Kinetic Resolution of Sulfur-Stereogenic Sulfoximines by Pd(II)-MPAA Catalyzed C–H Arylation and Olefination

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Supporting Information Placeholder

ABSTRACT: A direct Pd(II)-catalyzed kinetic resolution of heteroaryl-enabled sulfoximines through an *ortho*-C–H alkenylation/arylation of arenes has been developed for the first time. The coordination of sulfoximine pyridyl-motif and the chiral amino acid MPAA ligand to the Pd(II)-catalyst controls the enantiodiscriminating C(aryl)–H activation. This method provides access to a wide range of enantiomerically enriched unreacted aryl-pyridyl-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; which are inaccessible by conventional methods. 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.

The directing group (DG) assisted desymmetrization of prochiral C–H bonds provides a suitable way to construct carbon, phosphorus, silicon, and sulfur centred 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 centred 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 centred KR of arenes* remains unknown, although exceedingly appealing.

Sulfoximines, which are configurationally stable motifs with S-stereogenecity, 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 syntheses of enantioenriched sulfoximines have invariably relied on resolution techniques, stereoselective imination, and oxidation

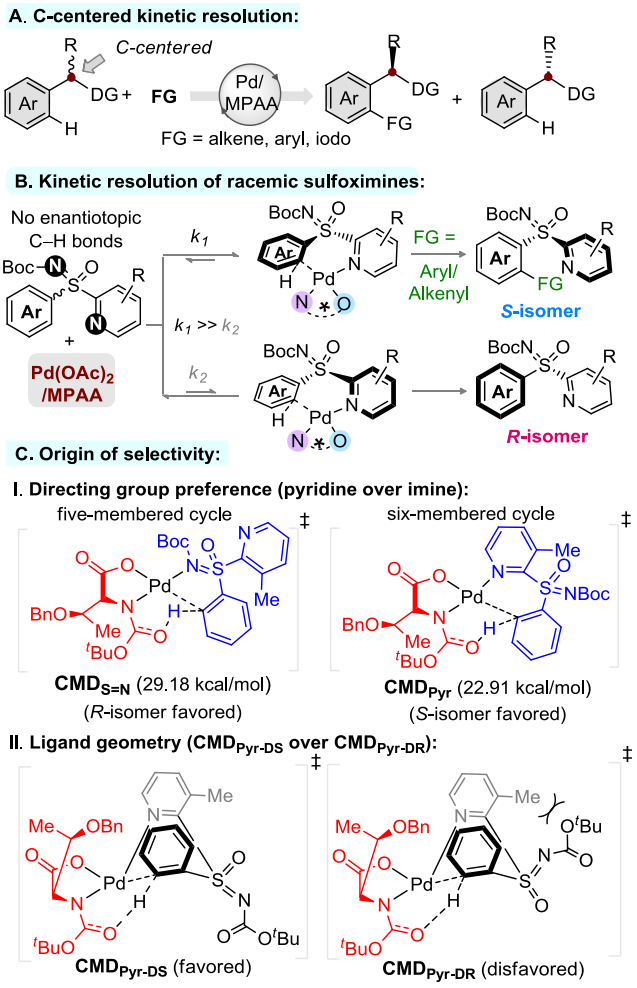
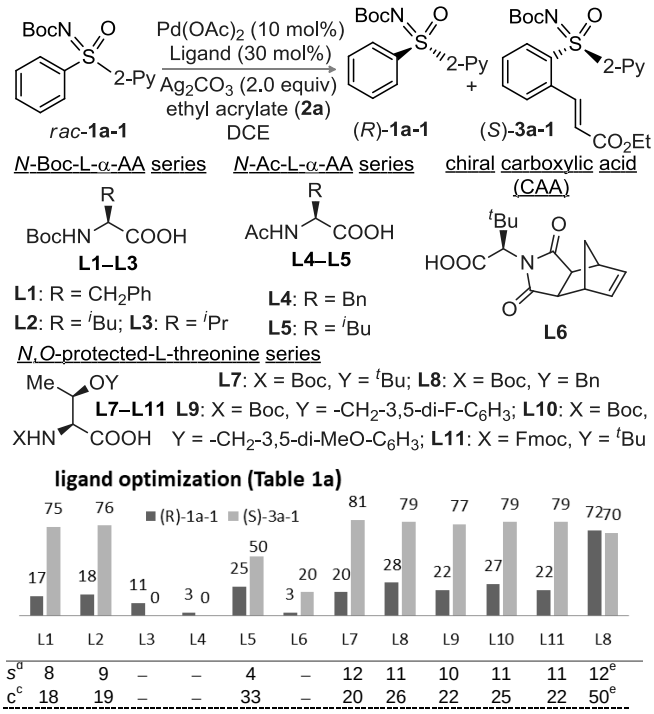


Figure 1. Kinetic resolution via C-H activation (Free energies at 343.15 K in DCE)

Table 1. Optimization for *o*-C–H Alkenylative Kinetic Resolution of Sulfoximines[a]

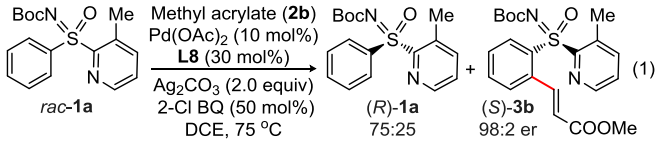


Entry	Additives	C[b]	ee (%)[c]		
			(*R*)-1a-1	(*S*)-3a-1	*s*[d]
1	BQ	18	17	78	10
2	2-chloro BQ	39	50	77	13
3	2, 5-dichloro BQ	35	40	75	10

[a]Reaction conditions: **rac-1a-1** (0.1 mmol), ethyl acrylate **2a** (0.6 equiv), $Pd(OAc)_2$ (10 mol%), ligand (30 mol%), Ag_2CO_3 (2.0 equiv), 2-Cl-BQ (0.3 equiv), 1,2-DCE (1.0 mL), N_2, 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

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 arylsulfoximines in presence of specially designed ligands.[9] On our side, we 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>>k_2, Fig 1B) through preferred coordination of pyridine over imine to Pd-MPAA (Fig 1C-I) and ligand geometry $\mathbf{CMD_{Pyr\text{-}DS}}$ over $\mathbf{CMD_{Pyr\text{-}DR}}$ (Fig 1C-II). The transformation is general, constructing a wide array of enantiomerically enriched C-olefinated/arylated aryl-pyridyl-*S*-sulfoximines, which are inaccessible by other routes.

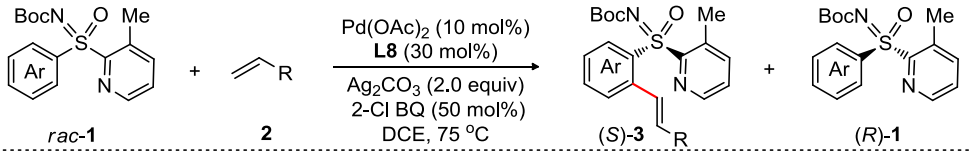
The study was initiated with the non-substituted N-Boc-phenyl-2-pyridyl sulfoximine *rac*-**1a-1** and ethyl acrylate (**2a**; 0.6 equiv) in presence of $Pd(OAc)_2$ (10 mol%), Boc-L-Phe-OH (**L1**; 30 mol%), Ag_2CO_3 (2.0 equiv) in $ClCH_2CH_2Cl$ (1,2-DCE) at 75 °C (Table 1a). The desired C2-alkenylation 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). To enhance sulfoximine resolution efficiency while maintaining conversion (~50%; Table 1a), we scrutinized the co-oxidant effect (Table 1b). 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). Upon a thorough DG and reaction parameters screening, 3-methyl pyridyl was found superior.[10] Thus, the reaction of **1a** (1.0 equiv), methyl acrylate (**2b**, 2.0 equiv), in presence of $Pd(OAc)_2$, **L8** ligand, Ag_2CO_3, and 2-Cl-BQ in 1,2-DCE led to (*S*)-**3b** (96% ee, *s* factor of 85 with 34% conversion) (eq 1).[10]



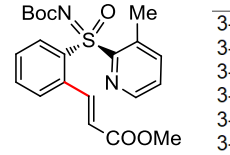
The generality of the Pd-catalyzed C–H alkenylative KR of sulfoximines was then surveyed (Table 2).[10] Compound **3b** (98.2:1.8 er) was isolated in 26% yield. The alkenylation occurred at the less-hindered arene C–H bond and the chiral sulfoximines **3c** and **3d** were obtained with *s* factors of 162 and 140, 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/^{t}Bu/^{i}Pr)-substituted aryl sulfoximines with **2b**/ vinyl-ketone (**2c**)/ vinyl-sulfone (**2f**) smoothly delivered **3i**–**m** in excellent enantioselectivity and *s* factor of 55 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).

Next, we investigated the feasibility of Pd-catalyzed C–H arylative KR of sulfoximines (Table 3).[10] The reaction of N-Boc-3-methoxyphenyl-2-(3-methylpyridyl) sulfoximine (**1b**) with (4-CF_3)Ph-Bpin (**4a**; 2.0 equiv) was performed under the catalytic conditions of eq 1. 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 Ag_2O played a vital role; 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

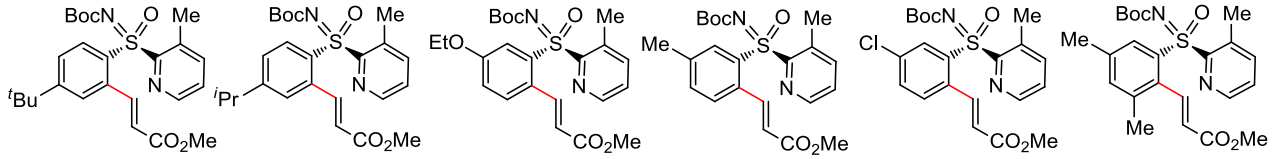
Table 2. Scope of C–H Alkenylative Kinetic Resolution of Sulfoximines[a,b]



Ar	R (**2a**–**f**)	Conv (%)	yield **3** (%)	er **3**	yield **1** (%)	er **1**	*s*
3-MeO-C_6H_4	CO_2Me[c]	42	35 (**3c**)	98.7:1.3	46 (**1b**)	85.5:14.5	162
3-MeO-C_6H_4	CO_2Et[c]	42	33 (**3d**)	98.5:1.5	44 (**1b**)	85.4:14.6	140
3-MeO-C_6H_4	COMe[c]	42	35 (**3e**)	95.6:4.4	43 (**1b**)	83.7:16.3	44
3-MeO-C_6H_4	SO_2Ph	35	27 (**3f**)	94.6:5.4	45 (**1b**)	73.8:26.2	28
3-MeO-C_6H_4	$PO(OEt)_2$[c]	40	33 (**3g**)	97.6:2.4	41 (**1b**)	81.2:18.8	77
3-MeO-C_6H_4	SO_2Me[c]	41	33 (**3h**)	99.6:0.4	42 (**1b**)	85:15	>200
4-Me-C_6H_4	CO_2Me	35	31[i] (**3i**)	97.8:2.2	46 (**1c**)	76.1:23.9	75
4-Me-C_6H_4	COMe	38	30 (**3j**)	97.8:2.2	45 (**1c**)	79.7:20.3	92
4-Me-C_6H_4	SO_2Me	35	31 (**3k**)	97.3:2.7	43 (**1c**)	75.1:24.9	58



3b: 26%, 98.2:1.8 er
1a: 51%, 76.2:23.8 er
C = 35, S = 92



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 = 55

3n: 42%, 92.7:7.3 er
1f: 34%, 94:6 er
C = 51, S = 37[c]

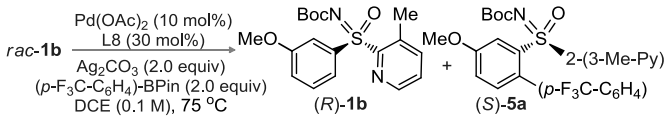
3o: 35%, 98.2:1.8 er
1g: 42%, 83.9:16.1 er
C = 41, S = 111

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]

[a]Reaction conditions: *rac*-**1** (0.25 mmol), olefin (2.0 equiv), $Pd(OAc)_2$ (10 mol%), **L8** (30 mol%), Ag_2CO_3 (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.

Table 3. Optimization *o*-C–H Arylative Kinetic Resolution of Sulfoximine [a]



Entry	Deviation	Conversion (c)	*ee* (%)		
			(*R*)-**1b**	(*S*)-**5a**	s
1	none	18	20	94	39
2	Ag_2O instead Ag_2CO_3	51	88	86	38
3[b]	60 °C instead 75 °C	43	70	92	50
4[b]	TFT instead 1,2-DCE	41	66	94	64
5[b,c]	20 mol% ligand	46	80	94	79
6[b,c,d]	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%), Ag_2CO_3 (2.0 equiv), 2-Cl-BQ (0.5 equiv), DCE (1.0 mL), N_2, 75 °C, 3 days. [b]Ag_2O oxidant. [c]TFT was used instead of 1,2-DCE, [d]**L8** (20 mol%) was used.

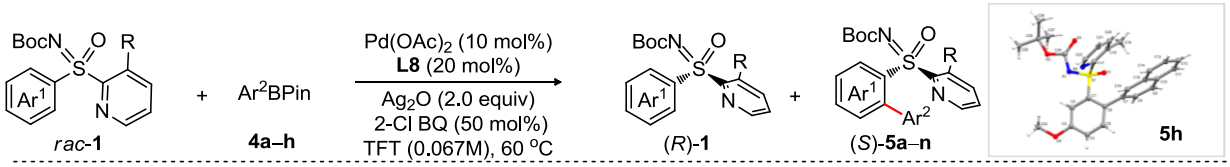
(entry 4). Performing the reaction with 20 mol% **L8** improved the outcome (entry 5). Importantly, reaction concentration from 0.1 M to 0.067 M led to (*S*)-**5a** (94% ee) and (*R*)-**1b** (88% ee) with 48% conversion and *s* factor of 95 (entry 6); this catalytic system thus able to provide a balanced outcome.

We next probed sulfoximines KR via enantioselective C–H aryla tion with arylpinacol boronate esters (Table-4).The reaction of **1b** with various arylpinacol boronate esters having electron withdrawing groups [*p*-CF_3 (**4a**), *m*-CF_3 (**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 arylative 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 69–171 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 112) was made from the arylation of 2-naphthyl containing sulfoximine **1j** with **4e**. The sterically bulky *o*-tolyl enabled sulfoximines, **1k** and **1l**, were successful in undergoing arylation with **4a**/**4c**/**4e** to afford **5k**–**n** in good enantioselectivity; the moderate *s* factor of 19–24 and conversion (*c* = 29–38%) is considered suitable.

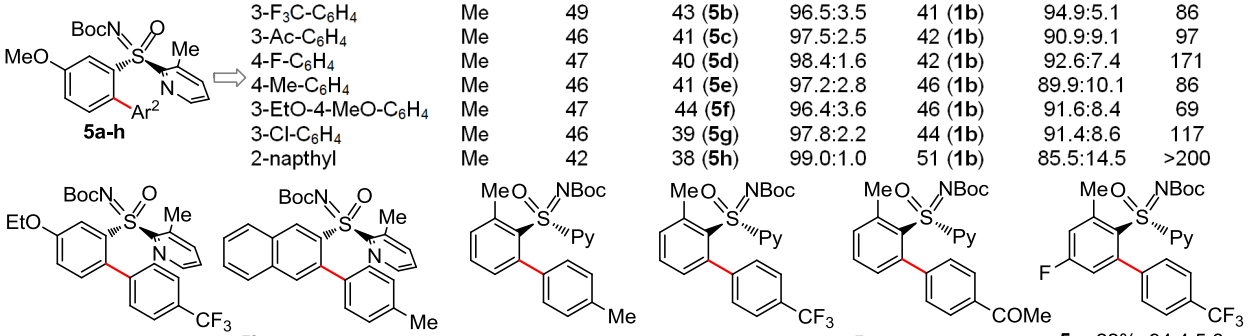
The synthetic potential of chiral sulfoximine was next probed (Scheme 1). The trifluoroacetic acid (TFA) mediated *N*-Boc deprotection of (*R*)-**1b** provided chiral sulfoximine (*R*)-**6** (95% ee). Next, reduction of (*R*)-**6** led to chiral sulfoxide (*R*)-**7** (90% ee) when exposed to *t*-$BuNO_2$ at rt for 2 h; chiral integrity of S-motif is preserved. 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).

We performed a theoretical study to unveil the reaction mechanism (Fig. 2 and Fig. 3).[10-12] The MPAA ligand coordination to the metal center lowers the energy barrier of the CMD step, forming a semi planar five membered ring.[12] We believe the CMD step could be the main responsible for the kinetic resolution. This hypothesis has been previously validated by Cheng *et al*, who also focused their study on the CMD as determining step.[11] 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

Table 4. Scope of C–H Arylative Kinetic Resolution of Sulfoximines[a,b]

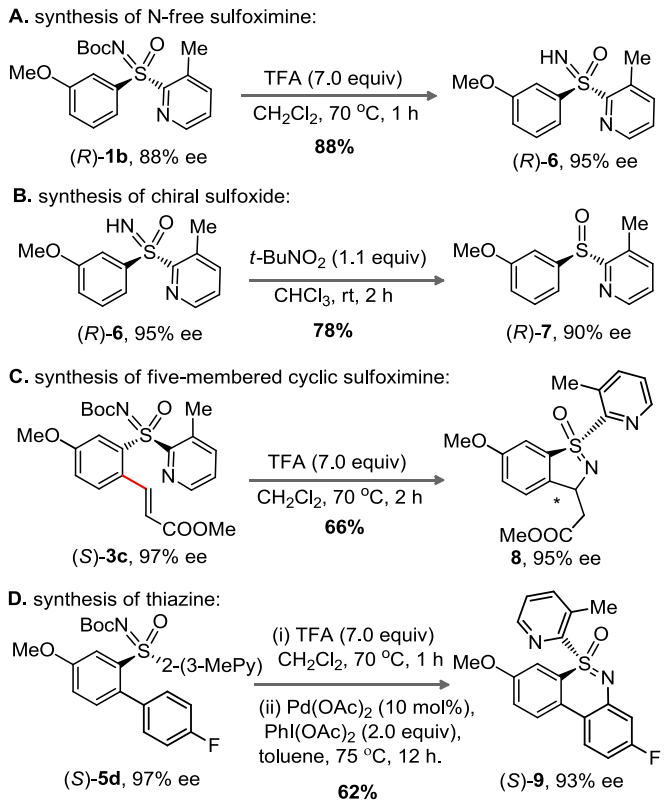


Ar² (**4a**–**h**)	R	Conv (%)	**5** (yield, %)	er **5**	yield **1** (%)	er **1**	s
4-F_3C-C_6H_4	Me	49	42 (**5a**)	96.1:3.9	44 (**1b**)	94.3:5.7	73
3-F_3C-C_6H_4	Me	49	43 (**5b**)	96.5:3.5	41 (**1b**)	94.9:5.1	86
3-Ac-C_6H_4	Me	46	41 (**5c**)	97.5:2.5	42 (**1b**)	90.9:9.1	97
4-F-C_6H_4	Me	47	40 (**5d**)	98.4:1.6	42 (**1b**)	92.6:7.4	171
4-Me-C_6H_4	Me	46	41 (**5e**)	97.2:2.8	46 (**1b**)	89.9:10.1	86
3-EtO-4-MeO-C_6H_4	Me	47	44 (**5f**)	96.4:3.6	46 (**1b**)	91.6:8.4	69
3-Cl-C_6H_4	Me	46	39 (**5g**)	97.8:2.2	44 (**1b**)	91.4:8.6	117
2-napthyl	Me	42	38 (**5h**)	99.0:1.0	51 (**1b**)	85.5:14.5	>200

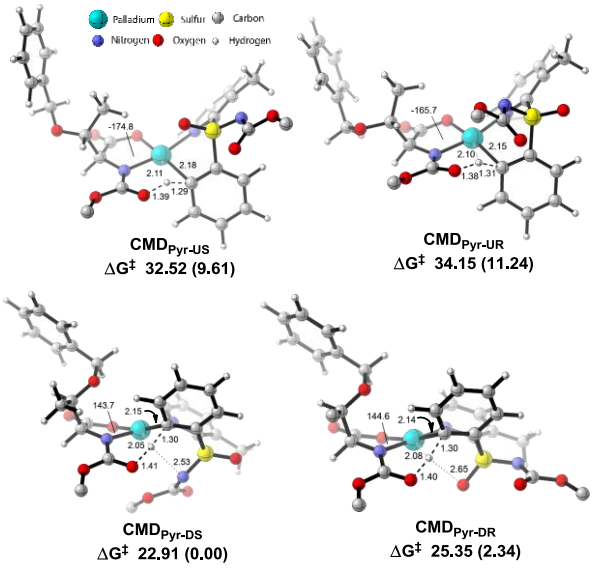


[a]Reaction conditions: ***rac*- 1** (0.2 mmol), **4** (2.0 equiv), $Pd(OAc)_2$ (10 mol%), **L8** (20 mol%), Ag_2O (2.0 equiv), 2-Cl-BQ (0.5 equiv), TFT (3.0 mL), 60 °C, 3 days. [b]Yield of the isolated arylation product

Scheme 1: Derivatization of Chiral Products



(above the plane) pushes the N-Boc moiety down to avoid steric hindrance (Fig 2 and Fig 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: **$CMD_{Pyr\text{-}UR}$**, **$CMD_{Pyr\text{-}US}$**, **$CMD_{Pyr\text{-}DR}$**, and **$CMD_{Pyr\text{-}DS}$**. The CMDs adopt a 6-membered palladacycle with twisted boat conformation.



- ᵗBu group from NBoc removed from all models to simplify visualization.
- Relative free energies in parentheses ($\Delta G^{\ddagger}$), distances in Å.

Figure 2. Transition structures for each CMD_{Pyr} approach.

In case of upward phenyl group linkage (**$CMD_{Pyr\text{-}UR}$** and **$CMD_{Pyr\text{-}US}$**), the sulfur atom and its substituents are located above the plane; while these substituents are below the plane for **$CMD_{Pyr\text{-}DR}$** and **$CMD_{Pyr\text{-}DS}$**. In agreement with Cheng's observations,[11] the C1-N2-Pd-O3 dihedral angle for **$CMD_{Pyr\text{-}UR}$** and **$CMD_{Pyr\text{-}US}$** is *ca* 170°, which generates a high steric interaction when compared with the *ca* 140° for **$CMD_{Pyr\text{-}DR}$** and **$CMD_{Pyr\text{-}DS}$**. 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 in each enantiomer.

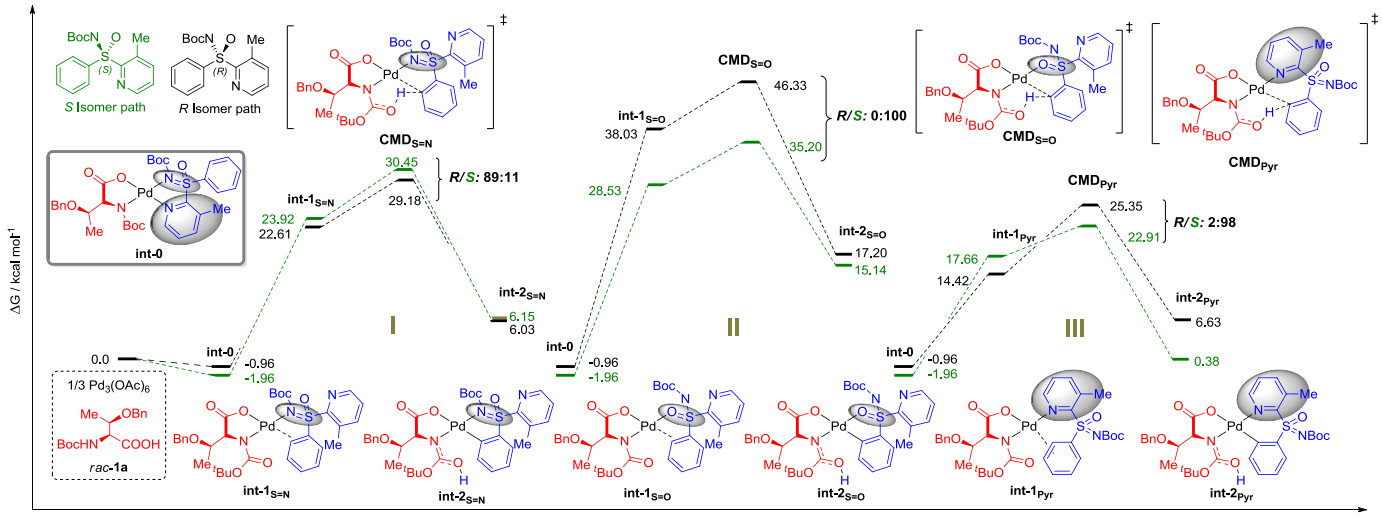


Figure 3. Free energies at 343.15 K in DCE in kcal/mol.

The preference for the S configuration by ~2.5 kcal/mol over the R isomer, lies in a steric clash of the NBoc group with the methyl group from the pyridine moiety and in consequence with the phenyl group, causing an energetically demanding 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 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-2$_{Pyr}$** is thermodynamically favored over ***R*-int-2$_{Pyr}$** isomer by 6 kcal/mol. In retrospect, the CMD transition states of **int-1$_{S=N}$** (Fig 3-I) and **int-1$_{S=O}$** (Fig 3-II) lie much higher than **int-1$_{Pyr}$** (Fig 3-III), and their respective $\Delta\Delta G^{\neq}$ do not coincide with the experimental findings. Further studies confirms that the CMD process is irreversible.[10]

In summary, a Pd(II)-catalyzed pyridyl substituted KR of sulfoximines through C(aryl)–H alkenylation and arylation has been revealed for the first time. 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 arylative 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.

ASSOCIATED CONTENT

Supporting Information

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Notes

The authors declare no competing financial interests.

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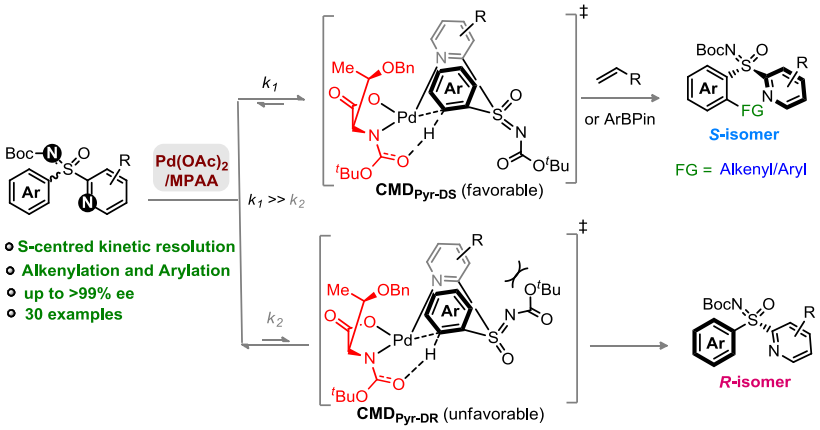
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