although unsymmetrical dual C–H activation has been described for prochiral biaryls (Figure 1 b),[9] no example was reported on the asymmetric variant of arene *o*- and *o*′-C–H functionalization to produce axially chiral and non-biaryl atropisomeric compounds. Inspired by previous reports on the synthesis of biaryl or non-biaryl atropisomers,[10] we anticipated that an ideal enantioselective construction could be realized from dynamic kinetic resolution (DKR) of racemic biaryls or non-biaryls relative to C–H functionalization. In the past years, DKR of racemic starting materials has become a powerful and practical alternative to prepare stereochemically pure final products based on the dynamic stereocontrol.[11] Several groups have discovered that the racemization of configurationally stable biaryls could proceed smoothly to give axially chiral biaryls based on DKR,[12] but there is no report on the enantioselective construction of non-biaryl atropisomers through DKR combined with C–H functionalization. In this regard, the development of an effective strategy for the synthesis of non-biaryl atropisomers that that are easily sensitive to temperature or organic solvent because of axial rotation and possible racemization, in particular dynamic kinetic resolution combined with C–H functionalization, is highly desired. Herein, we describe a straightforward approach to axially chiral styrene-type organosilanes through DKR of racemic starting materials through mono and double *ortho* C–H olefination/alkynylation (Figure 1 d).

Initially, to examine the feasibility of the dynamic kinetic resolution, we evaluated a palladium-catalyzed site-selective C–H olefination of 2-amino biaryls with readily available vinylsilanes as a family of unactivated alkenes.[13] However, our attempt to synthesize axially chiral vinylsilanes failed. Notably, while significant progress has been made on atroposelective C–H olefination of rigid biaryls under metal catalysis, most of successful examples are restricted to electronically activated or biased alkenes such as acrylates or styrenes.[14] The asymmetric C–H olefination of more flexible prochiral vinyl arenes with unactivated alkenes to access axially chiral styrenes bearing a chiral axis between a substituted alkene and an unsymmetrical arene remains a formidable task.[15,16] Previous observations showed the significance of judicious choice of the proper chiral catalysts and directing groups, which can cooperatively act to modulate the reactivity and exert chiral induction. Then, a series of reaction parameters have been evaluated in the model reaction of **1a** [(*E*)-3-methyl-2-(naphthalen-1-yl)cyclohex-2-enone *O*-methyl oxime] with vinylsilane **2a**, and the experimental results revealed the optimized reaction conditions as following: $Pd(OAc)_2$, Ac-L-Ala-OH as a chiral ligand, and AgOAc as an additive, in MeOH and at 40 °C (Tables S1 and S2 in the Supporting Information).

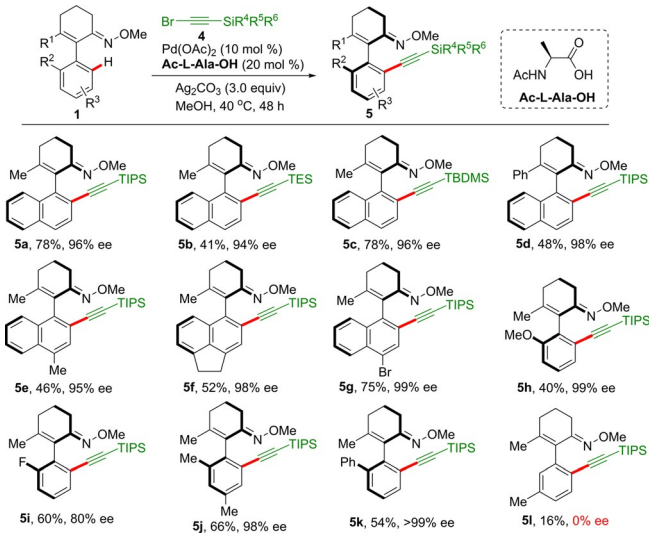
Next, the scope of DKR of styrene-type racemic starting material **1** through C–H olefination reaction was examined (Scheme 1). Generally speaking, the vinylsilanes coupled with vinyl arenes in inferior reactivities and enantioselectivities to



Scheme 1. Atroposelective synthesis of axially chiral vinylsilanes via mono *ortho*-olefination.

activated alkenes. It was demonstrated that the substituent at the nitrogen atom of the oxime directing group had major influence on the results of coupling reactions and OMe outperformed OBn and OH groups. As to the vinylsilane coupling partners, triethylvinylsilane and trimethyl(1-phenylvinyl)silane are also compatible affording the corresponding and stable non-biaryl atropisomers (for the determination of enantiomerization barrier, see the Supporting Information, e.g., $\Delta G^{\#\#} =$ 148.1 kJ mol^{-1} for **3g**) with excellent enantioselectivities, albeit in decreased yields (**3e** and **3f**). Changing the substituent from Me to Ph on the upper cyclohexene or bottom aromatic ring had negligible influence on reaction results (**3a** vs. **3d** and **3j** vs. **3m**). The substrates bearing electron-donating *o*-MeO group and electron-withdrawing *o*-Cl and *p*-Br atoms proceeded well. Furthermore, the reactive benzothiophene was also tolerated and delivered the desired **3n** in 52% yield and 90% enantiomeric excess (*ee*). Notably, the successful extension to vinylsilanes as the coupling partners constitutes the first example of asymmetric synthesis of axially chiral compounds by atroposelective olefination of arene C–H bonds using unactivated alkenes.

Unlike the C–H olefination reactions proceeding through $Pd^{II/0}$ manifold, the alkynylation of arene C–H bonds with alkynyl bromide as the coupling partner was thought to proceed through $Pd^{II/IV}$ catalytic cycle. The distinction in catalytic cycle may require arenes with different steric and electronic properties which will create chance for introducing two kind of different substituents. As demonstrated in Scheme 2, most of substrates **1** smoothly underwent dynamic kinetic resolution com-

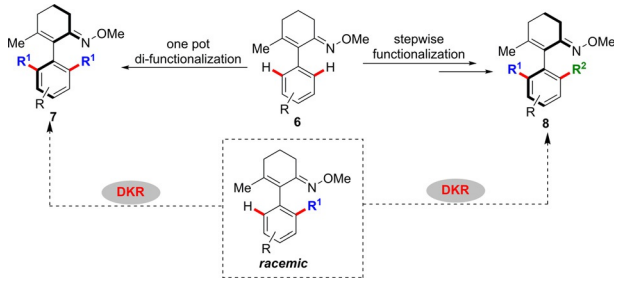


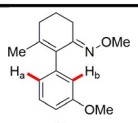
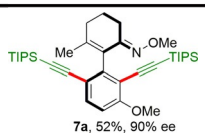
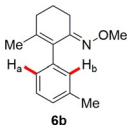
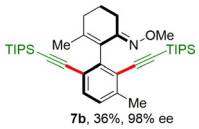
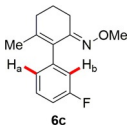
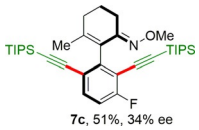
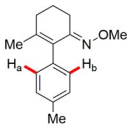
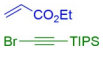
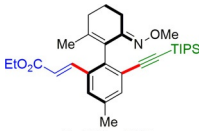
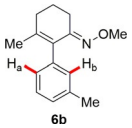
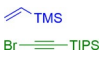
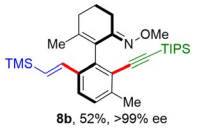
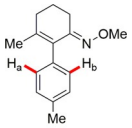
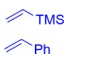
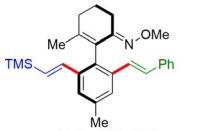
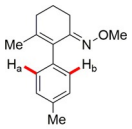
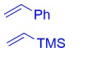
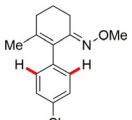
Scheme 2. Atroposelective synthesis of axially chiral alkynylsilanes via mono *ortho*-alkynylation.

bined with C–H alkynylation reactions with silyl-protected alkynyl bromides under a slightly modified conditions, furnishing the alkynylated products in moderate to good yields and up to >99% *ee*. Specifically, triethylsilyl (TES) and *tert*-butyldimethylsilyl (TBDMS)substituted alkynyl bromides were also well tolerated, exerting high level of chiral induction. The only exception is the product **5i** containing an electron-withdrawing F atom on the phenyl ring, which was obtained in comparable yield but with lower enantioselectivity (80% *ee*). In the absence of *ortho*-substituents, the alkynylated product was obtained in a racemic form (**5l**), further proving the high steric demand for axially chiral styrenes.

Having established the effective mono functionalization of arene C–H bonds as well as the dynamic kinetic resolution of racemic starting materials **1**, subsequently, we studied the substrate scope toward the asymmetric double C–H activation. As shown in Table 1, the steric and electronic properties of substituents on the aromatic ring had a remarkable effect on reactivity and enantioselectivity. When *meta*-substituted arenes were subjected to di-*o*-functionalization, asymmetric di-alkynylation was realized in one pot, whereas no di-olefination product was formed, probably because the latter is more sensitive to bulkiness around the olefination position. The di-alkynylation reaction of substrates with *meta* OMe and Me groups proceeded well in moderate yields and high enantioselectivities (**7a** and **7b**). Meanwhile, trace amounts of mono-alkynylated products were detected during the double C–H activation process (e.g., **5l** in Scheme 2). In contrast, **6c** containing an electron-withdrawing F atom at *meta* position only gave much lower enantioselectivity (34% *ee*) but still satisfactory reactivity (51% yield). For the substrates with symmetrically substituted arenes, a two-step method was adopted to obtain axially chiral products. To demonstrate the versatility of the present method, the different combinations of the coupling partners were tested. For example, **8a** was formed in 71% yield and >99% *ee* when coupling **6d** with the acrylate and triisopropylsilyl (TIPS) protected alkynyl bromide sequentially. If trimethylvinylsilane and TIPS-protected alkynyl bromide were used as olefinating and alkynylating partners in turn, **8b** containing

Table 1. Catalytic synthesis of axially chiral organosilanes via double *o*- and *o*′-C–H functionalization based on DKR.[a]



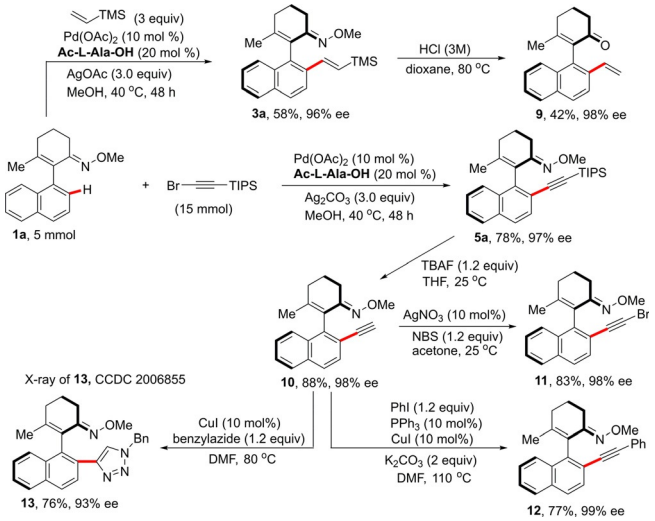
Entry	Substrate	Partner	Product
1	 **6a**		 **7a**, 52%, 90% ee
2	 **6b**		 **7b**, 36%, 98% ee
3	 **6c**		 **7c**, 51%, 34% ee
4	 **6d**		 **8a**, 71%, >99% ee
5	 **6b**		 **8b**, 52%, >99% ee
6	 **6d**		 **(+)-8c**, 41%, 98% ee
7	 **6d**		 **(-)-8c**, 20%, >99% ee
8	 **6e**		 **8d**, 36%, >99% ee

[a] Reaction conditions: **6a–e** (0.5 mmol), **2** or **4** (1.5 mmol), $Pd(OAc)_2$ (10 mol%), Ac-L-Ala-OH (20 mol%), Ag_2CO_3 (3 equiv.), MeOH (5 mL), at 40 °C under air atmosphere. [b] The olefins and alkynes applied in sequentially for entries 4–8, and the feeding sequence of olefin or alkyne that showed in the partner is from top to bottom.

both vinylsilane and alkynylsilane moiety was afforded in 52% yield and >99% *ee*. When activated and unactivated alkenes were tested, the coupling sequence had major influence on the coupling results (Table 1, entries 6 and 7). As a result, the yield of **8c** decreased from 41 to 20% while maintaining the excellent enantioselectivity. Similarly, successive *o*-and *o'*-alkynylation gave the atropoisomerically pure dialkynylated product **8d** in 36% isolated yield. In addition, we verified that the racemic starting materials obtained from the first step of C–H functionalization can also successfully complete the dynamic kinetic resolution process under the optimal reaction conditions.

To investigate the efficiency and practicality of this protocol, gram-scale syntheses of products **3a** and **5a** were carried out (Scheme 3). Satisfyingly, negligible deviation in the reactivity and enantioselectivity was observed by the DKR strategy. The utility of the developed method was further highlighted by selective transformations of the functional groups in the products (Scheme 3). The oxime ether directing group and silyl substituent in **3a** were readily removed in one step. Desilylation of **5a** was easily realized in the presence of tetrabutylammonium fluoride TBAF. It is worth mentioning that the terminal alkynes **10** are versatile synthetic intermediates that underwent smooth Sonogashira coupling, bromination, and click reaction, delivering the corresponding products in good yields without affecting the enantioselectivities. The configuration stability of the olefinated and alkynylated products was proved by HPLC analysis and the determined rotational barriers (see the Supporting Information for details). The structure of **13** was confirmed and the absolute configuration was determined to be *R* by XRD.[17]

In summary, we have developed a palladium-catalyzed atroposelective olefination/alkynylaton of arene C–H bonds under simple and mild conditions. This DKR strategy allows for the coupling of the flexible vinyl arenes with unactivated vinylsilanes and silyl-protected alkynyl bromides through a one-pot or two-step method, leading to unique axially chiral styrene-type organosilanes with excellent enantioselectivities. Both the oxime ether directing group and silyl substituent are readily modifiable so that the resulting products exhibit diverse synthetic applications in synthetic chemistry.



Scheme 3. Scale-up preparation of axially chiral organosilanes and its derivatization in the synthesis of structurally diverse products.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: atropisomer · C–H activation · dynamic kinetic resolution · organosilicon · palladium

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