A Journal of the Gesellschaft Deutscher Chemiker

Angewandte

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Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201801146
Angew. Chem. 10.1002/ange.201801146

Link to VoR: http://dx.doi.org/10.1002/anie.201801146
http://dx.doi.org/10.1002/ange.201801146

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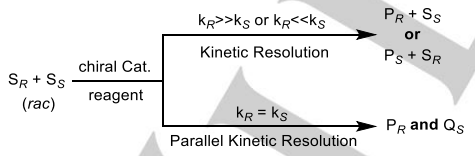
Palladium-catalyzed Enantioselective C-H Olefination of Diaryl Sulfoxides via Parallel Kinetic Resolution and Desymmetrization

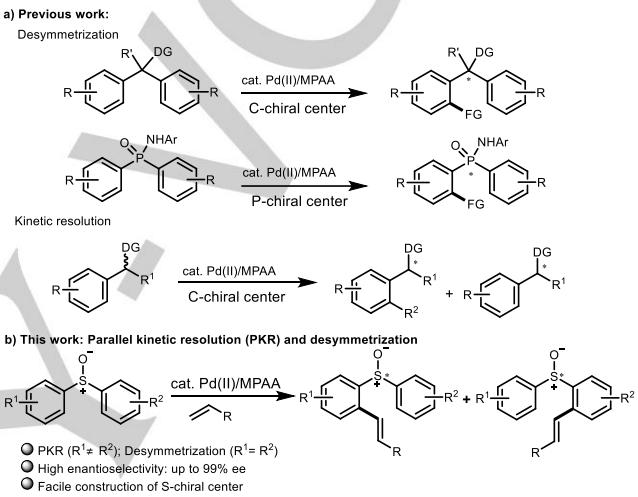
Yu-Chao Zhu[†], Yan Li[†], Bo-Chao Zhang, Feng-Xu Zhang, Yi-Nuo Yang and Xi-Sheng Wang*

Abstract: The first example of Pd(II)-catalyzed enantioselective C-H olefination with non-chiral or racemic sulfoxides as directing group has been developed. A variety of chiral diaryl sulfoxides with high enantioselectivity (up to >99%) have been synthesized through both desymmetrization and parallel kinetic resolution (PKR). This is the first report of transition-metal-catalyzed enantioselective C(sp^2)-H functionalization via PKR, and it represents a novel strategy to construct sulfur-chiral center.

Transition-metal-catalyzed C-H functionalization is emerging as a powerful strategy to offer novel retrosynthetic disconnection tactics for total synthesis of complex molecules.[1] In particular, the catalytic enantioselective activation of inert C-H bonds offers a highly atom- and step-economic approach towards the facile synthesis of optically active molecules and intermediates.[2] Starting from Yu's pioneer work with mono-protected amino acids (MPAA) used as efficient ligands to accelerate the C-H activation, Pd(II)-catalyzed enantioselective C-H functionalization has been developed as a reliable method to construct carbon and phosphine stereo centers,[3] in which desymmetrization[4] and kinetic resolution[5] are included as two main ways (Scheme 2a). However, transition-metal-catalyzed asymmetric C(sp^2)-H functionalization via parallel kinetic resolution (PKR, Scheme 1), in which both enantiomers of starting material could be transformed to different enantiomerically enriched products in one-pot, has never been reported and remains as a big challenge. Herein, we report the first example of Pd(II)-catalyzed enantioselective C-H olefination using non-chiral or racemic sulfoxide as directing group,[6] in which a variety of chiral diaryl sulfoxides were obtained with high enantioselectivities via desymmetrization or parallel kinetic resolution (PKR).[7] This method represents also a novel strategy to construct sulfur-chiral centers via transition-metal-catalyzed asymmetric C-H activation (Scheme 2b).



Scheme 1. Standard Kinetic Resolution and Parallel Kinetic Resolution



Scheme 2. Pd(II)-Catalyzed Enantioselective C(sp^2)-H Activation

The enantiopure sulfoxides are widely used as active ingredients of numerous biologically active molecules and market drugs,[8-14] and such chiral sulfoxides have also been utilized as an important class of ligands to realize numerous asymmetric transformations in organic synthesis due to their high optical stability.[15] The classical strategies towards facile synthesis of enantioriched sulfoxides, including kinetic resolution[16] and nucleophilic substitution of chiral sulfinate amides or esters,[17] have been widely utilized in both academic and industrial research. However, the use of stoichiometric amount of chiral pools rendered their synthetic applications. So far, the most popular routes were metal[18] or non-metal catalyzed[19] and biological[20] asymmetric sulfide oxidation processes, but the requirement of a prominent discrimination between the substituents of sulfides definitely limited their utilities. The only known method to synthesize chiral diaryl sulfoxides via catalysis is palladium-catalyzed enantioselective arylation of aryl sulfenate anions.[21] This reaction is not applicable for sterically hindered substrates, such as *ortho*-substituted aryl halides. Hence, more general and efficient methods based on novel strategies are still in demand for the rapid synthesis of optically active sulfoxides.

We commenced our study by using diphenyl sulfoxide **1a** as the model substrate and ethyl acrylate **3a** as the olefinating reagent. The reaction was carried out in the presence of a catalytic amount of $Pd(OAc)_2$ (10 mol %) in HFIP at 75 °C. Unfortunately,

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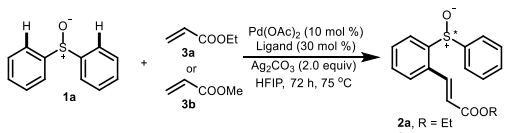
Table 1. Pd-catalyzed Enantioselective C-H Olefination of Diaryl Sulfoxides **1a**: Optimization of Conditions[a]

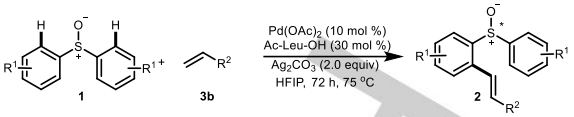


Entry	Ligand	Yield (%)[b]	ee (%)[c]
1	-	trace	-
2	Ac-Val-OH	26	77
3	Boc-Val-OH	N.R.	-
4	Fmoc-Val-OH	N.R.	-
5	Cbz-Val-OH	N.R.	-
6	Ac-Leu-OH	30	75
7	Ac-Tle-OH	23	77
8	Ac-Nle-OH	28	80
9	Ac-Gly-OH	20	70
10	$ClCH_2CO$-Leu-OH	20	73
11	*i*Pr-Leu-OH	14	11
12[d]	Ac-Leu-OH	30	87
13[d,e]	Ac-Leu-OH	47	86
14[d,e,f]	Ac-Leu-OH	43	92
15[e,f,g]	Ac-Leu-OH	51	91
16[e,f,g]	Ac-Val-OH	46	86
17[e,f,g]	Ac-Tle-OH	40	86
18[d,f,g,h]	Ac-Leu-OH	N.R.	-

[a] Unless otherwise noted, the reaction conditions were as follows: **1a** (0.2 mmol), **3a** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 equiv), ligands (30 mol %), HFIP (2.0 mL), 75 °C, 24 hours. [b] Isolated yield. [c] The ee value was determined by HPLC. [d] **1a** (0.1 mmol), **3a** (5.0 equiv). [e] 72 hours. [f] After prestirring of $Pd(OAc)_2$ and Ac-Leu-OH in HFIP (1.0 mL) at 50 °C for 2 hours, the other chemicals were added. [g] **3b** (5.0 equiv) instead of **3a**. [h] None of $Pd(OAc)_2$.

trace product **2a** was observed when 2.0 equivalents of Ag_2CO_3 was used as the oxidant (Table 1, entry 1). Inspired by the ligand-acceleration effect of mono-protected amino acids introduced by Yu,[5] we surveyed a range of MPAA as ligands to promote this transformation. To our delight, the olefinated product **2a** was obtained with moderate ee (77%) when Ac-Val-OH (30 mol %) was used as the ligand, albeit in a relatively low yield (26%, entry 2). Further examination of the *N*-protecting group on MPAA ligands showed that *t*-butyloxycarbonyl (Boc), 9-fluorenylmethoxycarbonyl (Fmoc) or benzyloxycarbonyl (Cbz) protected-amino acids failed to give **2a** (entries 3-5). With acetyl as the *N*-protecting group, we next screened different kinds of amino acids. It was revealed that coordination ability of sulfoxide could influence the complexation of MPAA and $Pd(OAc)_2$, the mixture of the ligand and $Pd(OAc)_2$ was prestirred in HFIP at 50 °C for 2 hours prior to the addition of substrates and Ag_2CO_3.

Table 2. Scope of Symmetric Diaryl Sulfoxides and Alkenes[a]



Entry	**1** (R^1)	**3** (R^2)	Rec. (%)[b]	Yield (%)[c]	ee (%)[d]
1	**1a** (H)	**3b** (CO_2Me)	39	51	91
2	**1b** (4-Me)	**3b**	30	68	71 (*S*)
3	**1c** (3-Me)	**3b**	30	61	78
4	**1d** (2-Me)	**3b**	34	61	98
5	**1e** (2,4-Me_2)	**3b**	52	47	97
6	**1f** (2,3-Me_2)	**3b**	8	72	96
7	**1g** (2-OMe)	**3b**	28	61	97
8	**1h** (5-F-2-Me)	**3b**	51	43	99
9	**1i** (3-F)	**3b**	42	52	99
10	**1j** (2-Cl)	**3b**	50	47	98
11	**1k** (4-F-2-Me)	**3b**	60	31	98
12[e]	**1l** (2-Et)	**3b**	29	54	99
13[e]	**1m** (2-F)	**3b**	32	51	93
14	**1n** (2-^{i}Pr)	**3b**	35	46	99
15	**1o** (4-Cl)	**3b**	44	47	88
16	**1p** (4-F)	**3b**	37	59	99
17	**1q** (3,4-Me_2)	**3b**	43	51	77
18	**1r** (3-OMe)	**3b**	37	59	70
19	**1a** (H)	**3a** (CO_2Et)	50	43	92
20	**1a**	**3c** ($CO_2{}^n$Bu)	26	70	86
21	**1a**	**3d** ($CO_2{}^i$Bu)	30	68	86
22	**1a**	**3e** (CO_2Cy)	61	34	85
23	**1a**	**3f** (CO_2Bn)	48	48	89
24	**1a**	**3g** (COPh(3-CF_3))	56	38	85
25	**1a**	**3h** ($PO(OEt)_2$)	28	36	86
26[f]	**1a**	**3i** (C_6F_5)	47	42	83

[a] Unless otherwise noted, the reaction conditions were as follows: **1** (0.1 mmol), **3** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 equiv), Ac-Leu-OH (30 mol %), HFIP (2.0 mL), 75 °C, 72 hours. [b] Recovery of isolated substrate **1**. [c] Isolated yield. [d] The ee value was determined by HPLC. [e] 96 hours. [f] $Pd(OAc)_2$ (15 mol%).

Gratefully, the ee was further improved to 92% as expected (entry 14). Notably, replacing ethyl acrylate **3a** with methyl acrylate **3b** slightly boosted the yield to 51% (entry 15). As a control experiment, no reaction happened at all in the absence of palladium catalyst (entry 18).

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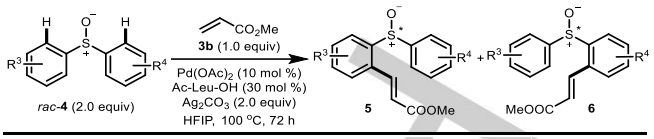
With the optimized conditions in hand, we next investigated the substrate scope of this novel protocol. The enantioselective C-H olefination of symmetric diaryl sulfoxides **1** was first carried out. As shown in Table 2, a wide range of diaryl sulfoxides bearing electron-donating groups, such as methyl, ethyl, isopropyl and methoxy, or weak electron-withdrawing groups, such as fluoro and chloro, afforded the corresponding products with excellent ee (71-99%, entries 2-16). Notably, *para*-, *meta*-, as well as *ortho*-substituents were well tolerated with good yields and excellent ee. All the diaryl sulfoxides with substituents at the *meta*-positions of the phenyl groups were regioselectively olefinated at the sterically less hindered *ortho*-C-H bond (entries 3, 6, 9, 17-18). The fluorine and chlorine atom in chiral products (entries 8-11, 13, 15-16) could offer the potential for subsequent synthetic elaboration via metal-catalyzed cross-coupling. 2,4- and 2,3-Disubstituted diaryl sulfoxides were also compatible with this palladium-catalyzed desymmetrization reaction. It is vital that *ortho*-substituents, including fluoro, chloro, methyl, ethyl, isopropyl and methoxy, on the benzene rings of substrates, improved the enantioselectivity of this asymmetric transformation to excellent level (97-99% ee; entries 4-8, 10-14), presumably due to the higher steric hindrance of *ortho*-substituted groups. To our satisfaction, mono-olefinated products were obtained as the mere species in all cases. Of note is that not only acrylates with different ester groups (**3a** and **3c-f**, entries 19-23), but also various electron-deficient alkenes (**3g-i**, entries 24-26) provided the desired olefinated products in similar yields and ee. The absolute configuration of product **2b** was confirmed to be methyl (*S,E*)-3-(5-methyl-2-(*p*-tolylsulfinyl)phenyl)acrylate by comparison with the known compound via reported method (for details, see the supporting information).[6b]

To further broaden the substrate scope, non-symmetric diaryl sulfoxides **4** were then examined in our catalytic system. To our delight, when the reaction was carried out at 100 °C with a slightly changed ratio of **4**/**3b** (2:1), olefination occurred at both of the aryl groups and therefore furnished products **5** and **6**. Not surprisingly, sulfoxides **4** with *ortho*- substituents on the benzene rings were olefinated in excellent ee and good yields (Table 3, entries 1-6, 8-9). In contrast, substrates without *ortho*-substituents on either benzene rings gave relatively lower but still acceptable ee (entry 11). For sulfoxides **4** with one *ortho*-substituted benzene ring, while a high ee was still obtained for one of the products, the ee was slightly lower for the other product (entries 7, 12-15). Both electron-donating groups, including methyl, ethyl, isopropyl, as well as methoxy, and weak electron-withdrawing groups, such as fluoro and chloro, were well-tolerated in this reaction. This reaction represents an efficient conversion of racemic compounds to two different and separable chiral sulfoxides of high enantioselectivity, and the regiodivergent C-H functionalization of racemic non-symmetric sulfoxides proceeded with catalyst control.

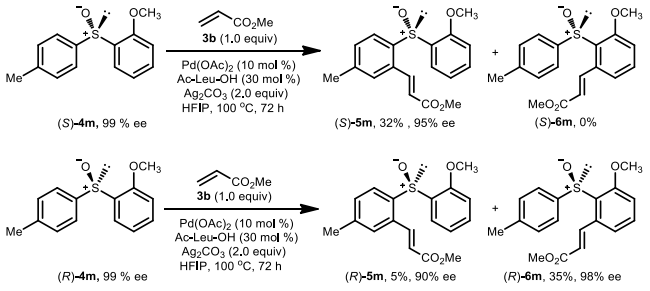
It should be noted that only moderate conversions of the prochiral sulfoxides **1** and racemic sulfoxides **4** have been observed, which suggests that the strong coordination of the sulfoxides to palladium may lead a possible catalyst deactivation. Depending on recovery rates of sulfoxides **1** or **4** in Table 2-3, sulfoxide substrates could be recovered without significant loss, and only trace amount of the corresponding sulfones could be detected. The recovery of substrates and the yields are consistent with mass balance basically.

Table 3. Scope of Non-symmetric Diaryl Sulfoxides[a]



Entry	*rac*-**4** (R^3;R^4)	Rec. (%)[b]	Yield (%)[c]		ee (%)[d]	
			5	**6**	**5**	**6**
1	*rac*-**4a** (2-^{i}Pr; 2'-Me)	72	21	20	90	95
2	*rac*-**4b** (2-Me; 2'-OMe)	65	36	33	98	98
3	*rac*-**4c** (2-Me; 2'-Et)	79	41(**5c**/**6c** mixture)		95	96
4	*rac*-**4d** (2-F; 2'-Cl)	69	32	27	98	90
5	*rac*-**4e** (2-Me; 2'-F)	62	40	25	98	99
6	*rac*-**4f** (2-OMe; 2'-Cl)	66	32	33	99	97
7	*rac*-**4g** (2-Me; H)	42	40	49	97	70
8	*rac*-**4h** (2-Et; 2'-Cl)	59	31	25	93	95
9	*rac*-**4i** (2-^{i}Pr; 2'-Cl)	59	33	23	96	96
10	*rac*-**4j** (2-Me; 3'-Me)	59	35	38	96	70
11	*rac*-**4k** (H; 4'-OMe)	60	27	24	71	82
12	*rac*-**4l** (2-Cl; 3'-Me)	69	18	31	99	85
13	*rac*-**4m** (4-Me; 2'-OMe)	62	36	23	77 (*S*)	95 (*S*)
14	*rac*-**4n** (3-Me; 2'-OMe)	64	36	24	83	97
15	*rac*-**4o** (2-Et; 3'-Me)	61	38	30	99	73

[a] Unless otherwise noted, the reaction conditions were as follows: **4** (0.2 mmol, 2.0 equiv), **3b** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), Ac-Leu-OH (30 mol %), Ag_2CO_3 (2.0 equiv), HFIP (2.0 mL), 100 °C, 72 hours. [b] Recovery of isolated substrate **4**. [c] Isolated yield. [d] The ee value was determined by HPLC.

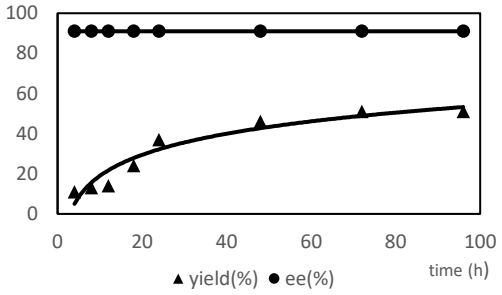


Scheme 3. Olefination of (*S*)-**4m** and (*R*)-**4m** under Standard Conditions

For in-depth research of the stereodivergent olefination, (*S*)-**4m** and (*R*)-**4m** were synthesized[6b] and subjected to the reaction conditions (Scheme 3). As expected, C-H olefination of (*S*)-**4m** occurred exclusively at the benzene ring bearing a *para*-methyl group, while olefination of (*R*)-**4m** happened mainly at the other

phenyl group. The reactions afforded the corresponding products **5m** and **6m** with high ee value, respectively. These results indicated that a regiodivergent parallel kinetic resolution (PKR) was involved in this transformation.

It is noted that a small amount of methyl (*E*)-3-(2-(phenylsulfonyl) phenyl acrylate was detected in the reaction of **1a**. We were concerned that the high enantioselectivities in our reactions could result from the selective oxidation of one of the olefinated sulfoxides via kinetic resolution. To rule out this possibility, we investigated the time dependence of the ee values and the relative yields of sulfoxides **2a**. As shown in Scheme 4, the ee of product **2a** remained around 91% while the yield increased from 13% to 51% as the reaction time prolonged, which clearly indicated that no kinetic resolution process was involved in the reaction procedure and the enantioselectivity of this transformation was induced in the step of Pd(II)/MPAA-catalyzed asymmetric C-H activation.



Scheme 4. Time Course of ee (%) and Yield (%) of Sulfoxides **2a**

In summary, we have developed a Pd(II)-catalyzed enantioselective C-H olefination for facile construction of sulfur-chiral centers. This methodology provides a novel approach for asymmetric synthesis of biologically active sulfoxides with excellent ee (up to 99%), and both symmetric and non-symmetric sulfoxides could be well functionalized via desymmetrization and parallel kinetic resolution (PKR). Further applications of these enantiopure diaryl sulfoxides and the development of more effective catalytic systems are still underway in our laboratory.

Acknowledgements

We gratefully acknowledge the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant No. XDB20000000), the National Basic Research Program of China (973 Program 2015CB856600), and the National Science Foundation of China (21602213, 21522208, 21372209) for financial support.

Keywords: enantioselective C-H activation • palladium • parallel kinetic resolution • desymmetrization • *S*-chiral centers

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[22] To make sure if there is an atropisomeric C-S bond in sulfoxide **2**, **5** and **6**, **2n** was selected as an example for DFT calculations to simulate the rotation process of C-S bond. The electronic energy barrier is 9.4 kcal/mol at 298.15 K, whose corresponding half-life is $t_{1/2} = 4.3 \times 10^{-7}$ s. Both results indicated that this rotation is free at room temperature. For details, see the Supporting Information.

10.1002/anie.201801146

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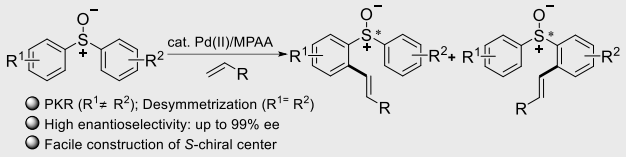

The first example of Pd(II)-catalyzed enantioselective C-H olefination with non-chiral or racemic sulfoxides as directing group has been developed. A variety of chiral diaryl sulfoxides with high enantioselectivity (up to >99%) have been synthesized through both desymmetrization and parallel kinetic resolution (PKR). This is the first report of transition-metal catalyzed enantioselective C(sp^2)-H functionalization via PKR, and it represents a novel strategy to construct sulfur-chiral center.

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Palladium-catalyzed Enantioselective C-H Olefination of Diaryl Sulfoxides via Parallel Kinetic Resolution and Desymmetrization