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Kinetic resolution of sulfur-stereogenic sulfoximines by Pd(II)–MPAA catalyzed C–H arylation and olefination†

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A direct Pd(II)-catalyzed kinetic resolution of heteroaryl-enabled sulfoximines through an *ortho*-C–H alkenylation/arylation of arenes has been developed. The coordination of the sulfoximine pyridyl-motif and the chiral amino acid MPAA ligand to the Pd(II)-catalyst controls the *enantio*-discriminating C(aryl)–H activation. This method provides access to a wide range of enantiomerically enriched unreacted arylpyridyl-sulfoximine precursors and C(aryl)–H alkenylation/arylation products in good yields with high enantioselectivity (up to >99% ee), and selectivity factor up to >200. The coordination preference of the directing group, ligand effect, geometry constraints, and the transient six-membered concerted-metalation–deprotonation species dictate the stereoselectivity; DFT studies validate this hypothesis.

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Introduction

The directing group (DG) assisted desymmetrization of prochiral C–H bonds provides a suitable way to construct carbon, phosphorus, silicon, and sulfur centered functionalized chiral molecules.^{1–3} However, this approach requires achiral precursors with two identical enantiotopic groups, which prevents its application for broad synthetic benefits. On the other hand, kinetic resolution (KR) of C–H bonds offers booming advantages for making functionalized enantioenriched molecules. In this regard, Yu's pioneering work on DG assisted chiral amino acid (MPAA) enabled Pd-catalyzed carbon centered KR of arene C–H bonds through alkenylation, arylation, and/or iodination is undoubtedly a breakthrough (Fig. 1A).⁴ In spite of this success, the related strategy of Pd-catalyzed heteroatom centered KR of arenes remains to be explored, although exceedingly appealing.

Sulfoximines, which are configurationally stable motifs with *S*-stereogenicity, are found in molecules of medicinal importance and agrochemicals.⁵ Notably, sulfoximines have emerged as chiral auxiliaries and DG for C–H functionalizations.⁶ The

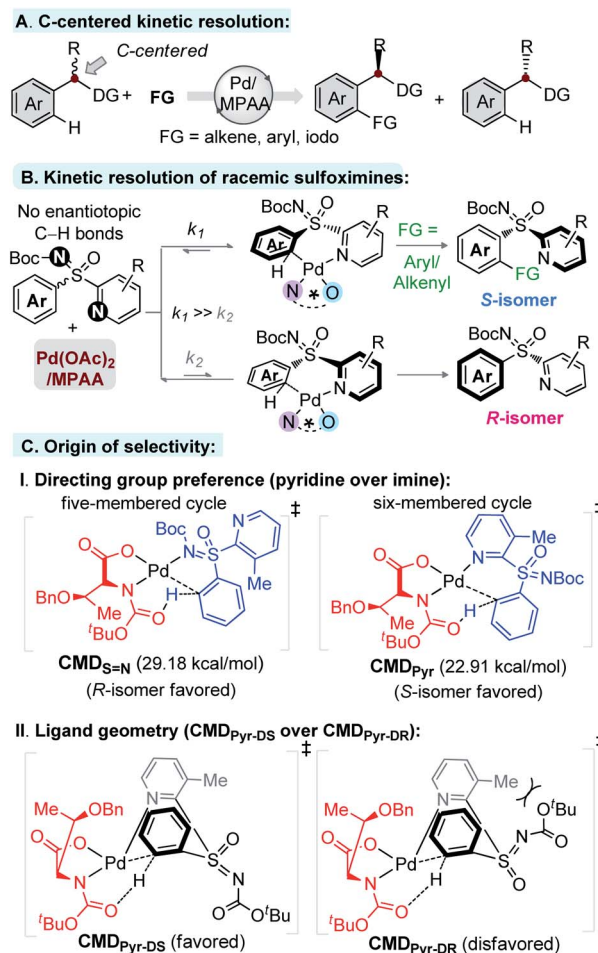


Fig. 1 Kinetic resolution via C–H activation (free energies at 343.15 K in DCE).

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syntheses of enantioenriched sulfoximines have invariably relied on resolution techniques, stereoselective imination, and oxidation processes.^{7,8}

Elegant enantioselective and KR routes to sulfoximines have been independently developed by Cramer, Li, Shi, and others, but all these approaches rely on Rh/Ru-catalyzed [4 + 2] annulation of diazoesters/sulfoxonium ylides and aryl-sulfoximines in the presence of specially designed ligands.⁹ On our side, we have devised an expedient Pd-catalyzed C–H functionalization method for KR of 2-pyridylaryl sulfoximines, using Pd(II) catalyst and MPAA ligand, *via* C(aryl)–H arylation and olefination (Fig. 1B). The concept relies on kinetically regulated concerted-metalation–deprotonation (CMD) step of C(aryl)–H activation ($k_1 \gg k_2$, Fig. 1B) through preferred coordination of pyridine over imine to Pd–MPAA (Fig. 1C-I)¹⁰ and ligand geometry **CMD_{Pyr-DS}** over **CMD_{Pyr-DR}** (Fig. 1C-II). The transformation is

general, constructing a wide array of enantiomerically enriched C-olefinated/arylated aryl-pyridyl-*S*-sulfoximines.

Results and discussion

The study was initiated with the non-substituted *N*-Boc-phenyl-2-pyridyl sulfoximine **rac-1a-1** and ethyl acrylate (**2a**; 0.6 equiv.) in presence of Pd(OAc)₂ (10 mol%), Boc-L-Phe-OH (**L1**; 30 mol%), Ag₂CO₃ (2.0 equiv.) in ClCH₂CH₂Cl (1,2-DCE) at 75 °C

Table 1 Optimization of reaction conditions^a

(a) Ligand optimization

Entry	Ligand	(R)-1a-1 (%)	(S)-3a-1 (%)	<i>s</i> ^d	<i>c</i> ^e
L1	R = CH ₂ Ph	17	75	8	18
L2	R = ⁱ Bu	18	76	9	19
L3	R = ⁱ Pr	11	0	–	–
L4	R = Bn	25	50	4	33
L5	R = ⁱ Bu	20	3	–	–
L6	Chiral CAA	20	81	12	20
L7	X = Boc, Y = ^t Bu	28	79	11	26
L8	X = Boc, Y = Bn	22	77	10	22
L9	X = Boc, Y = –CH ₂ –3,5-di-F–C ₆ H ₃	27	79	11	25
L10	X = Boc, Y = –CH ₂ –3,5-di-MeO–C ₆ H ₃	22	79	11	22
L11	X = Fmoc, Y = ^t Bu	22	79	11	22
L8	2a (2.0 equiv.)	72	70	12	50

(b) Additive screening

Entry	Additives	<i>C</i> ^b	(R)-1a-1 (%)	(S)-3a-1 (%)	<i>s</i> ^d
1	BQ	18	17	78	10
2	2-Chloro BQ	39	50	77	13
3	2,5-dichloro BQ	35	40	75	10

(b) Additive screening

Entry	Additives	<i>C</i> ^b	ee ^c (%)		<i>s</i> ^d
			(R)-1a-1	(S)-3a-1	
1	BQ	18	17	78	10
2	2-Chloro BQ	39	50	77	13
3	2,5-dichloro BQ	35	40	75	10

^a Reaction conditions: **rac-1a-1** (0.1 mmol), ethyl acrylate **2a** (0.6 equiv.), Pd(OAc)₂ (10 mol%), ligand (30 mol%), Ag₂CO₃ (2.0 equiv.), 2-Cl-BQ (0.3 equiv.), 1,2-DCE (1.0 mL), N₂, 75 °C, 3 days. ^b Calculated conversion, $C = eeSM/(eeSM + eePR)$. ^c Determined by chiral HPLC analysis. ^d Selectivity (*s*) = $\ln[(1 - C)(1 - eeSM)]/\ln[(1 - C)(1 + eeSM)]$. ^e **2a** (2.0 equiv.) used.

Table 2 Optimization of reaction conditions^a

(a) Protecting group screening

Entry	PG	<i>C</i> ^b	ee ^c (%)		<i>s</i> ^d
			(R)-1a-1	(S)-3a-1	
1	Me	0	–	–	–
2	Piv	45	54	66	8
3	Cbz	20	21	85	14

(b) DG screening

Entry	DG	Conversion ^{b,c}	ee (%)		<i>s</i>
			(R)-1	(S)-3	
1	DG ²	17	20	96	58
2	DG ³	Nr	–	–	–
3	DG ⁴	Nr	–	–	–
4 ^f	DG ⁵	–	20	96	–
5 ^f	DG ⁶	19	19	82	12
6 ^f	DG ⁷	20	20	80	11
7 ^f	DG ⁸	Nr	–	–	–
8 ^e	DG ²	22	27	95	48
9 ^{e,f}	DG ²	27	35	94	44
10 ^{e,f,g}	DG ²	34	50	96	85

^a Reaction conditions: **rac-1a-1** (0.1 mmol), ethyl acrylate **2a** (0.6 equiv.), Pd(OAc)₂ (10 mol%), ligand (30 mol%), Ag₂CO₃ (2.0 equiv.), 2-Cl-BQ (0.3 equiv.), 1,2-DCE (1.0 mL), N₂, 75 °C, 3 days. ^b Calculated conversion, $C = eeSM/(eeSM + eePR)$. ^c Determined by chiral HPLC analysis. ^d Selectivity (*s*) = $\ln[(1 - C)(1 - eeSM)]/\ln[(1 - C)(1 + eeSM)]$. ^e Olefin (2.0 equiv.) used. ^f Instead of **2a**, methyl acrylate was used. ^g 50 mol% 2-Cl-BQ was used.



(Table 1a). The desired C2-alkenylation product (*S*)-**3a-1** (18%, conversion after 3 days) along with precursor (*R*)-**1a-1** were obtained in 75% ee and 17% ee, respectively, exhibiting a low selectivity factor (*s*) of 8. This encouraging result unfolded our curiosity about examining the effect of other ligands. None of the *N*-Boc, *N*-acetyl-, and *N*-imide-protected commercially available α -amino acid ligands (**L2**–**L6**) with distinct side chains were effective. Assuming the additional coordination ability of the easily modifiable OH group in threonine, various *N,O*-protected threonine ligands were tested. The reaction *s* factor was improved a little for (*S*)-**3a-1** to 12 and 11 when Boc-*L*-Thr(*t*-Bu)-OH (**L7**) and Boc-*L*-Thr(Bn)-OH (**L8**) were used, respectively. Electronic perturbation in the *O*-benzyl moiety did not have any impact on the enantioselectivity (**L9** and **L10**). The use of **2a** (2.0 equiv.) in presence of ligand **L8** improved the conversion (50%) with (*S*)-**3a-1** (70% ee) (entry 13).

To enhance sulfoximine resolution efficiency while maintaining conversion (~50%; Table 1a), we scrutinized the co-oxidant effect (Table 1b).^{11,12} 2-Chlorobenzoquinone (2-Cl-BQ) was found to be the best, providing (*S*)-**3a-1** in 77% ee with 39% conversion (*s* factor of 13; entry-2, Table 1b). Next, sulfoximines having various *N*-protecting groups (PG) were screened; the results are shown in Table 2a. None of the *N*-Me/Piv/Cbz-protected sulfoximines were found effective.

Next, we studied the DG effect (Table 2b). Thus, various substituted 2-pyridyl containing sulfoximines were independently subjected to **2a**. After several trials, the 3-methyl pyridyl DG was found superior, affording the alkenylation resolution species (*S*)-**3a** in 96% ee with *s* factor of 58, although conversion was limited to 17% (entry 1). On the other hand, 3-Cl/Br substituted pyridyl DG were unsuccessful (entries 2 and 3). While trace of desired olefination product (*S*)-**3s** with 96% ee was noticed from the reaction of 3-phenyl-pyridyl (DG⁵) bearing

Table 3 Scope of C–H alkenylative kinetic resolution of sulfoximines^{a,b}

 3b : 26%, 98.2:1.8 er 1a : 51%, 76.2:23.8 er C = 35, S = 92	 3c : 35%, 98.7:1.3 er 1b : 46%, 85.5:14.5 er C = 42, s = 162 ^c	 3d : 33%, 95.2:4.8 er 1b : 45%, 86.8:13.2 er C = 45, s = 44 ^c	 3e : 35%, 95.6:4.4 er 1b : 43%, 83.7:16.3 er C = 42, S = 44 ^c	 3f : 27%, 94.6:5.4 er 1b : 45%, 73.8:26.2 er C = 35, S = 28	 3g : 33%, 97.6:2.4 er 1b : 41%, 81.2:18.8 er C = 40, S = 77 ^c
 3h : 33%, 99.6:0.4 er 1b : 42%, 85:15 er C = 41, S = >200 ^c	 3i : 31%, 97.8:2.2 er 1c : 46%, 76.1:23.9 er C = 35, S = 75	 3j : 30%, 97.8:2.2 er 1c : 45%, 79.7:20.3 er C = 38, S = 81	 3k : 31%, 97.3:2.7 er 1c : 43%, 75.1:24.9 er C = 35, S = 59	 3l : 32%, 99.1:0.9 er 1d : 43%, 79.6:20.4 er C = 38, S = >200	
 3m : 30%, 96.9:3.1 er 1e : 45%, 78.5:21.5 er C = 38, S = 56	 3n : 42%, 92.7:7.3 er 1f : 34%, 94:6 er C = 51, S = 37 ^c	 3o : 35%, 98.2:1.8 er 1g : 42%, 83.9:16.1 er C = 41, S = 111	 3p : 22%, 94.4:5.6 er 1h : 36%, 67.4:32.6 er C = 28, S = 24	 3q : 36%, 97.9:2.1 er 1i : 38%, 87.9:12.1 er C = 44, S = 107 ^c	 3r : 32%, 96.2:3.8 er 1m : 42%, 83.2:16.8 er C = 42, S = 51

^a Reaction conditions: *rac*-**1** (0.25 mmol), olefin (2.0 equiv.), Pd(OAc)₂ (10 mol%), **L8** (30 mol%), Ag₂CO₃ (2.0 equiv.), 2-Cl-BQ (0.5 equiv.), 1,2-DCE (2.5 mL), 75 °C, 3 days. ^b Yield of the isolated olefinated product. ^c Olefin (1.8 equiv.) was used and reaction was performed for 1.5 days. Calculated conversion, C = eeSM/(eeSM + eePR). Selectivity (*s*) = ln[(1 - C)(1 - eeSM)]/ln[(1 - C)(1 + eeSM)].



phenyl sulfoximine (**1a-4**) with methyl acrylate (**2b**, 0.6 equiv.; entry 4). The 4-Me/5-Cl substituted pyridyl DG were ineffective, providing a lower selectivity factor (*s*) of 12 and 11, respectively (entries 5 and 6). No desired olefination product was obtained when 3-F substituted (DG^b) pyridyl group was used (entry 7). The reaction conversion was improved to 22% when **2a** (2.0 equiv.) was employed under the reaction shown in entry 1 (entry 8). The identical transformation with **2b** (2.0 equiv.) could enhance the conversion to 27% (entry 9). Finally, a 50 mol% loading of 2-Cl-BQ led to (*S*)-**3b** (96% ee, *s* factor of 85 with 34% conversion; entry 10), which was found optimum.

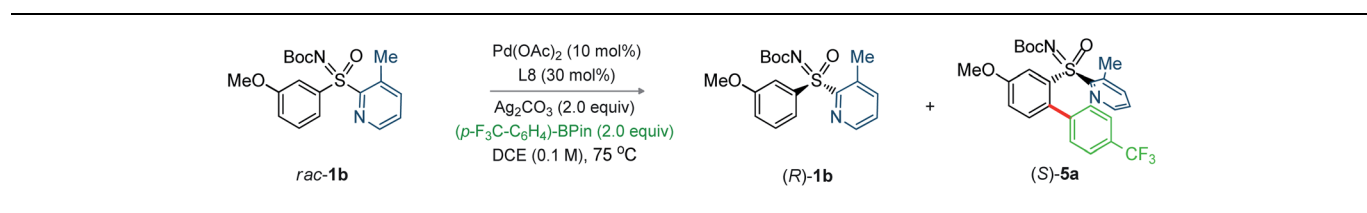
The generality of the Pd-catalyzed C–H alkenylative KR of sulfoximines was then surveyed (Table 3). Compound **3b** (98.2 : 1.8 er) was isolated in 26% yield. The alkenylation occurred at the less-hindered arene C–H bond and the chiral sulfoximines **3c** and **3d** were obtained with *s* factors of 162 and 44, respectively. The catalytic system was compatible with common functional groups, such as ketone, sulfone, and phosphate in the alkene, providing access to **3e** (95.6 : 4.4 er), **3f** (94.6 : 5.4 er), and **3g** (97.6 : 2.4 er). Notably, the reaction of methyl vinyl sulfone with **1b** displayed an exceptional *s* factor of >200 for compound **3h**. The reaction of *p*-(Me/^tBu/ⁱPr)-substituted aryl sulfoximines with **2b**/vinyl-ketone (**2c**)/vinyl-sulfone (**2f**) smoothly delivered **3i–m** in excellent enantioselectivity and *s* factor of 56 to >200. The *m*-substituted electron donating (OEt, Me) and chloro-bearing aryl-sulfoximines underwent olefination with **2b** to give the desired products **3n–p** with *s* factor of 24 to 111. Even the sterically hindered *m,m'*-dimethyl substituted aryl sulfoximine **1i** reacted well, yielding **3q** (36%, 97.9 : 2.1 er, *s* factor of 107). The reaction of heteroaryl bearing 2-thiophenyl-2-pyridylsulfoximines (**1m**) with **2b** afforded the olefination product **3r** (32%, 96.2 : 3.8 er, *s* factor of 51).¹³

Next, we investigated the feasibility of Pd-catalyzed C–H arylation of sulfoximines (Table 4).¹⁴ The reaction of *N*-Boc-3-

methoxyphenyl-2-(3-methylpyridyl) sulfoximine (**1b**) with (4-CF₃)Ph-Bpin (**4a**; 2.0 equiv.) was performed under the catalytic conditions of entry 10, Table 2. Pleasingly, the desired product (*S*)-**5a** was obtained in 94% ee with *s* factor of 39 along with the recovery of (*R*)-**1b** in 20% ee and 18% conversion (entry 1). The oxidant Ag₂O played a vital role; the conversion was increased to 51% (entry 2). Carrying out the reaction at 60 °C enhanced the *s* factor to 50 (entry 3). The *s* factor was raised to 64 with reaction conversion 41% and 94% ee of (*S*)-**5a**, when trifluorotoluene (TFT) was used (entry 4). Performing the reaction with 20 mol% **L8** improved the outcome (entry 5). Importantly, reaction concentration from 0.1 M to 0.067 M led to (*S*)-**5a** (94% ee) and (*R*)-**1b** (88% ee) with 48% conversion and *s* factor of 95 (entry 6); this catalytic system was thus able to provide a balanced outcome.

We next probed sulfoximines KR *via* enantioselective C–H arylation with arylpinacol boronate esters (Table 5). The reaction of **1b** with various arylpinacol boronate esters having electron withdrawing groups [*p*-CF₃ (**4a**), *m*-CF₃ (**4b**), *m*-COMe (**4c**), and *p*-F (**4d**)], electron donating groups [*p*-Me (**4e**) and *p*-OMe-*m*-OEt (**4f**)] at the aryl motif independently led to the arylation resolution products **5a** (96.1 : 3.9 er, 42%), **5b** (96.5 : 3.5 er, 43%), **5c** (97.5 : 2.5 er, 41%), **5d** (98.4 : 1.6 er, 40%), **5e** (97.2 : 2.8 er, 41%), and **5f** (96.4 : 3.6 er, 44%), respectively, with *s* factor of 70–168 and conversion 46–49%. Moreover, the precursor (*R*)-**1b** was isolated in 41–46% yield with good enantioselectivity. The labile –Cl group was tolerated under the Pd-catalytic system, making **5g** (97.8 : 2.2 er, 39%) with an *s* factor of 117. Notably, π -conjugated naphthyl-enabled sulfoximine resolution product **5h** (99.0 : 1.0 er, *s* factor of >200) was reliably accessed. Next, the arylation of *m*-OEt-phenyl bearing sulfoximine **1f** with **4a** provided **5i** (>99% ee) with *s* factor of >200. Likewise, **5j** (97.2 : 2.8 er, *s* factor of 110) was made from the arylation of 2-naphthyl containing sulfoximine **1j** with **4e**. The sterically bulky *o*-tolyl enabled sulfoximines **1k**

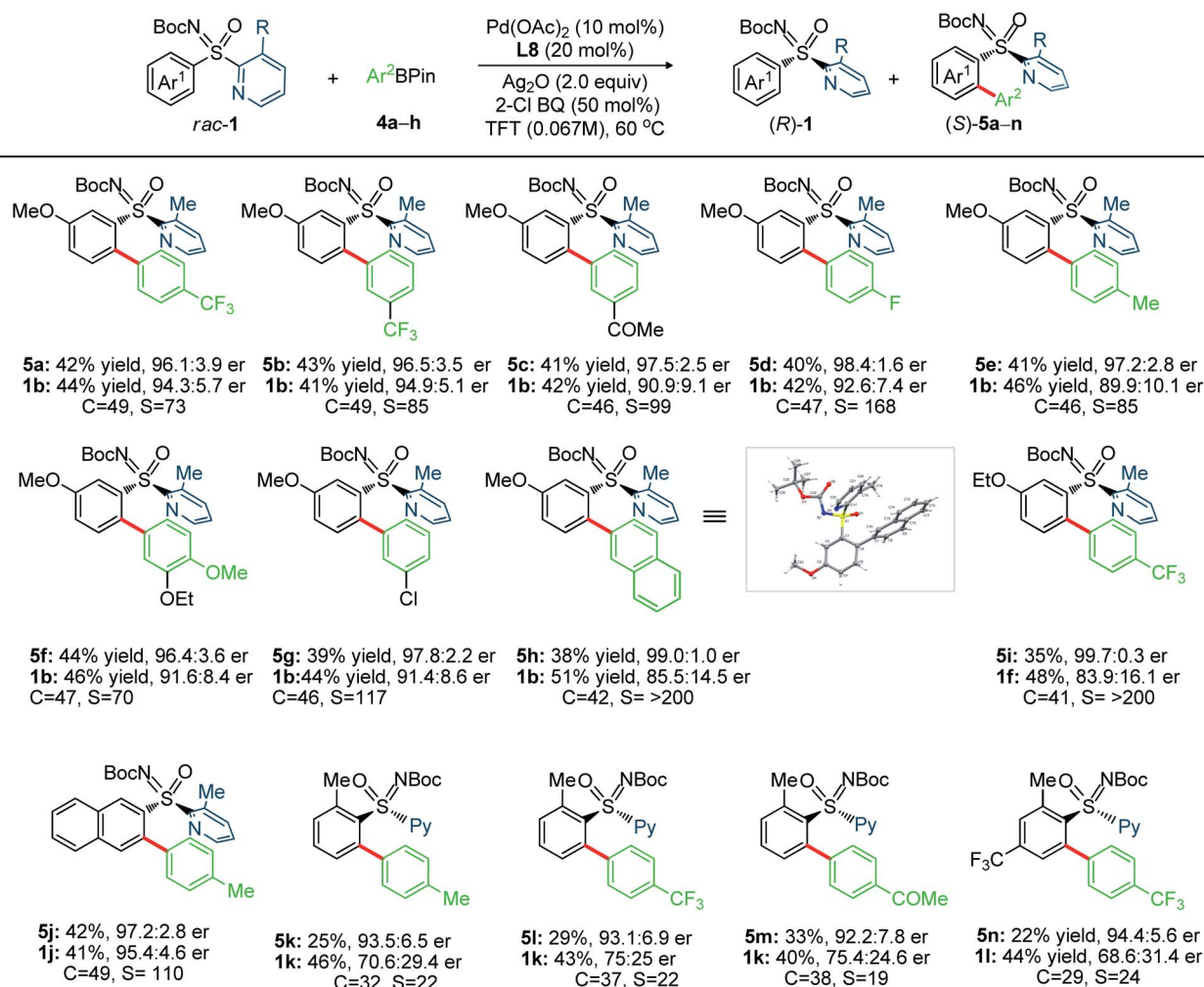
Table 4 Optimization *o*-C–H arylation kinetic resolution of sulfoximine^a



Entry	Deviation	Conversion (c)	ee (%)		<i>S</i>
			(<i>R</i>)- 1b	(<i>S</i>)- 5a	
1	None	18	20	94	39
2	Ag ₂ O instead Ag ₂ CO ₃	51	88	86	38
3 ^b	60 °C instead 75 °C	43	70	92	50
4 ^{b,c}	TFT instead 1,2-DCE	41	66	94	64
5 ^{b,c,d}	20 mol% ligand	46	80	94	79
6 ^{b,c,d,e}	0.067 M TFT	48	88	94	95

^a Reaction conditions: **1b** (0.1 mmol), **4a** (2.0 equiv.), Pd(OAc)₂ (10 mol%), **L8** (30 mol%), Ag₂CO₃ (2.0 equiv.), 2-Cl-BQ (0.5 equiv.), DCE (1.0 mL), N₂, 75 °C, 3 days. ^b Ag₂O oxidant. ^c Reaction was performed at 60 °C. ^d TFT was used instead of 1,2-DCE. ^e **L8** (20 mol%) was used. Calculated conversion, $C = ee_{SM}/(ee_{SM} + ee_{PR})$. Selectivity (*s*) = $\ln[(1 - C)/(1 - ee_{SM})]/\ln[(1 - C)/(1 + ee_{SM})]$.



Table 5 Scope of C–H arylation kinetic resolution of sulfoximines^{a,b}

^a Reaction conditions: *rac*-**1** (0.2 mmol), **4** (2.0 equiv.), Pd(OAc)₂ (10 mol%), **L8** (20 mol%), Ag₂O (2.0 equiv.), 2-Cl-BQ (0.5 equiv.), TFT (3.0 mL), 60 °C, 3 days. ^b Yield of the isolated arylation product. Calculated conversion, $C = eeSM/(eeSM + eePR)$. Selectivity (s) = $\ln[(1 - C)(1 - eeSM)]/\ln[(1 - C)(1 + eeSM)]$.

and **1l** were successful in undergoing arylation with **4a/4c/4e** to afford **5k–n** in good enantioselectivity; the moderate s factors of 19–24 and conversions ($c = 29$ –38%) are considered suitable.

We performed a theoretical study to unveil the reaction mechanism (Fig. 2 and 3).^{14–16} The MPAA ligand coordination to the metal center lowers the energy barrier of the CMD step, forming a semiplanar five membered ring.¹⁵ We believe the CMD step could be the main responsible for the kinetic resolution. This hypothesis has been previously validated by Wu *et al.*, who also focused their study on the CMD as determining step.¹⁵ Based on their findings, and considering the plane defined by the coordination of MPAA to the Pd, the bulky α -side chain of the ligand (above the plane) pushes the *N*-Boc moiety down to avoid steric hindrance (Fig. 2 and 1-C-II). Thus, sulfoximine phenyl group coordination complex with Pd–MPAA can point upward (U) or downward (D) on the plane, with *R* or *S* configurations. This translates to four possible CMDs: **CMD**_{Pyr-}

UR, **CMD**_{Pyr-US}, **CMD**_{Pyr-DR}, and **CMD**_{Pyr-DS}. The CMDs adopt a 6-membered palladacycle with twisted boat conformation.

In case of upward phenyl group linkage (**CMD**_{Pyr-UR} and **CMD**_{Pyr-US}), the sulfur atom and its substituents are located above the plane; while these substituents are below the plane for **CMD**_{Pyr-DR} and **CMD**_{Pyr-DS}. In agreement with Wu's observations,¹⁵ the C1–N2–Pd–O3 dihedral angle for **CMD**_{Pyr-UR} and **CMD**_{Pyr-US} is *ca.* 170°, which generates a high steric interaction when compared with the *ca.* 140° for **CMD**_{Pyr-DR} and **CMD**_{Pyr-DS}. These latter are favored by hydrogen bond interactions, making the combination of steric and electronic effects accounting for a difference of nearly 10 kcal mol^{−1} in each enantiomer (Fig. 2).

The preference for the *S* configuration by ~2.5 kcal mol^{−1} over the *R* isomer, lies in a steric clash of the *N*-Boc group with the methyl group from the pyridine moiety and in consequence with the phenyl group causing an energetically demanding



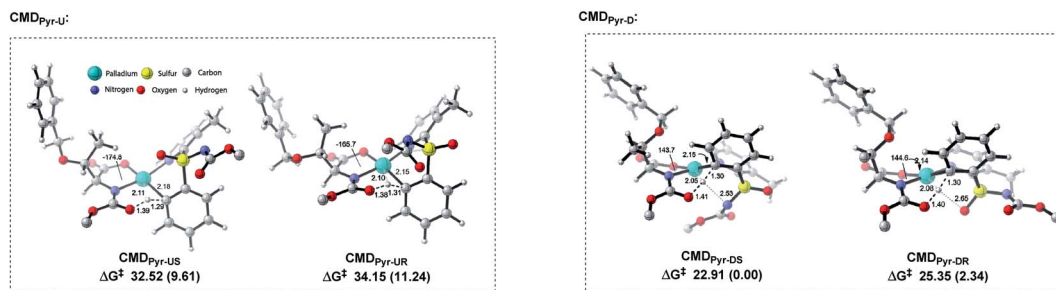


Fig. 2 Transition structures for each CMDPyr approach. *tert*-Butyl group from NBoc removed from all models to simplify visualization. Relative free energies in parentheses ($\Delta\Delta G^\ddagger$), distances in Å.

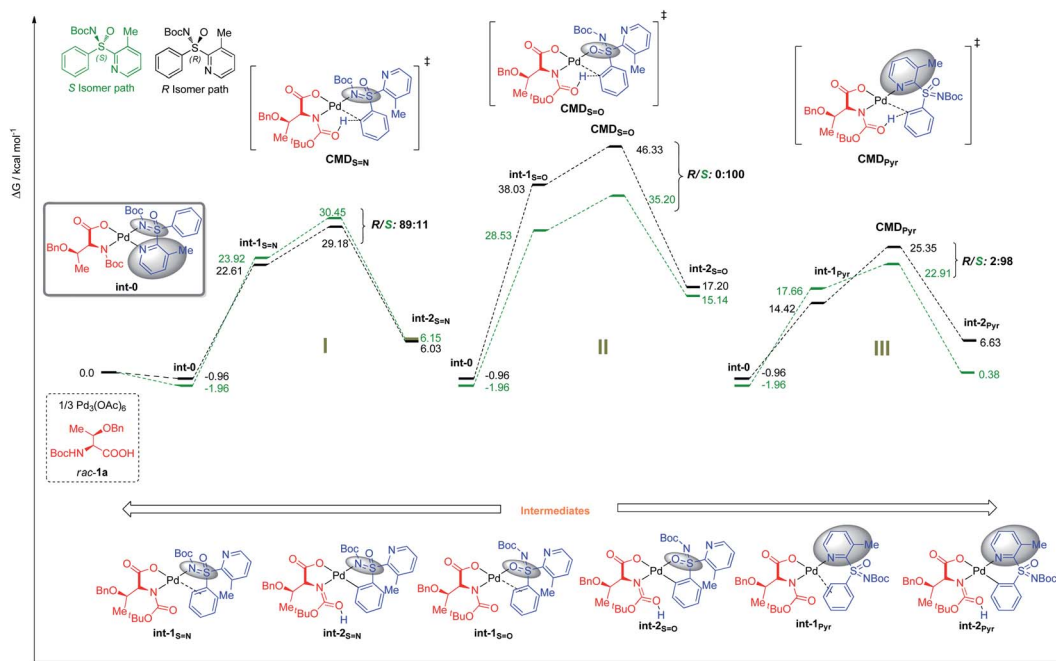


Fig. 3 Free energies at 343.15 K in DCE in kcal mol⁻¹.

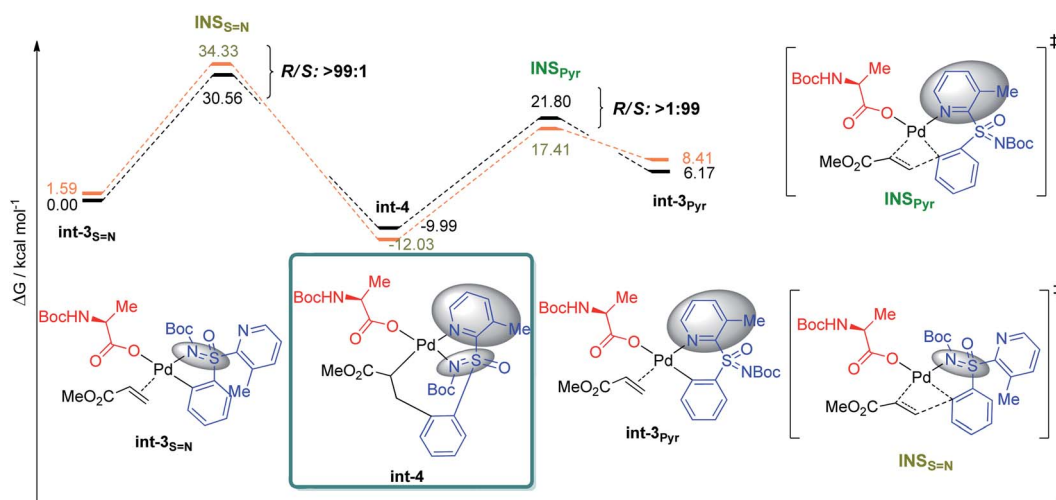


Fig. 4 Comparison of the different energy profiles for the insertion step (INS). Energies relative to the most stable int-3 system. Free energies at 343.15 K in DCE in kcal mol⁻¹. *R/S* selectivity highlighted at the transition state of each diagram (orange = *S*; black = *R*).



arrangement. The coordination of both 'N' atoms in sulfoximine **1a** forms int-0 with the displacement of acetic acid, where the *S*-configuration at sulfur is 1.0 kcal mol⁻¹ more stable than the *R* one (Fig. 3). Prior to deprotonation, a *cis* coordination of aryl group to the *N*-protected moiety of the MPAA-ligated intermediate occurs. This assists the CMD process by establishing the absolute configuration of the sulfur motif. This calculation fully complies with the experimental observations of the resolution selectivity (calc. 98 : 2, exp. 98 : 2; Fig. 3-III). Notably, the experimentally observed *S*-int-2Pyr is thermodynamically favored over *R*-int-2Pyr isomer by 6 kcal mol⁻¹. In retrospect, the CMD transition states of int-1S=N (Fig. 3-I) and int-1S=O (Fig. 3-II) lie much higher than int-1Pyr (Fig. 3-III), and their respective ΔG^\ddagger do not coincide with the experimental findings. Of note, the CMD process through int-1pyr is endergonic (Fig. 3-III); thus, the calculated R/S ratio is relevant if the next steps display lower free energies of activation than the CMD_{Pyr} transition states. However, the system becomes too large to study the insertion step; simplification is therefore needed. Since we aim to distinguish the absolute configuration at the sulfur atom, a monodentate ligand for example, acetyl-*L*-alanine instead of bulky mono-protected threonine moiety was used for modelling purposes.¹¹ The olefin insertion with metalated sulfoximine (made by the coordination of S=N and Pyr) is next considered (Fig. 4). The corresponding S=N coordination with *R* configuration **Int-3_{S=N}** is found most stable (Fig. 4). The detailed analysis of transition states (**INS**) occurred in the CMD revealed that the pyridine directed insertion (**INS_{Pyr}**) involves

lowest energy barriers (17.41 kcal mol⁻¹ for the *S* isomer and 21.80 for the *R* isomer); see Fig. 4. This results a final selectivity >99 : 1 (Fig. 4). This exergonic step, thus, funnels the reaction without affecting the ratio earlier dictated by the CMD. Interestingly, both **INS_{Pyr}** and **INS_{S=N}** structures are same (ignoring configuration); since both DGs (S=N and Pyr) are coordinated to the metal center in their corresponding products (**int-4**; Fig. 4).

The synthetic potential of chiral sulfoximine was next probed (Scheme 1). The trifluoroacetic acid (TFA) mediated *N*-Boc deprotection of (*R*)-**1b** provided chiral sulfoximine (*R*)-**6** (>88% ee). Next, reduction of (*R*)-**6** led to chiral sulfoxide (*R*)-**7** (90% ee) when exposed to *t*-BuNO₂ at rt for 2 h. The *N*-Boc deprotection and intramolecular Michael cyclization to the activated olefin moiety of (*S*)-**3c** smoothly delivered **8** (as a single diastereomer) in 95% ee. A TFA assisted *N*-Boc deprotection and oxidative intramolecular C–N bond formation of (*S*)-**5d** furnished (*S*)-**9** (93% ee, 62% yield).

Conclusions

In summary, a Pd(II)-catalyzed pyridyl substituted KR of sulfoximines through C(aryl)–H alkenylation and arylation has been revealed. The transformation addresses the inherent challenges in the KR of coordinatively active pyridyl-enabled sulfoximines (highly susceptible to TM-catalyst quenching) with no prochiral center in the presence of chiral amino acid MPAA ligands and Pd(II)-catalyst. The common functional groups were tolerated under Pd-catalysis exhibiting good substrate scope for C–H alkenylative and arylylative sulfoximines KR products in high enantioselectivity with *s* factor up to >200. In-depth DFT studies uncover the salient features of coordination selectivity of pyridyl-group over sulfoximine imine.

Data availability

Data for all compounds (experimental details, characterization and copies of ¹H and ¹³C NMR, HRMS spectra and HPLC data) in this manuscript are available in the ESI.† The computational details, additional computations, energies and coordinates of the computed intermediates and transition states are also provided in the ESI.† Crystallographic data for compound **3l** and **5h** have been deposited at the CCDC 2088890 and 2109210, respectively.

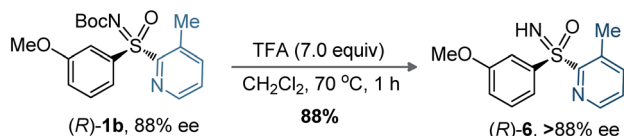
Author contributions

K. M., S. S., and A. K. S. designed and investigated. K. M. and S. S. performed the experiments. N. G. and V. G. performed the DFT studies. K. G. and M. S. reviewed the experimental data. A. K. S. and V. G. wrote the paper. Review, editing & supervision done by A. K. S.

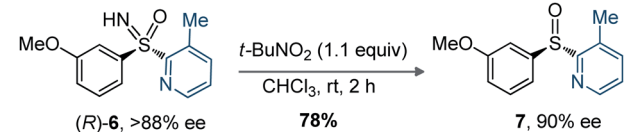
Conflicts of interest

There are no conflicts to declare.

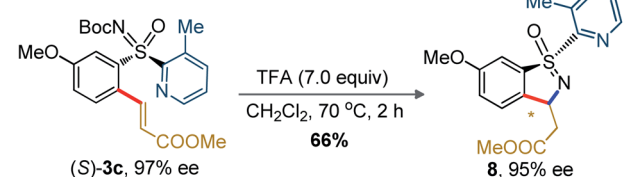
A. synthesis of N-free sulfoximine:



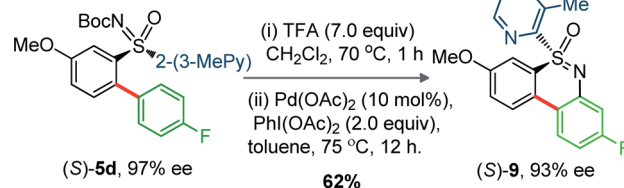
B. synthesis of chiral sulfoxide:



C. synthesis of five-membered cyclic sulfoximine:



D. synthesis of thiazine:



Scheme 1 Derivatization of chiral products.



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